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اکسیر

The Skin

PART XXIX

Chapter 685

Morphology of the Skin

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EPIDERMIS

The mature epidermis is a stratified epithelial tissue composed predominantly of keratinocytes (Fig. 685.1). The epidermis protects the organism from the external environment through physical, chemical, and immunologic barrier functions and prevents water loss. Epidermal differentiation results in the formation of a functional barrier to the external world. The epidermis comprises four histologically recognizable layers, described here from deepest to most superficial. The first or **basal layer** consists of columnar cells that rest on the dermal-epidermal junction. Basal keratinocytes are connected to the dermal-epidermal junction by hemidesmosomes. Basal keratinocytes are attached to themselves and to the cells in the spinous layer by desmosomal, tight, gap, and adherens junctions. The role of the basal keratinocyte is to serve as a continuing supply of keratinocytes for the normally differentiating epidermis and as a reservoir of cells to repair epidermal damage. The second layer is the **spinous layer**, composed of three to four layers of spinous cells. Their role is to synthesize keratin, which makes up the keratin intermediate filament network. The third layer is the **granular layer**, which consists of two to three layers of granular cells. Granular cells contain keratohyalin and lamellar granules, containing the protein and lipid components that make up the cornified layer. The fourth layer, or **cornified layer**, is composed of multiple layers of dead, highly compacted cells. The dead cells are composed mainly of disulfide-bonded keratins cross-linked by filaggrins. The intercellular spaces are composed of hydrophobic lipids, predominantly ceramides, cholesterol, and fatty acids, serving as an effective barrier against water and salt loss as well as permeation of water-soluble substances. As the cornified layer is replenished, the oldest or most superficial layer is shed in a highly regulated process. The normal process of epidermal differentiation, from basal cell to shedding of the cornified layer, takes 28 days.

The epidermis also contains three other cell types. The **melanocytes** are pigment-forming cells, which are responsible for skin color and protection from ultraviolet radiation. Epidermal melanocytes are derived from the neural crest and migrate to the skin during embryonic life. They reside in the interfollicular epidermis and in the hair follicles. Melanocytes produce intracellular organelles (melanosomes) containing melanin, which they transfer via dendrites to the keratinocytes to protect the keratinocyte nucleus from ultraviolet damage. **Merkel** cells are type I slow-adapting mechanosensory receptors for touch that differentiate within the epidermis from epidermal progenitor cells. **Langerhans** cells are dendritic cells of the mononuclear phagocyte system and are uniquely characterized by a specific organelle, the Birbeck granule, which resembles a tennis racket on electron microscopy. These cells are derived from bone marrow and participate in immune reactions in the skin, playing an active part in antigen presentation and processing.

The junction of the epidermis and dermis is the basement membrane zone. This complex structure is a result of contributions from both epidermal and mesenchymal cells. The dermal-epidermal junction extends from the basal cell plasma membrane to the uppermost region of the dermis. Ultrastructurally, the basement membrane appears as a trilaminar structure, consisting of a lamina lucida immediately adjacent to the basal cell plasma membrane, a central lamina densa, and the subbasal lamina on the dermal side of the lamina densa. Several structures within this zone act to anchor the epidermis to the dermis. The plasma membrane of basal cells contains electron-dense plates known as *hemidesmosomes;* tonofilaments course within basal cells to insert at these sites. The **hemidesmosomes** are composed of 180- and 230-kDa bullous pemphigoid antigens (BP180 [BPAG2, type XVII collagen] and BP230 [BPAG1], respectively), $\alpha_6\beta_4$ and $\alpha_3\beta_1$ integrins, and plectin. Anchoring filaments originate in the plasma membrane, primarily near the hemidesmosomes, and insert into the lamina densa. Anchoring fibrils, composed predominantly of type VII collagen, extend from the lamina densa into the uppermost dermis, where they loop through collagen fibrils before reinserting into the lamina densa.

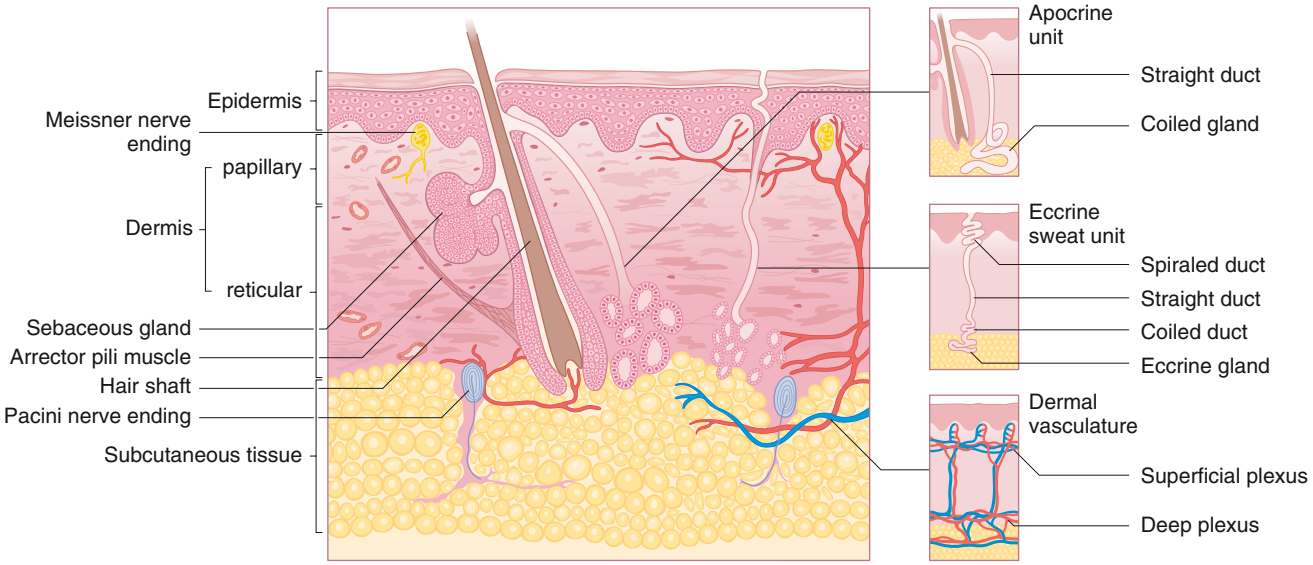

Fig. 685.1 Schematic of skin structure. *(From James WD, Berger T, Elston D. Andrews' Diseases of the Skin: Clinical Dermatology, 12th ed. Philadelphia: Elsevier; 2016: Fig. 1.1.)*

DERMIS

The dermis provides the skin with most of its mechanical properties (see Fig. 685.1). The dermis forms a tough, pliable, fibrous supporting structure between the epidermis and the subcutaneous fat. The predominant dermal cell is a spindle-shaped fibroblast that is responsible for the synthesis of collagen, elastic fibers, and mucopolysaccharides. Phagocytic histiocytes, mast cells, and motile leukocytes are also present. Within the dermis are blood vessels, lymphatics, neural structures, eccrine and apocrine sweat glands, hair follicles, sebaceous glands, and smooth muscle. Morphologically, the dermis can be divided into two layers: the superficial papillary layer that interdigitates with the rete ridges of the epidermis and the deeper reticular layer that lies beneath the papillary dermis. The papillary layer is less dense and more cellular, whereas the reticular layer appears more compact because of the coarse network of interlaced collagen and elastic fibers.

The extracellular matrix of the dermis consists of collagen and elastic fibers embedded in an amorphous ground substance. Collagen provides strength and stability to the dermis, and elastic fibers allow for elasticity. The gelatinous ground substance serves as a supporting medium for the fibrillar and cellular components and as a storage place for a substantial portion of body water.

SUBCUTANEOUS TISSUE

The **panniculus**, or subcutaneous tissue, consists of fat cells and fibrous septa that divide it into lobules and anchor it to the underlying fascia and periosteum (see Fig. 685.1). Blood vessels and nerves are also present in this layer, which serves as a storage depot for lipid, an insulator to conserve body heat, and a protective cushion against trauma.

APPENDAGEAL STRUCTURES

Appendageal structures are derived from aggregates of epidermal cells that become specialized during early embryonic development. Small buds (primary epithelial germs) appear in the third fetal month and give rise to hair follicles, sebaceous and apocrine glands, and the attachment bulges for the arrector pili muscles. Eccrine sweat glands are derived from separate epidermal downgrowths that arise in the second fetal month and are completely formed by the fifth month. Formation of nails is initiated in the third intrauterine month.

Hair Follicles

The pilosebaceous unit includes the hair follicle, sebaceous gland, arrector pili muscle, and, in areas such as the axillae, an apocrine gland. Hair follicles are distributed throughout the skin, except in the palms, soles, lips, and glans penis. Individual follicles extend from the surface of the epidermis to the deep dermis (see Fig. 685.1). The hair follicle is divided into four segments: the infundibulum, which extends from the skin surface to the opening of the sebaceous duct; the isthmus, extending from the sebaceous duct opening to the bulge; the lower follicle between the bulge and the hair bulb; and the hair bulb. The bulge is at the insertion of the arrector pili muscle and is a focus of epidermal stem cells. The bulb is where the matrix cells and the dermal papilla are involved in formation and maintenance of the hair. The growing hair consists of the hair shaft, made of dead keratinocytes, and its supporting inner and outer root sheaths.

Human hair growth is cyclic, with alternate periods of growth (anagen), transition (catagen), and rest (telogen). The length of the anagen phase varies from months to years, whereas catagen and telogen last approximately 3 weeks and 3 months, respectively. At birth, all hairs are in the anagen phase. Subsequent generative activity lacks synchrony, so an overall random pattern of growth and shedding prevails. At any time, approximately 85% of hairs are in the anagen phase. Scalp hair usually grows about 1 cm per month.

The types of hair are lanugo, vellus, and terminal hairs. **Lanugo hair** is thin and short; this hair is shed in utero and is replaced by vellus hair by 36-40 weeks of gestation. **Vellus hair** is short, soft, frequently unpigmented, and distributed over the body. **Terminal hair** is long and coarse and is found on the scalp, beard, eyebrows, eyelashes, and axillary and pubic areas. During puberty, androgenic hormone stimulation causes pubic, axillary, and beard hair to change from vellus hair to terminal hair.

Sebaceous Glands

Sebaceous glands occur in all areas except the palms, soles, and dorsal feet and are most numerous on the head, upper chest, and back (see Fig. 685.1). Their ducts open into the hair follicles except on the eyelids, lips, nipples, prepuce, and labia minora, where they emerge directly onto the skin surface. These holocrine glands are saccular structures that are often branched and lobulated and consist of a proliferative basal layer of small flat cells peripheral to the central mass of lipidized cells. The latter cells disintegrate as they move toward the duct and form the lipid secretion known as *sebum,* which consists of triglycerides, wax esters, squalene, and cholesterol esters. The purpose of sebum production likely relates to hydrophobic skin barrier function. Sebaceous glands depend on hormonal stimulation and are activated by androgens at puberty. Fetal sebaceous glands are stimulated by maternal androgens, and their lipid secretion, together with desquamated stratum corneum cells, constitutes the vernix caseosa.

Apocrine Glands

The apocrine glands are located in the axillae, areolae, perianal and genital areas, and periumbilical region (see Fig. 685.1). These large, coiled, tubular structures continuously secrete an odorless milky fluid that is discharged in response to adrenergic stimuli, usually because of emotional stress. Bacterial biotransformation of apocrine sweat components (fatty acids, thioalcohols, and steroids) accounts for the unpleasant odor associated with perspiration. Apocrine glands remain dormant until puberty, when they enlarge and secretion begins in response to androgenic activity. The secretory coil of the gland consists of a single layer of cells enclosed by a layer of contractile myoepithelial cells. The duct is lined with a double layer of cuboidal cells and opens into the pilosebaceous complex.

Eccrine Sweat Glands

Eccrine sweat glands are distributed over the entire body surface and are most abundant on the palms and soles (see Fig. 685.1). Those on the hairy skin respond to thermal stimuli and serve to regulate body temperature by delivering water to the skin surface for evaporation; in contrast, sweat glands on the palms and soles respond mainly to psychophysiologic stimuli.

Each eccrine gland consists of a secretory coil located in the reticular dermis or subcutaneous fat and a secretory duct that opens onto the skin surface. Sweat pores can be identified on the epidermal ridges of the palm and fingers with a magnifying lens but are not readily visualized elsewhere. Two types of cells constitute the single-layered secretory coil: small dark cells and large clear cells. These rest on a layer of contractile myoepithelial cells and a basement membrane. The glands are supplied by sympathetic nerve fibers, but the pharmacologic mediator of sweating is acetylcholine rather than epinephrine. Sweat from these glands consists of water; sodium; potassium; calcium; chloride; phosphorus; lactate; and small quantities of iron, glucose, and protein. The composition varies with the rate of sweating but is always hypotonic in normal children.

Nails

Nails are specialized protective epidermal structures that form convex, translucent, tight-fitting plates on the distal dorsal surfaces of the fingers and toes. The nail plate, which is derived from a metabolically active matrix of multiplying cells situated beneath the posterior nail fold, is composed of anucleate keratinocytes. Nail growth is relatively slow; complete fingernail regrowth takes 6 months, and complete toenail regrowth requires 12-18 months. The nail plate is bounded by the lateral and posterior nail folds; a thin eponychium (the cuticle) protrudes from the posterior fold over a crescent-shaped white area called the *lunula.* The eponychium serves as a sealant barrier to protect the germinal matrix of the nail plate. The hyponychium refers to the volar surface epithelium of the distal digit and seals the nail bed distally. The pink color beneath the nail reflects the underlying vascular bed. Nail health relies on several factors, including nutrition, hydration, local infection/irritation, and systemic disease.

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Chapter 686

Dermatologic Evaluation of the Patient

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HISTORY AND PHYSICAL EXAMINATION

A history and careful physical examination are often necessary for accurate assessment of skin disorders. A good skin exam is essential in dermatologic evaluation and should be performed under adequate illumination. In addition to the skin covering the entire body surface, mucous membranes (conjunctiva, oropharynx, nasal mucosa, and anogenital mucosa), hair, and nails should be examined when appropriate. The color, turgor, texture, temperature, and moisture of the skin and the growth, texture, caliber, and luster of the hair and nails should be noted. Erythema or other color changes may be challenging to appreciate in children with darker skin tones, and other features of the disorder should be relied upon to make the diagnosis. Skin lesions should be palpated, inspected, and classified on the basis of morphology, size, color, texture, firmness, configuration, location, and distribution. One must also decide whether the changes are those of the *primary* lesion itself or whether the clinical pattern has been altered by a *secondary* factor such as infection, trauma, or therapy.

Primary lesions are classified as macules, papules, patches, plaques, nodules, tumors, vesicles, bullae, pustules, wheals, and cysts. A **macule** represents an alteration in skin color but cannot be felt. When the lesion is >1 cm, the term **patch** is used. **Papules** are palpable solid lesions <1 cm. **Plaques** are palpable lesions >1 cm in size and have a flat surface. **Nodules** are palpable lesions >1 cm with a rounded surface. The word **tumor** may be used for a large nodule that is suspected to be neoplastic in origin. **Vesicles** are raised, fluid-filled lesions <1 cm in diameter; when larger, they are called **bullae**. **Pustules** are fluid-filled lesions containing purulent material. **Wheals** are flat-topped, palpable lesions of variable size, duration, and configuration that represent dermal collections of edema fluid. **Cysts** are circumscribed, thick-walled lesions; they are covered by a normal epidermis and contain fluid or semisolid material.

Primary lesions may change into secondary lesions, or secondary lesions may develop over time where no primary lesion existed. Primary lesions are usually more helpful for diagnostic purposes than secondary lesions. Secondary lesions include scales, purpura, petechiae, ulcers, erosions, excoriations, fissures, crusts, and scars. **Scales** consist of compressed layers of stratum corneum cells that are retained on the skin surface. **Purpuras** are the result of bleeding into the skin and have a red-purple color; they may be flat or palpable. **Petechiae** are small (<2-3 mm) purpura. **Erosions** involve focal loss of the epidermis, and they heal without scarring. **Ulcers** extend into the dermis and tend to heal with scarring. Ulcerated lesions inflicted by scratching are often linear or angular in configuration and are called **excoriations**. **Fissures** are caused by splitting or cracking. **Crusts** consist of matted, retained accumulations of blood, serum, pus, and epithelial debris on the surface of a weeping lesion. **Scars** are end-stage lesions that can be thin, depressed, and atrophic; raised and hypertrophic; or flat and pliable. **Lichenification** is a thickening of skin with accentuation of normal skin lines that is caused by chronic irritation (rubbing, scratching) or inflammation.

If the diagnosis is not clear after a thorough examination, one or more diagnostic procedures may be indicated.

BIOPSY OF SKIN

Biopsy of skin is occasionally required for diagnosis. The two most commonly used approaches are the shave biopsy and the punch biopsy. A shave biopsy is primarily used for superficial, raised lesions, whereas a punch biopsy is used when it is indicated to sample the dermis and subcutaneous tissue, as with most inflammatory dermatoses. Both are simple, relatively painless procedures and usually provide adequate tissue for examination if the appropriate lesion is sampled. The selection of a fresh, well-developed primary lesion is extremely important to obtain an accurate diagnosis. In cases of a punch biopsy, the site of the biopsy should have relatively low risk for damage to underlying dermal structures. After cleansing of the site, the skin is anesthetized by intradermal injection of 1–2% lidocaine, with or without epinephrine, with a 27- or 30-gauge needle. For a shave biopsy, a double-edged razor or scalpel is used to remove a thin disk of tissue down to the upper dermis. Hemostasis can be obtained with 20% aluminum chloride solution, and the biopsy site is then covered with petroleum jelly and a bandage. In the case of a punch biopsy, after anesthetizing the skin, a punch tool, usually 3 or 4 mm in diameter, is pressed firmly against the skin and rotated until it sinks to the proper depth. All three layers (epidermis, dermis, and subcutis) should be contained in the plug. The plug should be lifted gently with forceps or extracted with a needle and separated from the underlying tissue with iris scissors. Bleeding abates with firm pressure and with suturing. The biopsy specimen should be placed in 10% formaldehyde solution (Formalin) for appropriate processing.

WOOD LAMP

A Wood lamp emits ultraviolet light mainly at a wavelength of 365 nm. A skin examination under a Wood lamp, which is performed in a darkened room, is useful in accentuating changes in pigmentation and detecting fluorescence in certain infectious disorders. Discrete areas of altered pigment can often be visualized more clearly by using a Wood lamp, particularly if the pigmentary change is epidermal. Hyperpigmented lesions appear darker, and hypopigmented lesions (e.g., those seen in **tuberous sclerosis**) lighter than the surrounding skin. Blue-green fluorescence is detectable at the base of each infected hair shaft in ectothrix infections, such as tinea capitis caused by *Microsporum* species. Scales and crusts may appear pale yellow, but this color is not evidence of a fungal infection. Dermatophyte lesions of the skin (tinea corporis) do not fluoresce; macules of tinea versicolor have a golden fluorescence under a Wood lamp. **Erythrasma**, an intertriginous infection caused by *Corynebacterium minutissimum,* may fluoresce pink-orange, whereas *Pseudomonas aeruginosa* is yellow-green under a Wood lamp.

POTASSIUM HYDROXIDE PREPARATION

Potassium hydroxide (KOH) preparation is a rapid and reliable method for detecting fungal elements of both yeasts and dermatophytes. Scaly lesions should be scraped at the active border for optimal recovery of mycelia and spores. Vesicles should be unroofed, and the blister roof should be clipped and placed on a slide for examination. In tinea capitis, infected hairs must be plucked from the follicle; scales from the scalp do not usually contain mycelia. A few drops of 20% KOH are added to the specimen. Dimethyl sulfoxide is usually in solution with the KOH, negating the need to heat the specimen. If using KOH without dimethyl sulfoxide, the specimen is gently heated over an alcohol lamp or on a hot plate until the KOH begins to bubble. Alternatively, sufficient time (10-20 minutes) can be allowed for dissolution of the keratin at room temperature. The preparation is examined under low-intensity light microscopy for fungal elements.

TZANCK SMEAR

Tzanck smear had been useful in the diagnosis of infections caused by herpes simplex virus or varicella-zoster virus and for the detection of acantholytic cells in pemphigus. An intact, fresh vesicle is ruptured and drained of fluid. The roof and base of the blister are then carefully scraped with a No. 15 scalpel blade, with care taken to avoid drawing a significant amount of blood; the material is smeared on a clear glass slide and air dried. Staining with Giemsa stain is preferable, but Wright stain is acceptable. Balloon cells and multinucleated giant cells are diagnostic of herpes virus infection; acantholytic epidermal cells—large round epidermal cells with hypertrophic nuclei—are characteristic of pemphigus.

Table 686.1 Immunofluorescence Findings in Immune-Mediated Cutaneous Diseases

DISEASE	INVOLVED SKIN	UNINVOLVED SKIN	DIRECT IF FINDINGS	INDIRECT IF FINDINGS	CIRCULATING ANTIBODIES
Dermatitis herpetiformis	Negative	Positive	Granular IgA ± C in papillary dermis	None	IgA antiendomysial and transglutaminase antibodies
Bullous pemphigoid	Positive	Positive	Linear IgG and C band in BMZ, occasionally IgM, IgA, IgE	IgG to BMZ	IgG anti-BP180 and anti-BP230
Pemphigus (all variants)	Positive	Positive	IgG in intercellular spaces of epidermis between keratinocytes	IgG to intercellular spaces of epidermis between keratinocytes	IgG antidesmoglein 1 and 3 (pemphigus vulgaris and foliaceus). IgA antidesmocollin 1 (IgA pemphigus)
Linear IgA bullous dermatosis (chronic bullous dermatosis of childhood)	Positive	Positive	Linear IgA at BMZ, occasionally C	Low titer, rare IgA, anti-BP180	None
Discoid lupus erythematosus	Positive	Negative	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	Usually ANA-negative
Systemic lupus erythematosus	Positive	Variable; 30–50% of sun-exposed skin; 10–30% of photoprotected skin	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	ANA Anti-Ro (SSA), anti-La (SSB) Anti-RNP Anti-dsDNA Anti-Sm
IgA vasculitis (Henoch-Schönlein purpura)	Positive	Positive	IgA around vessel walls	None	None

ANA, Antinuclear antibody; BMZ, basement membrane zone at the dermal-epidermal junction; BP, bullous pemphigoid; C, complement; dsDNA, double-stranded deoxyribonucleic acid; IF, immunofluorescence; Ig, immunoglobulin; Sm, Smith; SSA/SSB, Sjögren syndrome A/B; RNP, ribonucleoprotein.

Direct fluorescent assay and polymerase chain reaction tests have largely replaced Tzanck smears in the diagnosis of herpes simplex and varicella-zoster infections. Both of these are rapid, sensitive, and specific, with the polymerase chain reaction even more so. When obtaining specimens for these tests, the vesicles should be ruptured before sample collection with the swab.

IMMUNOFLUORESCENCE STUDIES

Immunofluorescence studies of skin can be used to detect tissue-fixed antibodies to skin components and complement; characteristic staining patterns are specific for certain skin disorders (Table 686.1). Direct immunofluorescence detects autoantibodies bound to cutaneous antigens in the skin, and indirect immunofluorescence detects circulating autoantibodies present in the serum.

Skin biopsy specimens for direct immunofluorescence should be obtained from involved sites except in those diseases for which perilesional skin or uninvolved skin is required. A punch biopsy sample is obtained, and the tissue is placed in a special transport medium or immediately frozen in liquid nitrogen for transport or storage. Thin cryostat sections of the specimen are incubated with fluorescein-conjugated antibodies to the specific antigens.

Serum of patients can be examined by indirect immunofluorescence techniques using sections of normal human skin, guinea pig lip, or monkey esophagus as substrate. The substrate is incubated with fresh or thawed frozen serum and then with fluorescein-conjugated antihuman globulin. If the serum contains antibody to epithelial components, its specific staining pattern can be seen on fluorescence microscopy. By serial dilution, the titer of circulating antibody can be estimated.

686.1 Cutaneous Manifestations of Systemic Diseases

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Selected diseases have signature skin findings, often as the presenting signs of illness, which can facilitate the assessment of patients with complex medical states (Table 686.2).

CONNECTIVE TISSUE DISEASES

Lupus Erythematosus

Lupus erythematosus (LE; see Chapter 199) is an idiopathic autoimmune inflammatory disease that may be multisystemic (i.e., systemic LE or SLE) or confined to the skin. Distinct cutaneous lupus subtypes seen in children include acute cutaneous LE, subacute cutaneous LE, chronic cutaneous LE (including discoid LE, discussed under "Discoid Lupus Erythematosus"), and neonatal LE (discussed under "Neonatal Lupus Erythematosus").

Systemic Lupus Erythematosus

SLE is a chronic inflammatory multisystem disease with approximately 15–20% of cases diagnosed in childhood. It is diagnosed when 4 of 11 well-defined clinical and 6 immunologic criteria are present (see Chapter 199), where both one clinical and one immunologic criterion each must be met. Four of the clinical criteria are skin findings. **Criterion 1** is acute cutaneous lupus, which may involve the classic malar or "butterfly" rash (Fig. 686.1), bullous lupus lesions, psoriasiform and/or annular polycyclic lupus lesions that resolve without scarring, and photosensitive erythematous macular or papular eruption (Fig. 686.2).

Table 686.2 Characteristics of Cutaneous Signs of Systemic Diseases

DISEASE	AGE OF ONSET	SKIN LESIONS	DISTRIBUTION	DIAGNOSTIC EVALUATION(S) AND FINDINGS	ASSOCIATED SYMPTOMS/ SIGNS	DIFFERENTIAL DIAGNOSIS
Systemic lupus erythematosus	Any	Erythematous patches and plaques; palpable purpura; livedo reticularis; Raynaud phenomenon; urticaria	Photodistribution; "malar" face	ANA panel Anti-dsDNA Leukopenia/ lymphopenia Thrombocytopenia Complement levels Urinalysis	Arthritis Nephritis Cerebritis Serositis	Seborrheic dermatitis Atopic dermatitis Juvenile dermatomyositis
Discoid lupus erythematosus	Any	Annular, scaly plaques; atrophy; dyspigmentation	Photodistribution	ANA	Scarring	Subacute cutaneous lupus Polymorphous light eruption Juvenile dermatomyositis
Neonatal lupus erythematosus	Newborn	Annular, erythematous, scaly plaques	Head/neck	ANA Anti-Ro (SSA), anti-La (SSB)	Heart block Thrombocytopenia	Tinea capitis Atopic dermatitis Seborrheic dermatitis
Juvenile dermatomyositis	Any	Erythematous to violaceous scaly macules; discrete papules overlying joints	Periocular face; shoulder girdle; extensor extremities	ANA AST ALT Aldolase Creatine kinase Lactate dehydrogenase	Fatigue Proximal muscle weakness Calcifications Vasculopathy	Atopic dermatitis Allergic contact dermatitis Lupus erythematosus
Morphea	Any	Sclerotic plaques; resolve with hyperpigmentation and atrophy	Variable	Skin biopsy MRI brain if head and neck involvement	Neurologic (seizures, migraine headaches, focal neurologic deficits, asymptomatic MRI abnormalities) Musculoskeletal (joint contractures, limb length discrepancy, arthritis, arthralgias)	Systemic sclerosis
IgA vasculitis (Henoch-Schönlein purpura)	Childhood and adolescence	Purpuric papules and plaques	Buttocks; lower extremities	Urinalysis Blood urea nitrogen/ creatinine ratio Skin biopsy	Abdominal pain Arthritis	Vasculitis Drug eruption Infantile hemorrhagic edema Viral exanthem
Kawasaki disease	Infancy, childhood	Erythematous maculopapular to urticarial plaques; acral and groin erythema, edema, desquamation, digital cyanosis / gangrene	Diffuse	Leukocytosis ESR C-reactive protein Thrombocytosis	Strawberry tongue Conjunctivitis Lymphadenopathy Cardiovascular complications	Viral syndrome Drug eruption Staphylococcal/ streptococcal illness
Inflammatory bowel disease	Childhood and adolescence	Aphthae; erythema nodosum; pyoderma gangrenosum; lip swelling	Oral and perianal predominate	Skin biopsy Fecal calprotectin, ESR, CRP Gastroenterology evaluation	Abdominal pain Diarrhea Cramping Arthritis Conjunctivitis	Behçet syndrome Vasculitis *Yersinia* colitis
Sweet syndrome	Any	Infiltrated erythematous, edematous plaques	Head and neck predominate	Skin biopsy Leukocytosis ESR	Fever Flulike illness Conjunctivitis	Infection Urticaria Erythema multiforme Urticarial vasculitis Systemic autoinflammatory diseases*

Continued

Table 686.2 Characteristics of Cutaneous Signs of Systemic Diseases—cont'd

DISEASE	AGE OF ONSET	SKIN LESIONS	DISTRIBUTION	DIAGNOSTIC EVALUATION(S) AND FINDINGS	ASSOCIATED SYMPTOMS/ SIGNS	DIFFERENTIAL DIAGNOSIS
Graft-versus-host disease	Any	Acute: erythema, papules, vesicles, bullae	Diffuse with predilection for head/neck and palms/soles	Skin biopsy Liver function tests	Fever Mucositis Hepatitis	Drug eruption Infectious exanthem
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Any	Erythema; urticarial macules and plaques	Diffuse	Liver function Eosinophilia Atypical lymphocytosis	Facial edema Lymphadenopathy Fever Hepatitis	Stevens-Johnson syndrome Infectious exanthem
Serum sickness-like reaction (SSLR)	Any	Edematous, urticarial plaques	Diffuse	None	Fever Lymphadenopathy Arthritis, nephritis	Kawasaki disease Urticaria
Multisystem inflammatory syndrome in children (MIS-C) (see Table 686.3)						
Autoinflammatory diseases (see Table 686.4)						

*NOMID, Neonatal-onset multisystem inflammatory disease and other recurrent fever syndromes.
ALT, Alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; dsDNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; SSA/SSB, Sjögren syndrome A/B.

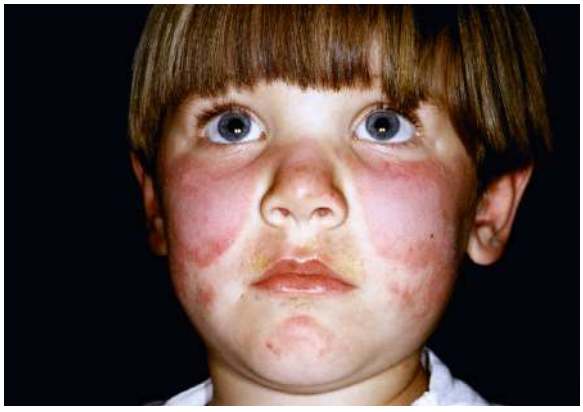

Fig. 686.1 Malar rash of systemic lupus erythematosus.

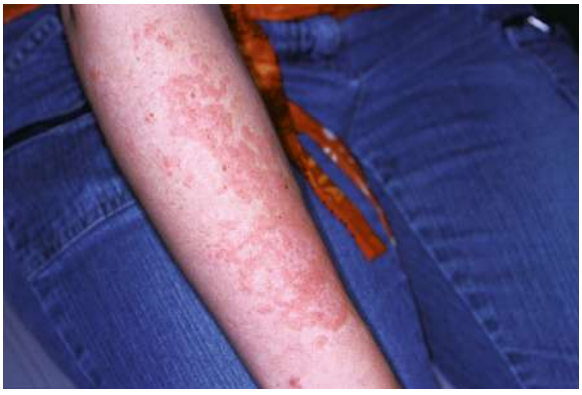

Fig. 686.2 Photosensitive rash of systemic lupus erythematosus.

The malar rash must be distinguished from other causes of a "red face," most notably seborrheic dermatitis, atopic dermatitis, and rosacea. **Criterion 2** is chronic cutaneous lupus, which includes discoid lupus lesions, hypertrophic (verrucous) lupus lesions, and lupus panniculitis, among others. **Criterion 3** is oral or nasal ulcers in the absence of other causes such as vasculitis, Behçet disease, infection (herpes simplex virus [HSV]), or inflammatory bowel disease. **Criterion 4** is nonscarring alopecia, which may include diffuse thinning or hair fragility in the absence of other causes such as alopecia areata, drugs, or iron deficiency. Patients may meet full SLE criteria based on skin findings alone with one immunologic criterion (such as positive antinuclear antibodies [ANA] or anti-dsDNA). Other associated but not diagnostic cutaneous findings include purpuric lesions, livedo reticularis, Raynaud phenomenon, and urticaria.

On histology, cutaneous LE demonstrates varying degrees of epidermal atrophy, plugging of hair follicles, and a vacuolar alteration at an inflamed dermal-epidermal junction. Deposition of immunoglobulins (IgM, IgG) and complement in lesional skin may help confirm the diagnosis. Immune deposits in nonlesional sun-exposed skin are found in the majority of patients with SLE (lupus band test), although clinical use of this test has been mostly abandoned in favor of serologic testing.

The skin lesions often respond to treatment of the SLE with systemic agents. Oral hydroxychloroquine is used most commonly, but many other systemic therapies are effective, including both classic and biologic immunosuppressants. Low- to mid-potency topical corticosteroids, topical calcineurin inhibitors, and intralesional corticosteroid injection may be considered for adjunctive therapy for skin lesions. A multispecialty approach is recommended, as pediatric patients are at significantly higher risk for long-term morbidity than adults.

Neonatal Lupus Erythematosus

Neonatal LE (see Chapter 199.1) manifests at birth or during the first few weeks of life as annular, erythematous, scaly plaques, typically on the head, neck, and upper trunk (Fig. 686.3). Telangiectasias are also common. Ultraviolet light may exacerbate or initiate cutaneous lesions. Passive transplacental transfer of maternal anti-Ro/SSA and anti-La/SSB antibodies causes the transient skin lesions, though most infants are born to mothers without a known rheumatologic diagnosis.

Table 686.3 Mucocutaneous Findings in Multisystem Inflammatory Syndrome in Children

LOCATION	DESCRIPTORS
Generalized, including: Perineal Trunk Face Ears Periorbital area Extremities	Urticarial Papular Maculopapular Macular Morbilliform Desquamative Edematous Erythematous Purpuric Targetoid Retiform Reticular Scarlatiniform Petechiae Livedoid EM-like RIME-like Lipschultz ulcer
Hands and Feet	Edematous Erythematous Desquamative Purpuric Petechiae
Tongue	Papillitis Strawberry tongue De-epithelialized
Lips	Cracked/fissured Erythematous
Eyes	Injected Swollen Nonpurulent discharge

RIME, Reactive infectious mucocutaneous eruption.
From Neale H, Hawryluk EB. COVID-19 pediatric dermatology. *Dermatol Clin.* 39(4):505–519, Table 1, p. 509.

Table 686.4 Dermatologic Manifestations of Monogenic Autoinflammatory Diseases

I. NONSPECIFIC MACULOPAPULAR RASHES WITH RECURRENT EPISODIC FEVER AND ABDOMINAL PAIN (HEREDITARY PERIODIC FEVER SYNDROME)
A. Recurrent fever attacks of short duration (typically ≤7 days)
1. Familial Mediterranean fever
2. Hyperimmunoglobulinemia D with periodic fever syndrome/ mevalonate kinase deficiency
B. Recurrent fever attacks of longer duration (typically >7 days)
1. Tumor necrosis factor receptor–associated periodic syndrome
II. NEUTROPHILIC URTICARIA (CAPS)
A. Recurrent fever attacks of short duration (typically <24 hours)
1. CAPS/familial cold autoinflammatory syndrome
2. CAPS/Muckle-Wells syndrome
B. Continuous low-grade fever
1. CAPS/neonatal-onset multisystem inflammatory disease/ CINCA
2. IL-18–mediated AID and IL-1–mediated AID: NLRC4-related macrophage activation syndrome
III. PUSTULAR SKIN RASHES AND EPISODIC FEVERS
A. IL-1–mediated pyogenic disorders with sterile osteomyelitis
1. Deficiency of IL-1 receptor antagonist
2. Majeed syndrome
B. Partially IL-1–mediated pyogenic disorders
1. Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome
2. Haploinsufficiency of A20 (monogenic form of Behçet disease)
C. Pyogenic disorders caused by non–IL-1 cytokine dysregulation
1. Deficiency of IL-36 receptor antagonist
2. CARD14-mediated psoriasis (monogenic form of psoriasis)
3. Early-onset inflammatory bowel disease
IV. VASCULOPATHY AND PANNICULITIS/LIPOATROPHY SYNDROMES
A. Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome or proteasome-associated autoinflammatory syndrome
V. VASCULOPATHY AND/OR VASCULITIS WITH LIVEDO RETICULARIS SYNDROMES
A. Without significant CNS disease
1. STING-associated vasculopathy with onset in infancy
B. With severe CNS disease
1. Aicardi-Goutières syndrome
2. Deficiency of adenosine deaminase 2
3. Spondyloenchondrodysplasia with immune dysregulation
VI. AUTOINFLAMMATORY DISORDERS WITH GRANULOMATOUS SKIN DISEASES
A. Without significant immunodeficiency
1. Blau syndrome (pediatric granulomatous arthritis, pediatric granulomatous arthritis)
B. With variable features of immunodeficiency and significant CNS disease
2. PLCγ2-associated antibody deficiency and immune dysregulation: cold-induced urticaria and/or granulomatous rash
VII. OTHER INFLAMMATORY SYNDROMES
A. LACC1-mediated monogenic Still disease

AID, Autoinflammatory disorder; CAPS, cryopyrin-associated periodic syndromes; CINCA, chronic infantile neurologic cutaneous and articular syndrome; CNS, central nervous system; STING, stimulator of interferon genes.
From Shwin KW, Lee CCR, Goldbach-Mansky. Dermatologic manifestations of monogenic autoinflammatory diseases. *Dermatol Clin.* 2017;35:21–38, Box 1, p. 24–25.

Antibody levels wane by 6 months old, generally resulting in clearance of the rash. Congenital heart block occurs in 30% of affected infants, but only 10% of affected infants have both skin and cardiac abnormalities. Noncardiac extracutaneous manifestations, such as anemia, thrombocytopenia, and cholestatic liver disease, are less common. Neonatal LE is often misdiagnosed as infantile eczema, seborrheic dermatitis, or tinea corporis. Skin lesions are typically managed conservatively, given the transient nature of neonatal LE, and strict sun avoidance and protection are important. If necessary, low- to mid-potency topical corticosteroids may be used. Systemic agents should be avoided. Maternal ANA testing is indicated.

Discoid Lupus Erythematosus

Discoid LE (DLE) is uncommon in early childhood and manifests in late adolescence. The signature skin findings in DLE are chronic, erythematous, scaly, atrophic plaques (Fig. 686.4) on sun-exposed skin that frequently heal with scarring and dyspigmentation. Extracutaneous features may include involvement of the nasal and oral mucosa, eyes, and nails. The differential diagnosis includes other photodermatoses, such as polymorphous light eruption, juvenile springtime eruption, and juvenile dermatomyositis (JDM). There is a distinct overlap between SLE and DLE, with common histopathologic features and photoexacerbation; most patients with DLE have normal laboratory results and do not progress to systemic disease.

First-line treatment of DLE consists of low- to mid-potency topical corticosteroids. Other topical options include calcineurin inhibitors and retinoids. Intralesional corticosteroid injection is also effective for severe localized lesions. Oral hydroxychloroquine is used first-line for severe skin disease or as a second-line agent when lesions are not controlled with topical or local agents. Strict ultraviolet light avoidance is important.

Juvenile Dermatomyositis

Characteristic skin findings are often the presenting sign of JDM (see Chapter 200). An ill-defined, erythematous to violaceous, scaly,

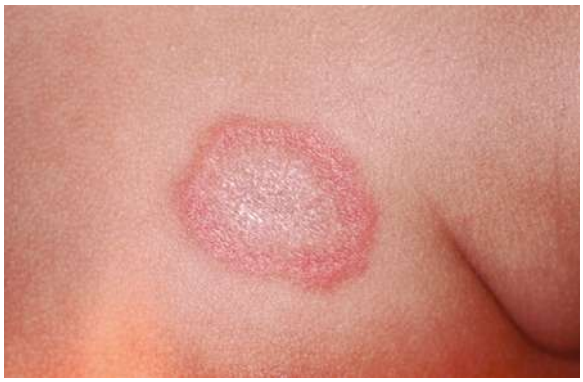

Fig. 686.3 Annular plaque in neonatal lupus erythematosus.

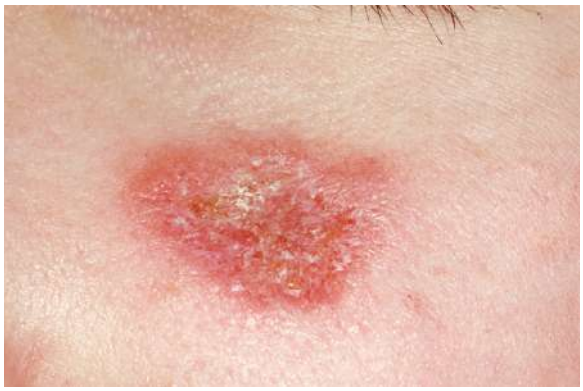

Fig. 686.4 Erythematous scaly plaque of discoid lupus erythematosus.

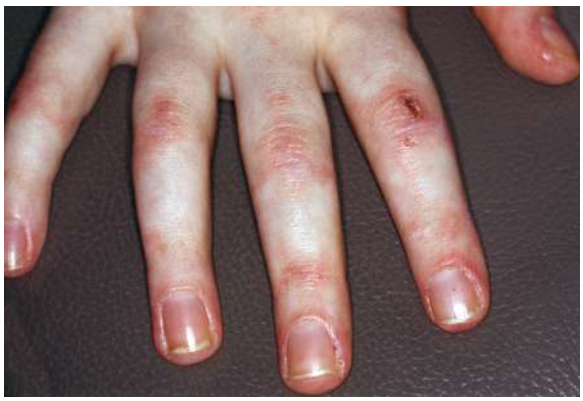

Fig. 686.5 Gottron papules in juvenile dermatomyositis.

minimally pruritic eruption occurs in photodistributed areas such as the face, upper trunk, and extensor extremities. Circumscribed periocular involvement of this **heliotrope** rash involving the eyelids may take the appearance of "raccoon eyes," particularly in young children. Distinctive erythematous, scaly papules overlying the knuckles and other joints **(Gottron papules)** are helpful in suggesting the diagnosis in the absence of associated muscle weakness (Fig. 686.5). Other cutaneous features include nail fold and gingival margin telangiectasia, palmar hyperkeratosis ("mechanic's hands"), ulceration resulting from vasculopathy or underlying calcinosis, lipodystrophy, and a poikilodermatous (dyspigmentation and telangiectasia) eruption over the shoulder girdle ("shawl sign"). Cutaneous features may precede the systemic illness, which is primarily characterized by muscle weakness and pain. The differential diagnosis includes atopic dermatitis, other connective tissue diseases, lichen planus, medication reactions, and infectious exanthems. Pathology of lesional skin demonstrates epidermal atrophy and vacuolar degeneration at the dermal-epidermal junction, often similar to LE. JDM is distinct from adult dermatomyositis in both presentation and prognosis. Pediatric patients have more difficulty with gastrointestinal (GI) vasculopathy and cutaneous calcifications, and JDM is not a paraneoplastic phenomenon as in adults. A rare clinical variant known as **amyopathic dermatomyositis** occurs when only skin, and not muscle, is involved.

Skin lesions benefit from systemic immunosuppressive therapy, as discussed in detail in Chapter 200. Adjunctive treatment options for skin disease include topical corticosteroids and calcineurin inhibitors. The cutaneous calcinosis of JDM is difficult to manage, with a variety of agents showing limited benefit, and no treatment consensus exists. Strict photoprotection and sunlight avoidance are vital to prevent cutaneous exacerbations.

Systemic Sclerosis

Systemic sclerosis is characterized by diffuse skin hardening and thickening, along with systemic features. It frequently manifests as acral (sclerodactyly, ulceration, nail fold telangiectasia, or Raynaud phenomenon) and facial changes (pinched nose, furrowed perioral skin, or "scleroderma facies") (see Chapter 201). Overlap syndromes such as **mixed connective tissue disease** may include some physical and laboratory features of scleroderma.

Morphea

Morphea, also called *localized scleroderma* (see Chapter 201), is another autoimmune connective tissue disease characterized by skin hardening and thickening. The lesions of morphea are generally more localized, and it is a distinct disorder from systemic sclerosis. There are five subtypes of morphea, including circumscribed (plaque), linear, generalized, pansclerotic, and mixed. Though morphea is not characterized by the degree of systemic involvement that systemic sclerosis has, it can have extracutaneous manifestations. Neurologic findings such as seizures, migraine headaches, focal neurologic deficits, and asymptomatic MRI abnormalities are seen in some patients, predominately those with linear morphea of the head and neck. Musculoskeletal complications can include joint contractures, limb length and girth discrepancies, arthritis, and arthralgias, and these are most common in children with linear morphea of a limb.

VASCULITIDES

The vasculitides (see Chapter 210) encompass a broad group of disorders having considerable overlap with connective tissue diseases. Immune-mediated inflammation of blood vessels of varying size may be caused by an underlying inflammatory state, infection, medication, or malignancy. Common clinical features include **palpable nonthrombocytopenic purpuric** skin lesions, arthritis, fever, myalgia, fatigue, and weight loss as well as an elevated erythrocyte sedimentation rate. Extracutaneous organs that may be involved include the joints, lungs, kidneys, and central nervous system.

Henoch-Schönlein Purpura (Immunoglobulin A Vasculitis)

Henoch-Schönlein purpura (see Chapter 210.1) is a vasculitis that manifests in school-age children as palpable purpuric lesions in gravity-dependent areas, predominantly the buttocks and lower extremities (Fig. 686.6). **Infantile hemorrhagic edema (IHE**; also called *acute hemorrhagic edema of infancy*) shares some clinical features with Henoch-Schönlein purpura but appears in infants and toddlers. IHE is characterized by the sudden onset of circumscribed edema with purpuric papules and plaques on the trunk and extremities but, unlike Henoch-Schönlein purpura, commonly affects the face and lacks other organ involvement. Henoch-Schönlein purpura must also be differentiated from infectious causes of purpuric skin lesions, such as meningococcemia, Rocky Mountain spotted fever, and purpuric viral exanthems such as those caused by enteroviruses, as well as from juvenile rheumatoid arthritis and other vasculitides. Diagnosis is

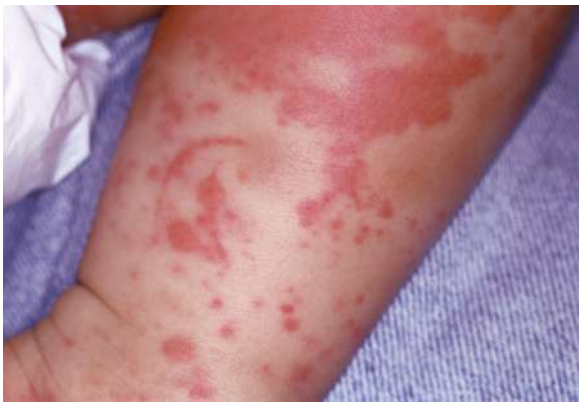

Fig. 686.6 Purpura of the lower leg in IgA vasculitis (Henoch-Schönlein purpura).

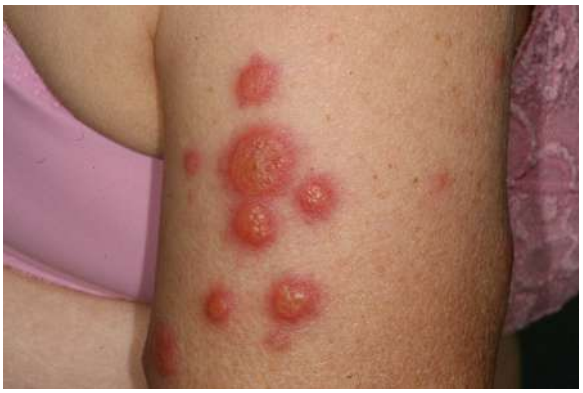

Fig. 686.7 Clinical picture of idiopathic Sweet syndrome. *(From Prat L, Bouaziz JD, Wallach D, et al. Neutrophilic dermatoses as systemic diseases. Clin Dermatol. 2014;32:376–388, Fig. 1.)*

confirmed by histologic confirmation of a small vessel vasculitis with the immunofluorescence finding of IgA in blood vessel walls. Skin lesions are generally managed conservatively and self-resolve in 3–4 weeks. Systemic treatment is discussed in detail in Chapter 210.1.

Kawasaki Disease

Kawasaki disease (see Chapter 208) is a common vasculitis usually seen in children younger than age 5 years. The skin eruption of Kawasaki disease is polymorphic, manifesting variously as maculopapular or morbilliform eruptions, urticaria, targetoid lesions, or psoriasiform lesions on the trunk and extremities. Early involvement with erythema and peeling in the perineum/inguinal region may be an initial clue to the diagnosis. Acral edema and desquamation are also prominent features but typically occur later. Classic mucocutaneous features include erythematous cracked lips, nonpurulent conjunctivitis with sparing of the limbus, and lingual plaques ("white strawberry tongue") that shed to produce denuded, erythematous patches with prominent papilla ("strawberry tongue"). Extracutaneous features include high fever, cervical lymphadenopathy, arthritis, and occasionally cardiac or GI disease. First-line treatment is with aspirin and intravenous immunoglobulin, as discussed in Chapter 208. **Multisystem inflammatory syndrome in children (MIS-C)** (Chapter 311) may resemble Kawasaki disease; cutaneous manifestations are noted in Table 686.3.

Behçet Disease

Behçet disease (see Chapter 202) is a multisystem disease that includes oral and genital ulceration and ocular disease (uveitis, relapsing iridocyclitis) in older children and adults. Recurrent aphthous stomatitis is present in almost all patients and is commonly the presenting symptom. Genital ulcerations may resemble aphthae; can occur on the penis, scrotum, or vulva; and may be particularly painful in females. Perianal ulceration is more common in children than in adults. Additional skin findings may include folliculitis, purpuric lesions, erythema nodosum, and pustule formation after venipuncture or skin trauma **(pathergy)**. Differential diagnosis of oral lesions includes recurrent aphthous stomatitis, herpes simplex, and rare oculocutaneous syndromes (e.g., MAGIC [mouth and genital ulcers with inflamed cartilage] syndrome). Skin biopsy demonstrates nongranulomatous vasculitis in all vessel sizes. Oral lesions may respond to swish and spit/swallow preparations variably, including corticosteroids, antihistamines, antibiotics, and analgesics. Skin lesions are managed with topical corticosteroids, topical anesthetics such as sucralfate, and systemic agents as outlined in Chapter 202.

GASTROINTESTINAL DISEASES

Inflammatory Bowel Disease

Inflammatory bowel disease includes ulcerative colitis (see Chapter 382.1) and Crohn disease (see Chapter 382.2). Skin lesions of inflammatory bowel disease are classified as specific or reactive. Specific cutaneous manifestations have the same histologic features and pathologic mechanism as the underlying inflammatory bowel disease lesions and include aphthous ulcers, granulomatous cheilitis, perianal fistulas and fissures, and metastatic Crohn disease (discussed later). Reactive cutaneous manifestations occur secondary to immune-mediated antigen cross reactivity between gut and skin components; examples include erythema nodosum and pyoderma gangrenosum.

Up to 30% of patients with **ulcerative colitis** present with cutaneous manifestations. Aphthous ulcers are common and may worsen with gastrointestinal exacerbations. Erythema nodosum, occurring in up to 10% of patients, manifests as warm, erythematous nodules, often on the distal lower extremities. Pyoderma gangrenosum is a focal, ulcerative process that has distinctive, inflamed, undermined borders and a purulent, boggy center. Thrombophlebitis also occurs at an increased rate in patients with ulcerative colitis.

Crohn disease classically manifests as perianal fissures and skin tags, abscesses, sinuses, and fistulas; these may be presenting signs. Enlargement of the lips and a cobblestone appearance of oral mucosa may also be present, known as *orofacial granulomatosis* or *cheilitis granulomatosa.* As in ulcerative colitis, aphthae, erythema nodosum, and pyoderma gangrenosum occur with increased frequency and may improve with treatment of the underlying disease. Noncaseating granulomatous inflammation is seen on routine histopathology, and when found in skin not contiguous with the intestinal tract, is labeled **metastatic Crohn disease**. Metastatic lesions may appear as solitary or multiple localized plaques or nodules and may be located on perianal, perioral, or other cutaneous surfaces, including scars and ileostomy sites. In most cases of inflammatory bowel disease–associated skin disease, treatment of the underlying condition improves the cutaneous sequelae.

Rarely, these associated skin findings may be seen without the classic GI manifestations, warranting continued GI surveillance for subsequent disease development. Isolated cutaneous involvement is treated similarly with systemic steroid-sparing and biologic agents with or without topical or intralesional corticosteroids. Azathioprine, a common treatment, causes increased risk for nonmelanoma skin cancers.

CUTANEOUS MANIFESTATIONS OF MALIGNANCY

Skin disease associated with malignancy has a wide variety of presentations, including both metastatic lesions and nonmalignant paraneoplastic conditions. Cutaneous metastases manifest as firm nodules and occur at any cutaneous site. Paraneoplastic reaction patterns are often distinctive and can aid in the diagnosis of the underlying malignancy. Some genetic syndromes have an increased malignancy risk that may be suggested initially by cutaneous signs. Other cutaneous findings that may signal an underlying malignancy include pruritus, ichthyosis, acanthosis nigricans, urticaria, pemphigus, and erythroderma.

Sweet Syndrome

Also known as **acute febrile neutrophilic dermatosis**, Sweet syndrome (see Chapter 213) occurs in several forms, including classical (usually idiopathic or infection-related, Fig. 686.7), malignancy-associated,

immunodeficiency-related, autoinflammatory (recurrent fever) syndromes, and drug-induced. Pathogenesis for all four forms remains unclear; however, new data are emerging implicating a potential interleukin (IL)-1–mediated pathway. Malignancy-associated Sweet syndrome is most commonly associated with hematologic malignancies, especially **acute myelogenous leukemia**. It manifests abruptly before, during, or after the malignancy course and is characterized by tender, erythematous, edematous plaques or nodules that may be pustular or targetoid, often accompanied by fever, anemia, and leukocytosis. Oral ulcers are more common in malignancy-associated Sweet syndrome than in other forms of the disease, and extracutaneous manifestations involving various organ systems may also occur. Diagnosis is confirmed by the presence of a dense neutrophilic infiltrate without evidence of vasculitis. The differential diagnosis includes other neutrophilic dermatoses such as pyoderma gangrenosum as well as cellulitis, erythema multiforme, Behçet disease, and erythema nodosum. First-line treatment for both malignancy-associated and nonmalignancy-associated Sweet syndrome is oral glucocorticoids (prednisone 1-2 mg/kg/day for 2-4 weeks) in combination with high-potency topical or intralesional corticosteroids. Systemic steroid-sparing agents include colchicine and dapsone.

Cutaneous manifestations of other autoinflammatory diseases are noted in Table 686.4.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH, see Chapter 556.1) is a neoplastic disorder characterized by proliferation of myeloid dendritic cells. Once thought to be Langerhans cells, which are skin-resident dendritic cells, the cells of LCH are now understood to represent a distinct cell type. LCH can be a single-system or multisystem disease, with the neoplastic infiltrate in organs such as the skin, bone, central nervous system, lung, hematopoietic system, liver, and spleen. When present on the skin, the lesions of LCH can be crusted erosions, scaly papules, or purpura. There is a predilection for the scalp, palms, soles, and intertriginous areas such as axillae and groin. Prognosis and treatment are variable depending on the organ systems involved.

Necrolytic Migratory Erythema (Glucagonoma Syndrome)

Necrolytic migratory erythema is a distinctive migratory erythema that often signals an underlying neoplasm, usually an α-cell pancreatic tumor. Polycyclic, weeping, erythematous patches and plaques on the face, extremities, and groin occur in association with glossitis and cheilitis. The lesions are painful or pruritic, enlarge and coalesce over time, and may develop central clearing with vesicles, crusts, and scales peripherally. Skin biopsy reveals superficial necrolysis with perivascular infiltrate. Elevated glucagon levels, hyperglycemia, and hypoaminoacidemia confirm the diagnosis, and tumor resection leads to resolution of the rash. Other treatments for necrolytic migratory erythema include somatostatin analogs (octreotide) and nutritional support; however, these measures do not affect the underlying tumor burden.

ERYTHROMELALGIA

This disorder may be primary (caused by pathogenic genetic variants in *SCN9A*) or secondary (myeloproliferative disorders, paraneoplastic, autoimmune) and is characterized by the triad of recurrent extremity pain, warmth, and redness. Warmth, exercise, sitting, or wearing shoes or gloves may initiate the episode. Cooling and elevation may relieve symptoms (see Chapter 211.5).

CUTANEOUS REACTIONS IN THE SETTING OF IMMUNOSUPPRESSION

Medication reactions, infectious etiologies, and graft-versus-host disease (GVHD) are included in the differential diagnosis in skin eruptions in immunosuppressed patients; cutaneous and histologic similarities can be confounding.

Medication Reactions

The majority of medication reactions are mild morbilliform or exanthematous eruptions of little clinical consequence. Identifying the suspect medication may be difficult owing to the many medications used in immunosuppressed patients. Features that may help identify suspect medications include rash onset relative to exposure, character of distribution and spread, associated symptoms, and laboratory data. Medication eruptions usually begin on the trunk **7-10 days after exposure**; they spread peripherally and are associated with pruritus and, less commonly, with fever, arthralgia, and lymphadenopathy. Eosinophilia may support a diagnosis of drug eruption but may be absent in the setting of bone marrow suppression. Penicillins, sulfa drugs, cephalosporins, nonsteroidal antiinflammatory drugs (NSAIDs), anticonvulsants, and aminoglycosides are common offenders. Medication eruptions may resolve despite continued use of the offending agent, or they may progress to more severe involvement. A careful drug history, elimination of all nonessential, suspect medications or change to medications of dissimilar class, and treatment of pruritus with emollients, topical steroids, antihistamines, and antipruritics are indicated. Skin biopsies are rarely useful in distinguishing medication eruptions from viral exanthems, although GVHD, if sufficiently advanced, may have signature histopathologic findings.

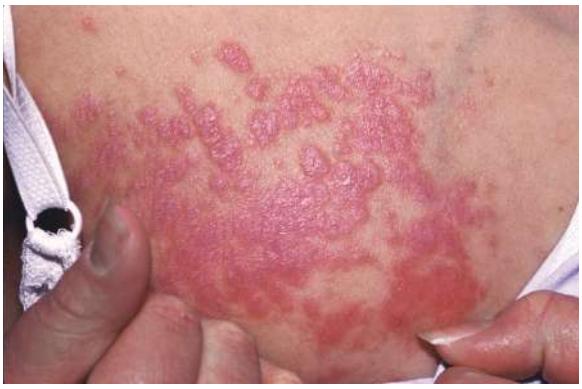

Fig. 686.8 Lichenoid eruption in chronic graft-versus-host disease.

Graft-Versus-Host Disease

GVHD (see Chapter 179) may have florid cutaneous expression in addition to characteristic extracutaneous features such as fever, mucositis, diarrhea, and hepatitis. It may be either acute or chronic. **Acute GVHD** occurs in 20–70% of hematopoietic stem cell transplants, depending on histocompatibility differences. It may be mistaken for a medication reaction or infectious exanthem because of the nonspecific erythematous maculopapular (morbilliform) eruption that often starts focally and then generalizes. Features that suggest acute GVHD include timing of eruption (typically 1-3 weeks after transplantation, at the time of hematopoietic reconstitution); initial involvement of the head and neck including the ears; and subsequent spread to the trunk, extremities, palms, and soles. In severe cases of acute GVHD, blistering, necrolysis, and erythroderma occur. **Chronic GVHD** occurs in approximately 65% of long-term transplant survivors, who may or may not have experienced prior acute GVHD. Cutaneous manifestations of chronic GVHD are distinctive, with sclerotic, poikilodermic scaly plaques and lichen planus–like papules predominating on the trunk and distal extremities (Fig. 686.8). Sclerotic areas are prone to contracture and chronic wound development. Involvement of the hair, nails, and oral mucosa is also common in chronic GVHD. First-line treatment for GVHD includes systemic glucocorticoids and other immunosuppressants supplemented by mid- to high-potency topical corticosteroids. In mild disease, topical corticosteroids or topical calcineurin inhibitors alone may be effective. Second-line treatment approaches include phototherapy (narrow-band UVB or UVA1) and extracorporeal photopheresis. All patients with GVHD benefit from sunlight protection, emollient use, and topical or oral antipruritics.

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686.2 Multisystem Medication Reactions

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See also Chapter 193.

Most cutaneous reactions that result from the use of systemic medications are confined to the skin and resolve without sequelae after discontinuation of the offending agent (Table 686.5). More severe drug eruptions may be life-threatening, making rapid recognition vital (Table 686.6 and see Chapter 695). Genetics and, particularly, ethnicity appear to play a major role in determination of the occurrence of multisystem medication reactions, particularly to anticonvulsants.

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) is also called *drug hypersensitivity syndrome* or *anticonvulsant hypersensitivity syndrome.* It is classically seen **2-6 weeks after initial exposure** to an anticonvulsant (carbamazepine, phenobarbital, phenytoin, lamotrigine) or other drugs (allopurinol, minocycline, sulfonamides [dapsone, sulfasalazine], other antibiotics) and often manifests as the triad of **fever**, **rash**, and **hepatitis** (Fig. 686.9). The skin rash is initially located on the head, upper trunk, and arms. A diffuse exanthem of pruritic, morbilliform papules

Table 686.5 Drug Eruptions in Pediatric Patients

ERUPTION	KEY DRUGS	LESIONAL PATTERN	MUCOSAL CHANGES
Urticaria	Penicillins, cephalosporins, sulfonamides, minocycline, aspirin/NSAIDs, antiepileptics, monoclonal antibodies, radiocontrast media	Pruritic erythematous wheals (Fig. 686.12)	None
Angioedema	Aspirin/NSAIDs, ACE inhibitors	Swelling of subcutaneous and deep dermal tissues	May be present
Serum sickness–like reaction	Cephalosporins, penicillins, minocycline, sulfonamides, macrolides, rifampin, ciprofloxacin, griseofulvin, itraconazole, bupropion, fluoxetine, rituximab, H1N1 vaccine	Urticarial or erythema multiforme–like (see Fig. 686.11)	None
Exanthematous	Penicillins, sulfonamides, cephalosporins, antiepileptics	Erythematous macules and/or papules	None
Drug hypersensitivity syndrome	Sulfonamides, phenytoin, phenobarbital, carbamazepine, lamotrigine, amoxicillin, allopurinol, sulfonamides, dapsone, minocycline, aspirin, vancomycin, azithromycin, abacavir, nevirapine, Chinese medicine	Edema (especially periorbital); erythematous macules and/or papules; sometimes vesicles or bullae (see Fig. 686.10)	May be present
Lichenoid	Captopril, enalapril, labetalol, nifedipine, propranolol, gold salts, hydrochlorothiazide, furosemide, spironolactone, hydroxychloroquine, ketoconazole, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs, hydroxyurea, imatinib, dapsone, sulfasalazine, allopurinol, iodides and radiocontrast media, IFN-γ, omeprazole, TNF inhibitors, sildenafil, leflunomide, human growth hormone	Discrete flat-topped, reddish-purple papules and plaques	May be present
Fixed drug	Sulfonamides, ibuprofen, acetaminophen, salicylates, tetracyclines, pseudoephedrine, loratadine, teicoplanin, metronidazole, macrolides, barbiturates, lamotrigine, potassium iodide, quinine, phenolphthalein, foods and food flavorings (especially tartrazine)	Solitary to few erythematous, hyperpigmented plaques (see Fig. 686.13)	Unusual
Pustular (AGEP)	β-Lactam antibiotics, cephalosporins, macrolides, clindamycin, terbinafine, paroxetine, hydroxychloroquine, contrast agents	Generalized small pustules and papules (see Fig. 686.14)	None
Acneiform	Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid, methotrexate	Follicular-based inflammatory papules and pustules predominate	None
Pseudoporphyria	NSAIDs, COX-2 inhibitors, tetracyclines, furosemide	Photodistributed blistering and skin fragility	None
Vasculitis	Penicillins, NSAIDs, sulfonamides, cephalosporins	Purpuric papules, especially on the lower extremities; urticaria, hemorrhagic bullae, digital necrosis, pustules, ulcers	Rarely
Stevens-Johnson/ toxic epidermal necrolysis	Sulfonamides, antiepileptics (especially phenytoin, carbamazepine, and lamotrigine), NSAIDs, acetaminophen, allopurinol, dapsone, barbiturates	Target lesions, bullae, epidermal necrosis with detachment (see Figs. 695.3 and 695.4)	Present
Drug-induced lupus	Minocycline, procainamide, hydralazine, isoniazid, penicillamine	Urticarial, vasculitic, erythematous	Rare

ACE, Angiotensin converting enzyme; AGEP, acute generalized exanthematous pustulosis; COX-2, cyclooxygenase-2; IFN, interferon; NSAID, Nonsteroidal antiinflammatory drug; TNF, tumor necrosis factor.

Adapted from Paller AS, Mancini AJ, eds. *Hurwitz Clinical Pediatric Dermatology*, 6th ed. St Louis: Elsevier; 2022: p. 541.

Table 686.6 Main Clinical and Histologic Characteristics of Severe Cutaneous Adverse Reactions

DRUG TO SCAR INTERVAL	GENERAL SYMPTOMS	SKIN FEATURES	LABORATORY VALUES	MAIN ORGANS INVOLVED	HISTOLOGIC FEATURES
SJS and TEN	4-28 days	Fever ≥38°C, Influenza- like syndrome, respiratory tract symptoms	Blisters, large skin detachment, confluent erythema, atypical target lesions, purpura, Nikolsky sign; skin detachment Stevens-Johnson syndrome <10%, toxic epidermal necrolysis ≥30%, SJS-TEN 10–30%; two or more mucous membranes involved	Lymphopenia, transitory neutropenia, mild cytolysis, renal impairment	Full-thickness epidermal necrosis, focal adnexal necrosis, necrotic keratinocytes, mild mononuclear cell dermal infiltrate, negative direct immunofluorescence test
DRESS syndrome	2-6 wk	Fever ≥38°C, Influenza- like syndrome	Maculopapular rash Erythroderma, facial or extremity edema, pustules, focal monopolar mucous membrane involvement	Eosinophilia >700 cells/μL Atypical lymphocytes, elevated transaminase concentration, impaired renal function, herpesvirus reactivation (HHV-6, HHV-7, EBV, CMV), parvovirus B19 reactivation	Lichenoid infiltrate or Eczematous pattern (spongiosis, edema), focal necrotic keratinocytes, mononuclear infiltrate, focal eosinophil and neutrophil infiltrates, mild vasculitis
AGEP	1-11 days	Fever ≥38°C	Intertriginous erythema, edema, widespread nonfollicular sterile pustules, postpustular pinpoint desquamation, Nikolsky sign, rare oral mucous membrane involvement	Hyperleukocytosis, neutrophils ≥7,000 cells/μL, mild eosinophilia	Subcorneal or intraepidermal spongiform or nonspongiform pustules with or without papillary edema, focal necrotic keratinocytes, neutrophilic, sometimes with eosinophils, mild vasculitis

*General symptoms can precede or occur at the same time as skin manifestations.
AGEP, Acute generalized exanthematous pustulosis; CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; HHV, human herpesvirus; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
From Duong TA, Valeyrie-Allanore L, Wolkenstein P, et al. Severe cutaneous adverse reactions to drug. *Lancet.* 2017;390: 1996–2011. Table 1.

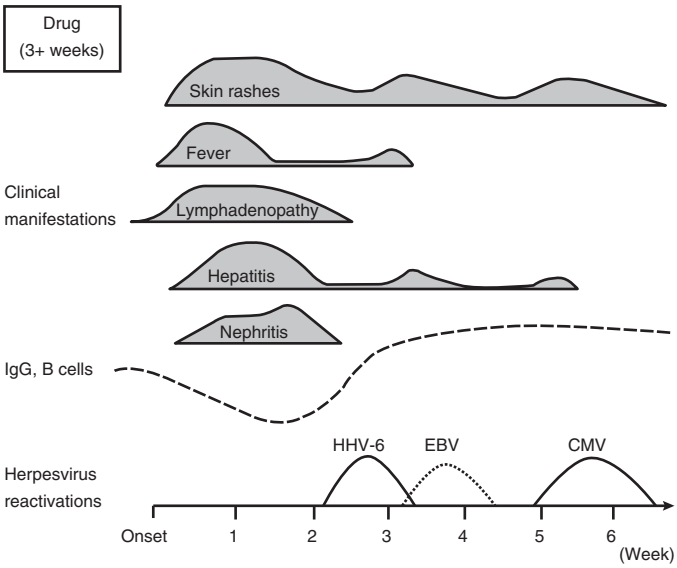

Fig. 686.9 Clinical symptoms and laboratory findings of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms. CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus. *(From Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. Med Clin N Am. 2010;94:743–759, Fig. 1, p. 745).*

are most common, though any morphology may be present (Fig. 686.10). Exfoliation early in the course, as seen in toxic epidermal necrolysis, is uncommon. If mucous membrane involvement occurs, it is usually mild. Prominent periocular or facial edema, cervical lymphadenopathy, pharyngitis, and malaise accompany this dramatic cutaneous eruption. *Eosinophilia (≥500/μL) and atypical lymphocytosis are common but not always present.* Hepatitis ranging from mild elevation of liver transaminase values to frank hepatic failure may also be accompanied by interstitial nephritis, pneumonitis, myocarditis, shock, and encephalitis; mortality rate from these complications approaches 10%. Late-onset thyroiditis and hypothyroidism may occur months later as a result of antimicrosomal antibodies directed against thyroid peroxidases involved in drug metabolism.

DRESS syndrome is caused by a T-cell response specific to the drug. Reactivation of herpesviruses, especially human herpesvirus 6, also contributes to DRESS syndrome via an unknown pathogenic mechanism. Genetic predisposition with particular HLA allele types has also been implicated with specific ethnic groups and drugs, such as HLA-A*3101 with carbamazepine. The differential diagnosis includes Stevens-Johnson syndrome, viral exanthem, macrophage activation, hemophagocytic syndromes, and GVHD in the appropriate clinical setting. DRESS syndrome is often distinguished from other medication reactions by its later onset after drug exposure and more persistent course.

Withdrawal of the medication is the primary therapeutic intervention. Lymphocyte transformation tests and patch testing may be

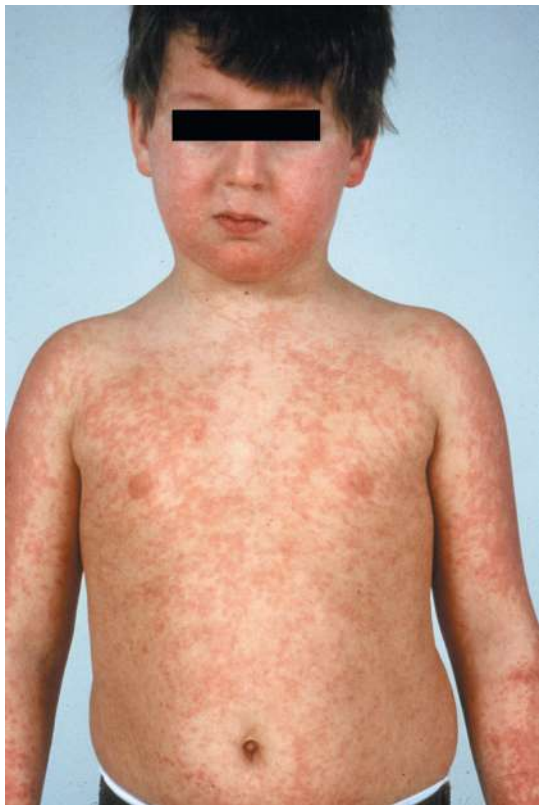

Fig. 686.10 A 9-yr-old with cerebral palsy and seizures treated with carbamazepine. Seventeen days after start of therapy he demonstrated fever, rash (exanthematous), lymphadenopathy, and nephritis, all part of a drug-induced hypersensitivity syndrome. *(From Schachner LA, Hansen RC, eds. Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 2003: p. 1269.)*

helpful for identifying the offending drug when multiple suspect agents are present, but drug discontinuation should not be delayed while awaiting results. Symptomatic treatment of pruritus and pain can be accomplished with emollients and mid- to high-potency topical corticosteroids (twice daily for 1-2 weeks). Systemic corticosteroid therapy is necessary in the setting of rapidly evolving or severe hepatic or renal involvement. Counseling about increased risk with similar medications and in family members is important. DRESS syndrome can have a relapsing course, both in the skin and other organ systems, well after the medication has been withdrawn and initial improvement achieved, necessitating close follow-up for several months.

SERUM SICKNESS–LIKE REACTION

Serum sickness–like reaction (SSLR) manifests as annular, urticarial, sharply marginated, coalescing plaques, often with a lavender hue to the center (Fig. 686.11). In addition, acral erythema/edema, arthritis/arthralgia, lymphadenopathy, and fever are often present. Unlike with true serum sickness (see Chapter 191), laboratory evidence of circulating immune complexes and multisystem involvement of vasculitis are typically absent. The differential diagnosis includes Kawasaki disease, connective tissue diseases, acute annular urticaria, and DRESS syndrome. SSLR is most commonly seen 10-14 days after exposure to various drugs (especially cephalosporins, penicillins, minocycline, and other antibiotics), as well as after certain infections and vaccinations. The cause of drug-related SSLR is unknown, but a toxic metabolite is suspected. In contrast to DRESS syndrome, SSLR typically occurs after repeated drug exposures.

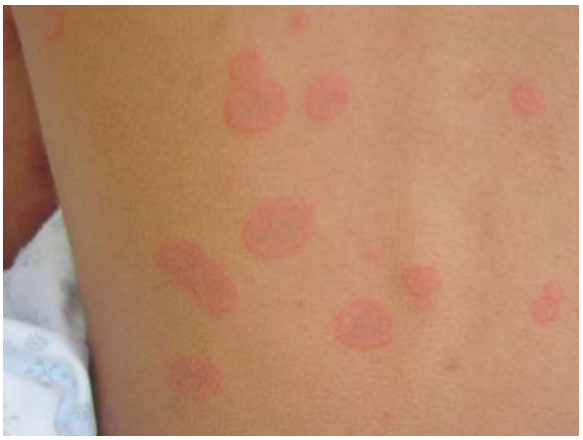

Fig. 686.11 Serum sickness–like reaction is composed of urticarial plaques with an erythematous border and violaceous centers.

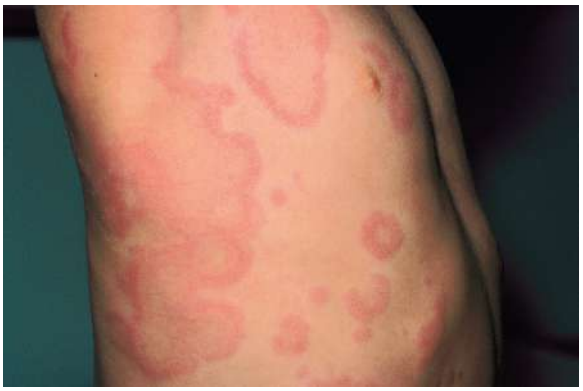

Fig. 686.12 Urticaria. Transient well-circumscribed, erythematous wheals occurred in this girl as a reaction to administration of cefixime. Note the edematous center and halo of erythema. Circling a lesion and noting whether it is clear 24 hours later facilitates diagnosis. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 5th ed. Philadelphia: Elsevier; 2016: Fig. 20-2, p. 469.)*

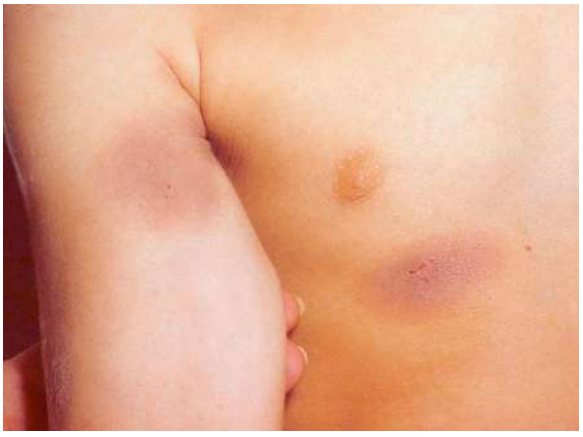

Fig. 686.13 Multiple fixed-drug eruption.

Medication withdrawal and symptomatic treatment with oral antihistamines and analgesics are recommended. Systemic glucocorticoids are indicated for severe joint involvement or extensive rashes.

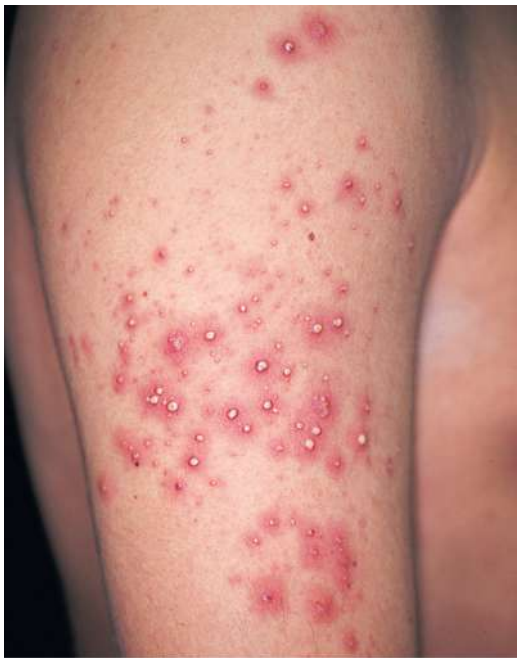

Fig. 686.14 Acute generalized exanthematous pustulosis is characterized by the acute onset of fever and generalized erythema with numerous small, discrete, sterile, nonfollicular pustules. Pustules may appear in a few days after the drug therapy is started. Pustules resolve in <15 days, followed by desquamation. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004: p. 490.)*

FIXED-DRUG ERUPTION

Fixed-drug eruption (FDE) occurs minutes to hours after exposure to a drug and is characterized by mild pruritus or burning of a well-circumscribed, dusty red, brown, gray or, if severe, violaceous patch appearing on the extremities, trunk, lips, or genitals (Fig. 686.13). There is usually one lesion that, on reexposure to the drug, appears in the same (fixed) location as the previous episode, often appearing more rapidly. On occasion, there may be two or more lesions. Stopping the offending agent is required; the FDE will then resolve within 10-14 days, often with residual hyperpigmentation. Offending medications include sulfonamides, tetracyclines, NSAIDs, and acetaminophen.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis is often drug-related (most commonly aminopenicillins, macrolides, sulfonamides), occurring **within hours to days after drug exposure**. It is characterized by many nonfollicular sterile pustules with underlying edema and erythema, typically beginning on the face and intertriginous regions (Fig. 686.14). Neutrophilia and fever are common, whereas eosinophilia is less common than in DRESS syndrome. The rash may burn or itch; mucous membrane involvement is rare and often mild. Internal organ involvement is not common and often is asymptomatic. A pustular smear is always indicated to rule out infection in the setting of leukocytosis, fever, and a pustular rash. Differential diagnosis includes generalized pustular psoriasis, bullous impetigo, IgA pemphigus, and subcorneal pustular dermatosis. Therapy consists of stopping the causative drug and offering symptomatic relief with moist dressings, emollients, and mid-potency topical corticosteroids (applied twice daily for 1-2 weeks).

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Chapter 687

Principles of Dermatologic Therapy

Stephen R. Humphrey

Competent skin care requires an appreciation of primary versus secondary lesions, a specific diagnosis, and knowledge of the natural course of the disease. If the diagnosis is uncertain, it is better to err on the side of less aggressive rather than more aggressive treatment.

In the use of topical medication, consideration of vehicle is as important as the specific therapeutic agent. Acute **weeping lesions** respond best to wet compresses, followed by lotions or creams. For **dry, thickened,** scaly skin, or for treatment of a contact allergic reaction possibly the consequence of a component of a topical medication, an ointment base is preferable, as it helps to occlude and moisten the affected area. Gels and solutions are most useful for the scalp and other hairy areas because of their faster absorption. The site of involvement is of considerable importance because the most desirable vehicle may not be cosmetically or functionally appropriate, such as an ointment on the face or hands. A patient's preference should also play a part in the choice of vehicle because compliance is poor if a medication is not acceptable to a patient. Ointments tend to sting less and are the least irritating. Cosmetically acceptable foam delivery systems have been developed, and the number of products and formulations available is increasing.

Most **lotions** are mixtures of water and oil that can be poured. After the water evaporates, the small amount of remaining oil covers the skin. Some shake lotions are a suspension of water and insoluble powder; as the water evaporates, cooling the skin, a thin film of powder covers the skin. **Creams** are emulsions of oil and water that are viscous and do not pour (more oil than in lotions). **Ointments** have oils and a small amount of water or no water at all; they feel greasy, lubricate dry skin, trap water, and aid in occlusion. Ointments without water usually require no preservatives because microorganisms require water to survive. Because of this, ointments often have the lowest number and concentration of ingredients, decreasing the risk of sensitizing the skin.

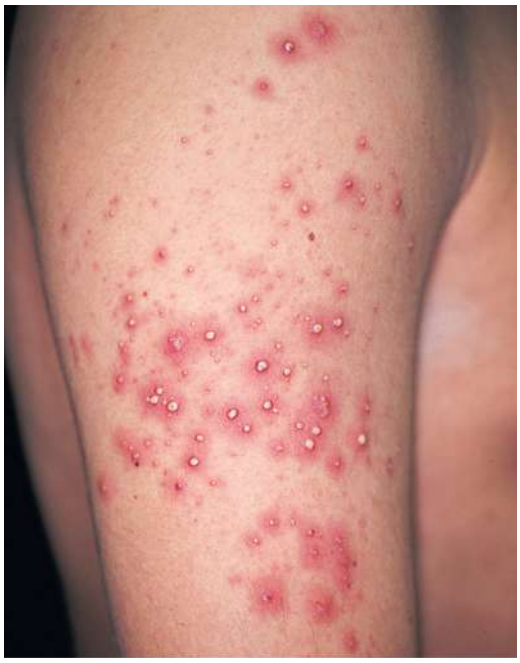
Therapy should be kept as simple as possible, and specific written instructions about the frequency and duration of application should be provided. Physicians should become familiar with one or two preparations in each category and should learn to use them appropriately. Prescribing nonspecific proprietary medications that may contain sensitizing agents should be avoided. Certain preparations, such as topical antihistamines and sensitizing anesthetics, are never indicated.

WET DRESSINGS

Wet dressings cool and dry the skin by evaporation and cleanse it by removing crusts and exudate, which would cause further irritation if permitted to remain. The dressings decrease pruritus, burning, and stinging sensations and are indicated for acutely inflamed moist or oozing dermatitis. Although various astringent and antiseptic substances may be added to the solution, cool or tepid tap water compresses are just as effective. Dressings of multiple layers of Kerlix, gauze, or soft cotton material may be saturated with water and remoistened as often as necessary. Compresses should be applied for 10-20 minutes at least every 4 hours and should usually be continued for 24-48 hours.

Alternatively, cotton pajamas can be soaked in water and then wrung as dry as possible. These are placed on the child and covered with dry pajamas, preferably sleeper pajamas with feet. The child should sleep in these overnight. This type of dressing can be used nightly for up to 1 week.

Wet dressings or wet wraps in conjunction with topical steroids may also be used in more severe cases of dermatitis (e.g., atopic dermatitis). In this method, a thin layer of the topical steroid is applied to the affected areas, which are then covered with warm, wet wraps



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for approximately 30 minutes to 1 hour 2-3 times daily. This method is especially effective in children with extensive and severe dermatitis.

BATH OILS, COLLOIDS, AND SOAPS

Bath oil has little benefit in the treatment of children. It offers little moisturizing effect but increases the risk of injury during a bath. Bath oil may lubricate the surface of the bathtub, causing an adult or child to fall when stepping into the tub. Tar bath solutions can be prescribed and may be helpful for psoriasis and atopic dermatitis. Colloids such as starch powder and colloidal oatmeal are soothing and antipruritic for some patients when added to the bathwater. Oilated colloidal oatmeal contains mineral oil and lanolin derivatives for lubrication if the skin is dry. These can also lubricate the bathtub surface. Ordinary bath soaps may be irritating and drying if patients have dry skin or dermatitis. Synthetic soaps are much less irritating. Fragrance-free soaps and cleansers are often better tolerated and less likely to irritate skin. Additionally, solid soaps tend to be less irritating, as they do not have as many preservatives as liquid soap might. When skin is acutely inflamed, avoidance of soap is advised.

LUBRICANTS

Lubricants, such as lotions, creams, and ointments, can be used as moisturizers for dry skin and as vehicles for topical agents such as corticosteroids and keratolytics. In general, ointments are the most effective emollients. Numerous commercial preparations are available. Some patients do not tolerate ointments, and some may be sensitized to a component of the lubricant; some preservatives in creams are also sensitizers. These preparations can be applied several times a day if necessary and tolerated. Maximal effect is achieved when they are applied to dry skin 2 or 3 times daily. Lotions containing menthol and camphor in an emollient vehicle can help control pruritus and dryness, but the use of moisturizers in addition to these products is best to decrease skin dryness.

SHAMPOOS

Special shampoos containing sulfur, salicylic acid, zinc, and selenium sulfide are useful for conditions in which there is scaling of the scalp, such as seborrheic dermatitis or psoriasis. Tar-containing shampoos are useful in these conditions. Most shampoos also contain surfactants and detergents. They should be used as frequently as necessary to control scaling. Patients should be instructed to leave the lathered shampoo in contact with the scalp for 5-10 minutes before thorough rinsing.

POWDERS

Powders are hygroscopic and serve as absorptive agents in areas of excessive moisture. When dry, powders decrease friction between two surfaces. They are most useful in the intertriginous areas and between the toes, where maceration and abrasion may result from friction on movement. Coarse powders may cake; therefore they should be of fine particle size and inert, unless medication has been incorporated in the formulation. The use of cornstarch-based powders in inflamed or broken skin may serve as a good growth environment for microorganisms and should be avoided.

PASTES

Pastes contain fine powder in ointment vehicles and are not often prescribed in current dermatologic therapy; in certain situations, however, they can be used effectively to protect vulnerable or damaged skin. A stiff zinc oxide paste is bland and inert and can be applied to the diaper area to prevent further irritation caused by diaper dermatitis. Zinc oxide paste should be applied in a thick layer, completely obscuring the skin, and is removed more easily with mineral oil than with soap and water.

KERATOLYTIC AGENTS

Urea-containing agents are hydrophilic; they hydrate the stratum corneum and make the skin more pliable. In addition, because urea dissolves hydrogen bonds and epidermal keratin, it is effective in treating scaling disorders. Concentrations of 10–40% are available in several commercial lotions and creams, which can be applied once or twice daily as tolerated. Salicylic acid is an effective keratolytic agent and can be incorporated into various vehicles in concentrations up to 6% to be applied 2 or 3 times daily. Salicylic acid preparations should not be used in treating small infants or on large surface areas or denuded skin; percutaneous absorption may result in salicylism. The α-hydroxy acids, particularly lactic acid and glycolic acid, are available in commercial preparations or can be incorporated in an ointment vehicle in concentrations up to 12%. Some creams contain both urea and lactic acid. The α-hydroxy acid preparations are useful for the treatment of keratinizing disorders and may be applied once or twice daily. Some patients complain of burning with the use of these agents; in such cases, the frequency of application should be decreased.

Table 687.1 Potency of Topical Glucocorticosteroids

CLASS 1—SUPER-POTENT
Betamethasone dipropionate, 0.05% gel, ointment
Clobetasol propionate cream, ointment, 0.05%
Halobetasol propionate cream, ointment, 0.05%
CLASS 2—POTENT
Betamethasone dipropionate cream 0.05%
Desoximetasone cream, ointment, gel 0.05% and 0.25%
Fluocinonide cream, ointment, gel, 0.05%
CLASS 3—UPPER MID-STRENGTH
Betamethasone dipropionate cream, 0.05%
Betamethasone valerate ointment, 0.1%
Fluticasone propionate ointment, 0.005%
Mometasone furoate ointment, 0.1%
Triamcinolone acetonide cream, 0.5%
CLASS 4—MID-STRENGTH
Desoximetasone cream, 0.05%
Fluocinolone acetonide ointment, 0.025%
Triamcinolone acetonide ointment, 0.1%
CLASS 5—LOWER MID-STRENGTH
Betamethasone valerate cream/lotion, 0.1%
Fluocinolone acetonide cream, 0.025%
Fluticasone propionate cream, 0.05%
Triamcinolone acetonide cream/lotion, 0.1%
CLASS 6—MILD STRENGTH
Desonide cream, 0.05%
CLASS 7—LEAST POTENT
Topicals with hydrocortisone, dexamethasone, flumethasone, methylprednisolone, and prednisolone

From Weston WL, Lane AT, Morelli JG. *Color Textbook of Pediatric Dermatology*, 4th ed. St. Louis: Mosby; 2007: p. 418.

TAR COMPOUNDS

Tars are obtained from bituminous coal, shale, petrolatum (coal tars), and wood. They are antipruritic and astringent and appear to promote normal keratinization. They may be useful for chronic eczema and psoriasis, and their efficacy may be increased if the affected area is exposed to UV light after the tar has been removed. Tars should not be used for acute inflammatory lesions. Tars are often messy and unacceptable because they may stain and they have an odor. They may be incorporated into shampoos, bath oils, lotions, and ointments. A useful preparation for pediatric patients is liquor carbonis detergens (LCD) 2–5% in a cream or ointment vehicle. Tar gel and tar in light body oil are relatively pleasant cosmetic preparations that cause minimal staining of skin and fabrics. Tars can also be incorporated into a vehicle with a topical corticosteroid. The frequency of application varies from 1-3 times daily, according to tolerance. Many children refuse to use tar preparations because of their odor and staining characteristics.

ANTIFUNGAL AGENTS

Antifungal agents are available as powders, lotions, creams, ointments, and solutions for the treatment of dermatophyte and yeast infections. Nystatin, naftifine, and amphotericin B are specific for *Candida albicans* and are ineffective in other fungal disorders. Tolnaftate is effective against dermatophytes but not against yeast. The spectrum for ciclopirox olamine includes the dermatophytes, *Malassezia furfur,* and *C. albicans.* The azoles clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, and sulconazole have a similar broad spectrum. Butenafine has a similar broad

spectrum and also has antiinflammatory properties. Terbinafine has greater activity against dermatophytes but poorer activity against yeasts than the azoles. The topical antifungal agents should be applied 1-2 times a day for most fungal infections. All have low sensitizing potential; additives such as preservatives and stabilizers in the vehicles may cause allergic contact dermatitis. Ointments containing 6% benzoic acid and 3% salicylic acid are potent keratolytic agents that have also been used for the treatment of dermatophyte infections. Irritant reactions are common.

TOPICAL ANTIBIOTICS

Topical antibiotics have been used for many years to treat local cutaneous infections, although their efficacy, with the exception of mupirocin, fusidic acid, and retapamulin, has been questioned. Ointments are the preferred vehicles (except in the treatment of acne vulgaris; see Chapter 710), and combinations with other topical agents such as corticosteroids are, in general, inadvisable. Whenever possible, the etiologic agent should be identified and treated specifically. Antibiotics in wide use as systemic preparations should be avoided because of the risk of bacterial resistance. The sensitizing potential of certain topical antibiotics, such as neomycin and nitrofurazone, should be kept in mind and avoided when possible. Mupirocin, fusidic acid, and retapamulin are the most effective topical agents currently available and are as effective as oral erythromycin in treatment of mild to moderate impetigo. Polysporin and bacitracin are not as effective.

TOPICAL CORTICOSTEROIDS

Topical corticosteroids are potent antiinflammatory agents and effective antipruritic agents. Successful therapeutic results are achieved in a wide variety of skin conditions. Corticosteroids can be divided into seven different categories on the basis of strength (Table 687.1), but for practical purposes, four categories can be used: low, moderate, high, and super. Low-potency preparations include hydrocortisone, desonide, and hydrocortisone butyrate. Medium-potency compounds include betamethasone, flurandrenolide, fluocinolone, mometasone furoate, and triamcinolone. High-potency topical steroids include fluocinonide and halcinonide. Betamethasone dipropionate, halobetasol, and clobetasol propionate are superpotent preparations and should be prescribed with care. Some of these compounds are formulated in several strengths according to clinical efficacy and degree of vasoconstriction. Physicians using topical steroids should become familiar with preparations within each class.

All corticosteroids can be obtained in various vehicles, including creams, ointments, solutions, gels, and aerosols. Some are available in a foam vehicle. Absorption is enhanced by an ointment or gel vehicle, but the vehicle should be selected on the basis of the type of disorder and the site of involvement. Frequency of application should be determined by the potency of the preparation, the location on the body, and the severity of the eruption. Applying a thin film 2 times daily usually suffices. Adverse local effects include cutaneous atrophy, striae, telangiectasia, acneiform eruptions, purpura, hypopigmentation, and increased hair growth. Systemic adverse effects of high-potency and superpotent topical steroids occur with long-term use and include poor growth, cataracts, and suppression of adrenal function.

The relative skin thickness should be considered in regard to the selection of class of steroid (see Table 687.1). Thin skin such as the eyelids, face, groin, and genitalia will absorb a substantial amount of medication compared to the thickest skin on the palms and soles. One adult fingertip's worth of medication is enough to cover an area the size of an adult palm and is approximately half a gram of medication. Knowing the area being treated and which medication class to prescribe can decrease the potential for side effects.

In selected circumstances, corticosteroids may be administered by intralesional injection (acne cysts, keloids, psoriatic plaques, alopecia areata, persistent insect bite reactions). Only experienced physicians should use this method of administration.

TOPICAL NONSTEROIDAL ANTIINFLAMMATORY AGENTS

Calcineurin-inhibiting antiinflammatory agents that inhibit T-cell activation may be used instead of topical steroids for the treatment of atopic dermatitis and other inflammatory conditions. These agents are pimecrolimus and tacrolimus. They do not have the adverse local effects seen with topical steroids. Stinging with application is the most common complaint and may be lessened by mixing the medication with an ointment such as petrolatum jelly for the initial applications. These agents are only as strong as medium-potency topical steroids. In 2006, the FDA issued a boxed warning for topical calcineurin inhibitors because data from animal experiments and case reports suggested potential for an increased risk of lymphoma with systemic use. No clear link between topical calcineurin inhibitor use and lymphoma risk has been established despite multiple epidemiologic and clinical studies. Crisaborole, a novel PDE4 inhibitor, is now approved for mild to moderate atopic dermatitis, and is another option for nonsteroidal treatments.

SUNSCREENS

Sunscreens are of two general types: (1) those, such as zinc oxide and titanium dioxide, that absorb all wavelengths of the UV and visible spectrums and (2) a heterogeneous group of chemicals that selectively absorb energy of various wavelengths within the UV spectrum. In addition to the spectrum of light that is blocked, other factors to be considered include cosmetic acceptance, sensitizing potential, retention on skin while swimming or sweating, required frequency of application, and cost. Sunscreen ingredients include para-aminobenzoic acid (PABA) with ethanol, PABA esters, cinnamates, and benzophenone. These block transmission of the majority of solar UVB and some UVA wavelengths. Avobenzone and ecamsule are more effective in blocking UVA. Antioxidants may also be found in some sunscreens. Lip protectants that absorb in the UVB range are also available. Some chemical sunscreens (oxybenzone, octocrylene, and octinoxate) have been implicated in harming coral reefs and are banned in certain areas of the world.

Sunscreens are designated by sun protection factor (SPF). The SPF is defined as the amount of time to develop a mild sunburn with the sunscreen compared with the amount of time without the sunscreen. A minimum SPF factor of 30 should be recommended most often. The higher the SPF, the better the protection is against UVB rays. Sunscreens do not include any measurement of the efficacy in blocking UVA. The efficacy of these agents depends on careful attention to instructions for use. Chemical sunscreens should be applied at least 30 minutes before sun exposure to permit penetration into the epidermis, again on arrival at the destination, and every subsequent hour when exposed to direct sunlight. Most patients with photosensitivity eruptions require protection by agents that absorb both UVB and UVA wavelengths (see Chapter 697).

Although sunscreens do confer photoprotection and may decrease the development of nevi, protection is incomplete against all harmful UV light. Midday (10 AM to 4 PM) sun avoidance is the primary method of photoprotection. Clothing, hats, and staying in the shade offer additional sun protection.

LASER THERAPY

The vascular-specific pulsed dye laser therapy is used mainly for the treatment of capillary malformations (port-wine stains). Spider telangiectasia, small facial pyogenic granulomas, superficial and ulcerated hemangioma, and warts may also be treated. Vascular-specific pulsed dye lasers produce light that is readily absorbed by oxyhemoglobin, producing selective photothermolysis of vascular lesions.

Ultraviolet Phototherapy

Phototherapy can be a useful treatment for many cutaneous inflammatory disorders, including atopic dermatitis, psoriasis, pityriasis lichenoides, vitiligo, and a few others. Some benefits of phototherapy include the fact that it is well tolerated, may treat a large area of the body, and may enable a patient to avoid systemic immunosuppressive agents. There are two traditional modalities of treatment: psoralen (a photosensitizer) + UVA (PUVA) or narrow-band UVB phototherapy (NBUVB). NBUVB phototherapy is most often used, typically dosed between 1 and 3 times per week, depending on the condition. There is an increased risk of skin cancers with long-term use of PUVA, but there does not seem to be an increased risk for NBUVB. Risks include burns, though this is quite rare if performed properly.

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Chapter 688

Dermatologic Diseases of the Neonate

Sarah B. Younger and Kari L. Martin

Minor evanescent lesions of newborn infants, particularly when florid, may cause undue concern. Most of these entities are relatively common, benign, and transient and do not require therapy.

SEBACEOUS HYPERPLASIA

Minute, profuse, yellow-white papules are frequently found on the forehead, nose, upper lip, and cheeks of a term infant; they represent hyperplastic sebaceous glands (Fig. 688.1). These tiny papules diminish gradually in size and disappear entirely within the first few weeks of life; no treatment is required.

MILIA

Milia are superficial epidermal inclusion cysts that contain laminated keratinized material. The lesion is a firm cyst, 1-2 mm in diameter, and pearly, opalescent white. Milia may occur at any age, but in neonates are most frequently scattered over the face and gingivae and on the midline of the palate, where they are called *Epstein pearls.* Milia exfoliate spontaneously in most infants and may be ignored; those that appear in scars or sites of trauma in older children may be gently unroofed and the contents extracted with a fine-gauge needle.

SUCKING BLISTERS

Solitary or scattered superficial bullae present at birth on the upper limbs of infants are presumably induced by vigorous sucking on the affected part in utero. Common sites are the radial aspect of the forearm, thumb, and index finger. These bullae resolve rapidly without sequelae. They may occur in conjunction with sucking pads (calluses), which are found on the lips and are a result of combined intracellular edema and hyperkeratosis. No treatment is required.

CUTIS MARMORATA

When a newborn infant is exposed to low environmental temperatures, an evanescent, lacy, reticulated red and/or blue cutaneous vascular pattern appears over most of the body surface. This vascular change represents an accentuated physiologic vasomotor response that disappears with increasing age, although it is sometimes discernible even in older children. No treatment is needed.

Cutis marmorata telangiectatica congenita presents in a similar fashion but is a vascular anomaly in which the lesions are more intense, may be segmental, and are persistent despite warming of the infant. They may be associated with loss of dermal tissue, epidermal atrophy, and ulceration (Fig. 688.2). The lower extremities are usually affected, with limb atrophy noted on the affected side. Gradual fading of the livid erythema occurs over 3-5 years, but limb asymmetry is permanent. Extracutaneous findings such as ocular and neurologic abnormalities may be associated in 20–80% of cases. There is no specific treatment.

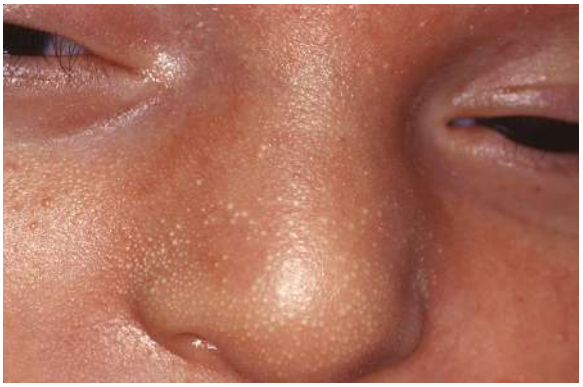

Fig. 688.1 Sebaceous hyperplasia. Minute white-yellow papules on the nose of a newborn.

HARLEQUIN COLOR CHANGE

A dramatic vascular event, harlequin color change occurs transiently in up to 10% of newborns, most commonly on days 2-52 of life. It probably reflects an imbalance in the autonomic vascular regulatory mechanism. When the infant is placed on one side, the body is bisected longitudinally into a pale upper half and a deep red dependent half. The color change lasts only for a few minutes and occasionally affects only a portion of the trunk or face. Changing the infant's position may reverse the pattern. Muscular activity causes generalized flushing and obliterates the color differential. Repeated episodes may occur but do not indicate permanent autonomic imbalance. There is generally no need for treatment. This disorder should be readily distinguishable from harlequin syndrome, which is associated with paroxysmal hemifacial flushing and sweating with or without a Horner syndrome. Symptoms are induced by heat, stress, or exercise. Some cases are secondary to trauma, cervical cord syrinx, or neuroblastoma. Although rarely congenital, most cases occur in older children.

NEVUS SIMPLEX (SALMON PATCH)

Nevus simplex is a small, pale pink, ill-defined, vascular macule that occurs most commonly on the glabella, eyelids, upper lip, and nuchal area of 40–60% of normal newborn infants. These lesions persist for several months and may become more visible during crying or changes in environmental temperature. Most lesions on the face eventually fade and disappear completely, although lesions occupying the entire central forehead often do not. Those on the posterior neck and occipital areas usually persist. Treatment is not usually indicated, though pulsed dye laser treatment can be helpful in lightening lesions that are persistent and cosmetically bothersome. Lesions located in the midline lumbosacral area and associated with other changes such as a sinus or pit, patch of hair, or asymmetric gluteal cleft warrant imaging with ultrasound to evaluate the underlying spinal cord for spinal dysraphism.

Nevus simplex should not be confused with a port-wine stain (capillary malformation), which is a permanent lesion and may be associated with Sturge-Weber syndrome. Nevus simplex is usually symmetric, with lesions on both eyelids or on both sides of the midline. Port-wine stains are often larger and unilateral, and they usually end along the midline (see Chapter 691).

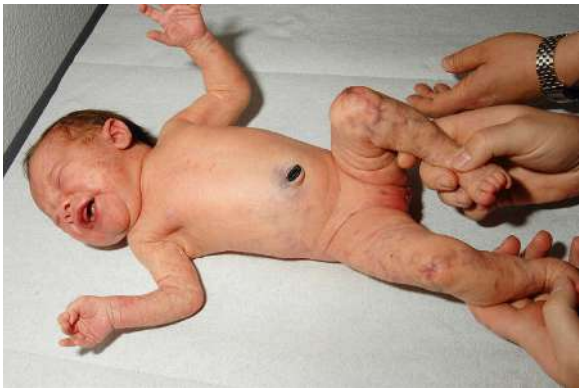

Fig. 688.2 Newborn girl with reticulate erythema/livedo on legs, right arm, and cheeks. *(From Pleimes M, Gottler S, Weibel L. Characteristic congenital reticular erythema: cutis marmorata telangiectatica congenital. J Pediatr. 2013;163:604, Fig. 1.)*

CONGENITAL DERMAL MELANOCYTOSIS (SLATE GRAY NEVUS)

Congenital dermal melanocytosis, which appears as blue or slate-gray macular lesions, has variably defined margins. It occurs most commonly in the sacral area but may be found over the posterior thighs, legs, back, and shoulders (Fig. 688.3). The spots may be solitary or numerous and often involve large areas. The peculiar hue of these macules is a result of the dermal location of melanin-containing melanocytes (mid-dermal melanocytosis) that are presumably arrested in their migration from neural crest to epidermis. They usually fade during the first few years of life as a result of darkening of the overlying skin; no therapy is required. If lesions persist, they may be treated with lasers, if desired. Malignant degeneration does not occur. The characteristic appearance and congenital onset distinguish these spots from the bruises of child abuse. Rarely dermal melanocytosis is associated with Hurler or Hunter syndrome, GM1 gangliosidosis, Niemann-Pick disease, mucolipidosis, and mannosidosis. These lesions have previously been referred to as "Mongolian spots." This term should be avoided, as it derives from racist terminology.

ERYTHEMA TOXICUM

A benign, self-limited, evanescent eruption, erythema toxicum occurs in approximately 50% of full-term infants; preterm infants are affected less commonly. The lesions are firm, yellow-white, 1- to 2-mm papules or pustules with a surrounding erythematous flare (Fig. 688.4). At times, splotchy erythema is the only manifestation. Lesions may be sparse or numerous and either clustered in several sites or widely dispersed over much of the body surface. The palms and soles are usually spared. Peak incidence occurs on the second day of life, but new lesions may erupt during the first few days as the rash waxes and wanes. Onset may occasionally be delayed for a few days to weeks in premature infants. Eosinophils can be demonstrated in Wright-stained smears of the intralesional contents. Cultures are sterile.

The cause of erythema toxicum is unknown. The lesions can mimic pyoderma, candidiasis, herpes simplex, transient neonatal pustular melanosis, and miliaria but can be differentiated by the characteristic infiltrate of eosinophils and the absence of organisms on a stained smear. The course is brief (3-7 days), and lesions generally resolve without pigmentation. No therapy is required. Incontinentia pigmenti and eosinophilic pustular folliculitis also have eosinophilic infiltration but can be distinguished by their distribution, histologic type, and chronicity.

TRANSIENT NEONATAL PUSTULAR MELANOSIS

Pustular melanosis is a transient, benign, self-limited dermatosis of unknown etiology that is characterized by three types of lesions: (1) evanescent superficial pustules, (2) ruptured pustules with a collarette of fine scale, at times with a central hyperpigmented macule, and (3) hyperpigmented macules (Fig. 688.5). Lesions are present at birth, and one or all types of lesions may be found in a profuse or sparse distribution. Pustules represent the early phase of the disorder, and macules, the late phase. The pustular phase rarely lasts more than 2-3 days; hyperpigmented macules may persist for as long as 3 months. Sites of predilection are the anterior neck, forehead, and lower back, although the scalp, trunk, limbs, palms, and soles may be affected.

The active phase shows an intracorneal or subcorneal pustule filled with polymorphonuclear leukocytes, debris, and an occasional eosinophil. The macules are characterized only by increased melanization of epidermal cells. Cultures and smears can be used to distinguish these pustules from those of pyoderma and erythema toxicum, because the lesions of pustular melanosis do not contain bacteria or dense aggregates of eosinophils. No therapy is required.

INFANTILE ACROPUSTULOSIS

Onset of infantile acropustulosis generally occurs at 2-10 months of age; lesions are occasionally noted at birth (Fig. 688.6). The cause is unknown. The lesions are initially discrete erythematous papules that become vesiculopustular within 24 hours and subsequently crust over before healing.

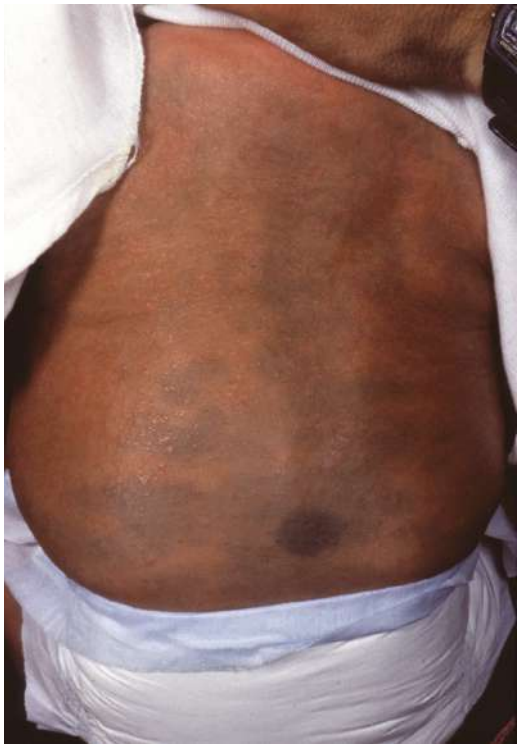

Fig. 688.3 Extensive dermal melanocytosis on the back of a newborn. *(Courtesy Fitzsimons Army Medical Center teaching file.)*

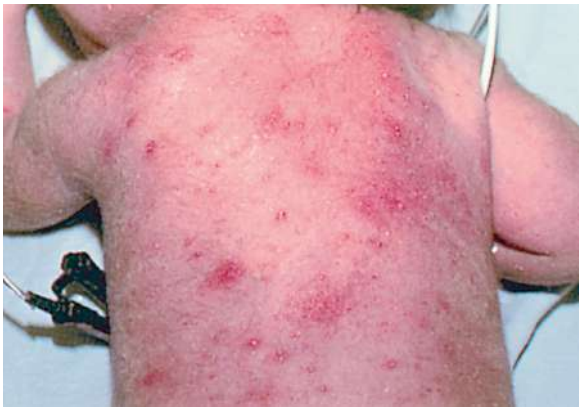

Fig. 688.4 Erythema toxicum on the trunk of a newborn infant.

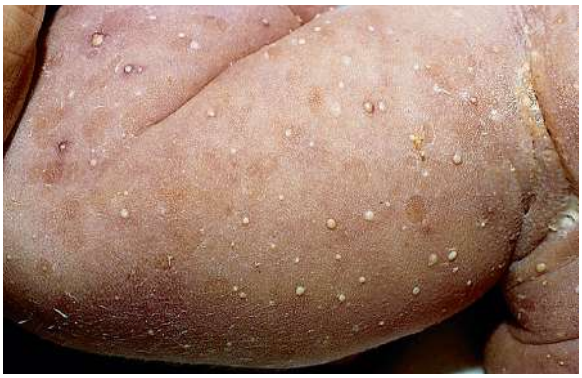

Fig. 688.5 Transient neonatal pustular melanosis. Multiple papules present at birth on the arm of an infant. *(From Weston WL, Lane AT, Morelli JG, eds. Color Textbook of Pediatric Dermatology, 3rd ed. Philadelphia: Mosby; 2002:331.)*

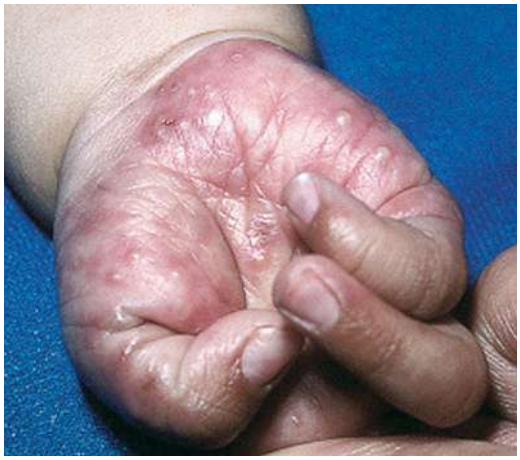

Fig. 688.6 Acropustulosis of infancy. Multiple tense erythematous papules and pustules on the palm of this 4-mo-old girl. *(From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, eds. Nelson Pediatric Symptom-Based Diagnosis. Philadelphia: Elsevier; 2017: Fig. 47.3, p. 854.)*

They are intensely pruritic. Preferred sites are the palms of the hands and the soles and sides of the feet, where the lesions may be extensive. A less dense eruption may be found on the dorsum of the hands and feet, ankles, and wrists. Pustules occasionally occur elsewhere on the body. Each episode lasts 7-14 days, during which time pustules continue to appear in crops. After a 2- to 4-week remission, a new outbreak follows. This cyclic pattern continues for approximately 2 years; permanent resolution is often preceded by longer intervals of remission between periods of activity. Infants with acropustulosis are otherwise well.

Wright-stained smears of intralesional contents show abundant neutrophils or, occasionally, a predominance of eosinophils. Histologically, well-circumscribed, subcorneal, neutrophilic pustules, with or without eosinophils, are noted.

The differential diagnosis in neonates includes transient neonatal pustular melanosis, erythema toxicum, milia, cutaneous candidiasis, and staphylococcal pustulosis. In older infants and toddlers, additional diagnostic considerations include scabies, dyshidrotic eczema, pustular psoriasis, subcorneal pustular dermatosis, and hand-foot-and-mouth disease. A therapeutic trial of a scabicide is warranted in equivocal cases.

Therapy is directed at minimizing discomfort for infants. Topical mid- to high-potency corticosteroids and/or oral antihistamines may decrease the severity of the pruritus and an infant's irritability. Dapsone (1-2 mg/kg/day by mouth, divided in one to two doses) is effective but has potentially serious side effects, notably, hemolytic anemia and methemoglobinemia; its use should be limited to particularly severe cases.

EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis is defined as recurrent crops of pruritic, coalescing, follicular papulopustules on the face, trunk, and extremities. Fifty percent of patients have peripheral eosinophilia, with eosinophil counts exceeding 5%, and approximately 30% have leukocytosis (>10,000 leukocytes/mm^3).

Infants account for <10% of all cases of eosinophilic pustular folliculitis. The clinical and histologic appearances of this disorder in infants closely resemble those in immunocompetent adults, with minor exceptions. In infants, the lesions are most prominent on the scalp, although they also occur on the trunk and extremities and occasionally are found on the palms and soles. The classic annular and polycyclic appearance with centrifugal enlargement is not seen in infants. The differential diagnosis includes erythema toxicum neonatorum, infantile acropustulosis, localized pustular psoriasis, pustular folliculitis, and transient neonatal pustular melanosis. High-potency topical corticosteroids are the most effective treatment (see Table 687.1).

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Chapter 689

Cutaneous Defects

Kari L. Martin

SKIN DIMPLES

Cutaneous depressions over bony prominences and in the sacral area, at times associated with pits and creases, may occur both in normal children and in association with dysmorphic syndromes. Skin dimples may develop in utero because of interposition of tissue between a sharp bony point and the uterine wall, which leads to decreased subcutaneous tissue formation.

Dimples may also be present overlying an area of bone hypoplasia. Bilateral acromial skin dimples are usually an isolated finding, but they are also seen in association with deletion of the long arm of chromosome 18. Dimples tend to occur over the patella in congenital rubella, over the lateral aspects of the knees and elbows in prune-belly syndrome, on the pretibial surface in campomelic syndrome, and in the shape of an H on the chin in Freeman-Sheldon ("whistling face") syndrome.

Sacral dimples are common and usually are isolated findings. They may be seen in multiple syndromes or in association with spina bifida occulta and diastematomyelia. Association with a mass or other cutaneous stigma (hair, aplasia cutis, lipoma, hemangioma) should increase concern for underlying **spinal dysraphism** (see Chapter 631). Simple sacral dimples do not predict underlying spinal cord malformations, and spinal ultrasounds should not be performed in these cases because most of the abnormal findings reported in them are of no clinical significance. In infants younger than 3 months who warrant imaging, ultrasound is an initial, cost-effective, noninvasive method. If there is serious concern of an underlying defect, MRI is indicated. *MRI of the spine is the imaging modality of choice for patients older than 3 months if there is a strong suspicion of a spinal dysraphism.*

REDUNDANT SKIN

Loose folds of skin must be differentiated from a congenital defect of elastic tissue or collagen such as cutis laxa, Ehlers-Danlos syndrome, or pseudoxanthoma elasticum. Redundant skin over the posterior part of the neck is common in Turner, Noonan, Down, and Klippel-Feil syndromes and monosomy 1p36; more generalized folds of skin occur in infants with trisomy 18 and short-limbed skeletal dysplasia.

AMNIOTIC CONSTRICTION BANDS

Partial or complete constriction bands that produce defects in extremities and digits are found in 1 in 10,000-45,000 otherwise normal infants. Constrictive tissue bands are caused by primary amniotic rupture, with subsequent entanglement of fetal parts, particularly limbs, in shriveled fibrotic amniotic strands. This event is probably sporadic, with negligible risk of recurrence. Formation of constrictive tissue bands is associated with maternal history of abdominal trauma, amniocentesis, and hereditary defects of collagen such as Ehlers-Danlos syndrome and osteogenesis imperfecta. Treatment traditionally involves multiple surgical elongating procedures such as Z- and W-plasties. A surgical alternative uses lipoinjection and multiple internal incisions on the deep surface of the band.

Adhesive bands involve the craniofacial area and are associated with severe defects such as encephalocele and facial clefts. Adhesive bands result from broad fusion between disrupted fetal tissue and an intact amniotic membrane. The craniofacial defects appear not to be caused by constrictive amniotic bands, but to result from a vascular disruption sequence with or without cephaloamniotic adhesion (see Chapter 100).

The limb–body wall complex involves vascular disruption early in development, affecting several embryonic structures; it includes at least two of the following three characteristics: exencephaly or encephalocele with facial clefts, thoracoschisis and/or abdominoschisis, and limb defects.

PREAURICULAR SINUSES AND PITS

Pits and sinus tracts anterior to the pinna may be a result of imperfect fusion of the tubercles of the first and second branchial arches. These anomalies may be unilateral or bilateral, may be familial, and at times are associated with other anomalies of the ears and face. **Preauricular pits** are present in **branchiootorenal dysplasia 1 syndrome** (*EYA-1* gene), an autosomal dominant disorder that consists of external ear malformations, branchial fistulas, hearing loss, and renal anomalies. When the tracts become chronically infected, retention cysts may form and drain intermittently; such lesions may require excision.

ACCESSORY TRAGI

An accessory tragus typically appears as a single pedunculated, flesh-colored papule in the preauricular region anterior to the tragus. Less commonly, accessory tragi are multiple or bilateral and may be located in the preauricular area, on the cheek along the line of the mandible (Fig. 689.1), or on the lateral aspect of the neck anterior to the sternocleidomastoid muscle. In contrast to the rest of the pinna, which develops from the second branchial arch, the tragus and accessory tragi derive from the first branchial arch. Accessory tragi may occur as isolated defects or in chromosomal first branchial arch syndromes that include anomalies of the ears and face, such as cleft lip, cleft palate, and mandibular hypoplasia. An accessory tragus is consistently found in oculoauriculovertebral syndrome (Goldenhar syndrome). Other associated syndromes include mandibulofacial dysostosis (Treacher Collins syndrome), Townes-Brocks, VACTERL, and Wolf-Hirschhorn syndrome. Surgical excision is appropriate if cosmetically desired.

Studies are controversial on whether patients with accessory tragi and preauricular pits have a higher prevalence of hearing loss and urinary tract anomalies. *Renal ultrasound should be performed when found with at least one of the following: other malformations or dysmorphic features; family history of deafness, auricular, and/or renal malformation; or a maternal history of gestational diabetes.*

BRANCHIAL CLEFT AND THYROGLOSSAL CYSTS AND SINUSES

Cysts and sinuses in the neck may be formed along the course of the first, second, third, or fourth branchial clefts as a result of improper closure during embryonic life. Second branchial cleft cysts are the most common. The lesions may be unilateral or bilateral (2–3%) and may open onto the cutaneous surface or drain into the pharynx. Secondary infection is an indication for systemic antibiotic therapy. These anomalies may be inherited as autosomal dominant traits.

Thyroglossal cysts and fistulas are similar defects located in or near the midline of the neck; they may extend to the base of the tongue. A pathognomonic sign is vertical motion of the mass with swallowing and tongue protrusion. In nearly 50% of affected children, the cyst or fistula manifests as an infected midline upper neck mass. Cysts in the tongue base may be differentiated from an undescended lingual thyroid by radionuclide scanning. Unlike branchial cysts, a thyroglossal duct cyst often appears after an upper respiratory infection (see Chapter 601).

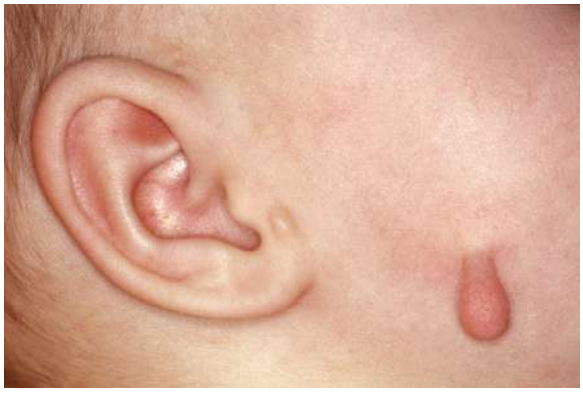

Fig. 689.1 Accessory tragus on cheek along jaw line.

PILONIDAL SINUS AND ABSCESS

The etiology of pilonidal disease remains unknown; three hypotheses explaining its origin have been proposed. The first states that trauma, such as can occur with prolonged sitting, impacts hair into the subcutaneous tissue, which serves as a nidus for infection. The second suggests that in some patients, hair follicles exist in the subcutaneous tissues, perhaps the result of some embryologic abnormality, and that they serve as a focal point for infection, especially with secretion of hair oils. The third speculates that motion of the buttocks disturbs a particularly deep midline crease and works bacteria and hair beneath the skin. This theory arises from the apparent improved short-term and long-term results of operations that close the wound off the midline, obliterating the deep natal cleft.

Pilonidal disease usually manifests in adolescents or young adults with significant hair over the midline sacral and coccygeal areas. It can occur as an acute abscess with a tender, warm, flocculent, erythematous swelling or as draining sinus tracts. This disease does not resolve with nonoperative treatment. An acute abscess should be drained and packed open, using appropriate anesthesia. Oral broad-spectrum antibiotics covering the usual isolates (*Staphylococcus aureus* and *Bacteroides* species) are prescribed, and the patient's family withdraws the packing over the course of a week. When the packing has been totally removed, the area can be kept clean by a bath or shower. The wound usually heals completely in 6 weeks. Once the wound is healed, most pediatric surgeons feel that elective excision should be scheduled to avoid recurrence. There are some reports, however, that this is only necessary if the disease recurs. Usually, patients who present with sinus tracts are managed with a single elective excision.

Most surgeons carefully identify the extent of each sinus tract and excise all skin and subcutaneous tissue involved to the fascia covering the sacrum and coccyx. Some close the wound in the midline; others leave it open and packed for healing by secondary intention. This method has been modified by the application of a vacuum-assisted (VAC sponge) dressing. This is a system that applies continuous suction to a porous dressing. It is usually changed every 3 days and can be done at home with the assistance of a nurse. Some marsupialize the wound by suturing the skin edges down to the exposed fascia covering the sacrum and coccyx. There appears to be improved success with excision and closure in such a way that the suture line is not in the midline. Currently there appears to be enthusiasm for the less radical methods that Bascom has introduced, treating simple sinus tracts with small local procedures and limiting excision to only diseased tissues, while still keeping the incision off the midline. Recurrence or wound-healing problems are relatively common, occurring in 9–27% of cases. The variety of treatments and procedures currently being described indicates that all are associated with significant complications and delays in return to normal activity. Still, it is rare for problems to persist beyond 1-2 years. Recalcitrant cases are treated by a large, full-thickness gluteal flap or skin grafting.

SUPERNUMERARY NIPPLES

Solitary or multiple accessory nipples may occur in a unilateral or bilateral distribution along a line from the anterior axillary fold to the inguinal area. Accessory nipples may or may not have areolae and may be mistaken for congenital nevi. They may be excised for cosmetic reasons, but otherwise, treatment is not necessary. Renal or urinary tract anomalies, malignancies—especially genitourinary cancers—and hematologic abnormalities may rarely occur in children with this finding (see Chapter 588).

APLASIA CUTIS CONGENITA (CONGENITAL ABSENCE OF SKIN)

Developmental absence of skin is usually noted on the scalp as multiple or solitary (70%), noninflammatory, well-demarcated, oval or circular 1- to 2-cm ulcers (Table 689.1). The appearance of lesions varies, depending on when they occurred during intrauterine development. Those that form early in gestation may heal before delivery and appear as atrophic, fibrotic scars with associated alopecia, whereas more recent defects may

Table 689.1 Freiden's Classification of Aplasia Cutis Congenita

GROUP	DEFINITION	INHERITANCE
1	Isolated scalp involvement; may be associated with single defects	AD
2	Scalp ACC with limb reduction defects (Adams-Oliver syndrome); may be associated with encephalocele	AD
3	Scalp ACC with epidermal nevus	Sporadic
4	ACC overlying occult spinal dysraphism, spina bifida, or meningoencephalocele	Sporadic
5	ACC with placental infarcts and/or fetus papyraceus (disappearing twin syndrome)	Sporadic
6	ACC with epidermolysis bullosa; Bart phenotype*	AD or AR
7	ACC localized to extremities without blistering; usually affecting pretibial areas and dorsum of hands and feet	AD or AR
8	ACC caused by teratogens (e.g., varicella, herpes, methimazole, valproic acid, misoprostol)	Sporadic
9	ACC associated with malformation syndromes (e.g., trisomy 13, deletion 4p−, deletion Xp22.1, ectodermal dysplasia, Johanson-Blizzard syndrome, Adams-Oliver syndrome)	Variable

*Bart phenotype ACC with epidermolysis bullosa and dystrophic nails.
ACC, Aplasia cutis congenital; AD, autosomal dominant; AR, autosomal recessive.
Modified from Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol.* 1986;14:646–660.

manifest as ulcerations. Most occur at the vertex of the scalp just lateral to the midline, but similar defects may also occur on the face, trunk, and limbs, where they are often symmetric and usually associated with an intrauterine fetal demise of a twin **(fetus papyraceus)**. The depth and size of the ulcer vary. Only the epidermis and upper dermis may be involved, resulting in minimal scarring or hair loss, or less often, the defect may extend to the deep dermis; to the subcutaneous tissue; and, rarely, to the periosteum, skull, and dura. Lesions may be surrounded by a ring of hair known as the **hair collar sign** (Fig. 689.2). The hair collar sign may also be associated with an encephalocele, meningocele, heterotopic glial tissue, or a meningothelial hamartoma.

Diagnosis is made on physical findings indicative of in utero disruption of skin development. Lesions are sometimes mistakenly attributed to scalp electrodes or obstetric trauma. Most are sporadic, but autosomal dominant and recessive cases also occur; some are caused by pathogenic variants in *BMS1*.

Although most individuals with aplasia cutis congenita have no other abnormalities, these lesions may be associated with isolated physical anomalies or with malformation syndromes, including Opitz, Adams-Oliver, oculocerebrocutaneous, Johanson-Blizzard, and 4p(−), X-p22 microdeletion syndromes; trisomy 13-15; and chromosome 16-18 defects (see Table 689.1). Aplasia cutis congenita may also be found in association with an overt or underlying embryologic malformation, such as congenital pulmonary malformations, meningomyelocele, gastroschisis, omphalocele, or spinal dysraphism. Aplasia cutis congenita in association with the vanishing twin syndrome (fetus papyraceus) is apparently caused by ischemic or thrombotic events in the placenta and fetus such as the hypovolemia that occurs with acute transfusion from a surviving to a dying twin. Blistering or skin fragility and/or absence or deformity of nails in association with aplasia cutis congenita is a well-recognized manifestation of epidermolysis bullosa.

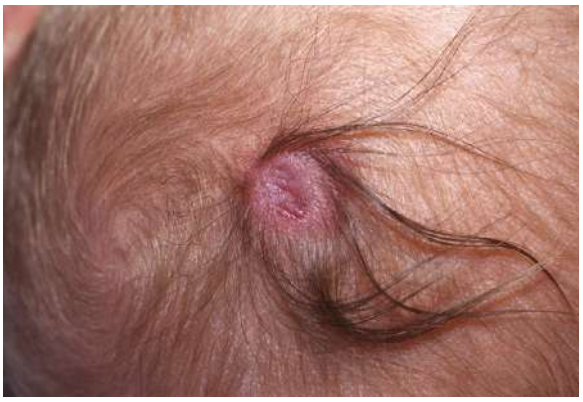

Fig. 689.2 Solitary scalp vertex lesion of aplasia cutis congenita with hair collar sign.

Fig. 689.3 An elastic protruding hairless nodule measuring up to 1.5 cm in diameter, with a ring of dark, coarse, long hairs surrounding the nodule forming a "hair collar." *(From Chien MM, Chen KL, Chiu HC. The "hair collar" sign. J Pediatr. 2016;168:246.)*

Major complications are rare and more often associated with large, stellate lesions of the midline parietal scalp. Hemorrhage, secondary local infection, and meningitis have been reported. If the defect is small, recovery is uneventful, with gradual epithelialization and formation of a hairless atrophic scar over a period of several weeks. Small bony defects usually close spontaneously in the first year of life. Large or numerous scalp defects may require repair, but care must be taken, as abnormal underlying venous structures have complicated surgical repair. Truncal and limb defects, despite being large, usually epithelialize and form atrophic scars, which can later be revised.

Although the hair collar sign is often associated with aplasia cutis, it may also be seen with encephaloceles, meningoceles, heterotopic glial elements, or hamartoma. Brain MRI is often indicated to evaluate for these lesions in patients with the hair collar sign without aplasia cutis (Fig. 689.3).

FOCAL FACIAL DERMAL DYSPLASIAS

The focal facial dermal dysplasias (FFDDs) are a rare group of conditions sharing bitemporal or preauricular lesions resembling scars or aplasia cutis congenita. FFDD1 **(Brauer syndrome)** is inherited in an autosomal dominant fashion and typically has mild associated facial features. FFDD2 **(Brauer-Setleis syndrome)** and FFDD3 **(Setleis syndrome)** are associated with thin, puckered periorbital skin, distichiasis

and/or absent eyelashes, upslanting palpebral fissures, flat nasal bridge, large lips, and redundant facial skin. FFDD2 is inherited in an autosomal dominant fashion, whereas FFDD3 is autosomal recessive and caused by pathogenic variants in *TWIST2;* autosomally dominant cases of FFDD3 have been reported and are caused by chromosome duplication/triplication of the 1p36.22p36.21 region. FFDD4 has no other related skin findings; it is inherited both in autosomal dominant and recessive manners and is caused by pathogenic variants in *CYP26C1*.

FOCAL DERMAL HYPOPLASIA (GOLTZ-GORLIN SYNDROME)

A rare congenital mesoectodermal and ectodermal disorder, focal dermal hypoplasia is characterized by dysplasia of connective tissue in the skin and skeleton. This disorder is an X-linked dominant disorder caused by pathogenic variants in the *PORCN* gene. It manifests as numerous soft tan papillomas. Other cutaneous findings include linear atrophic lesions, reticulated hypopigmentation and hyperpigmentation, telangiectasias, congenital absence of skin, angiofibromas presenting as verrucous excrescences, and papillomas of the lips, tongue, circumoral region, vulva, anus, and the inguinal, axillary, and periumbilical areas. Partial alopecia, sweating disorders, and dystrophic nails are additional, less common ectodermal anomalies. The most frequent skeletal defects are syndactyly, clinodactyly, polydactyly, and scoliosis. **Osteopathia striata** are fine parallel vertical stripes noted on radiographs in the metaphyses of long bones of patients with this disorder; these are highly characteristic of focal dermal hypoplasia but are not pathognomonic. Many ocular abnormalities, the most common of which are colobomas, strabismus, nystagmus, and microphthalmia, are also characteristic. Small stature, enamel hypoplasia, soft tissue anomalies, and peculiar dermatoglyphic patterns are also common. Cognitive impairment occurs occasionally. There is no specific treatment.

DYSKERATOSIS CONGENITA (ZINSSER-ENGMAN-COLE SYNDROME)

Dyskeratosis congenita (DKC), a rare familial syndrome, consists classically of the triad of reticulated hyperpigmentation of the skin (Fig. 689.4), dystrophic nails, and mucous membrane leukoplakia in association with immunologic and hematologic abnormalities. Patients with DKC also show signs of premature aging and increased occurrence of cancer, especially squamous cell carcinoma. DKC may be X-linked recessive (*DKC-1* gene), autosomal dominant (*hTERC* and *TINF2* genes), or autosomal recessive (*NOLA3* gene). Onset occurs in childhood, most commonly as nail dystrophy. The nails become atrophic and ridged longitudinally with progression to pterygia and complete nail loss. Skin changes usually appear after onset of nail changes and consist of reticulated gray-brown pigmentation, atrophy, and telangiectasia, especially on the neck, face, and chest. Hyperhidrosis and hyperkeratosis of the palms and soles, sparse scalp hair, and easy blistering of the hands and feet are also characteristic. Blepharitis, ectropion, and excessive tearing because of atresia of the lacrimal ducts are occasional manifestations. Oral leukokeratosis may give rise to squamous cell carcinoma. Other mucous membranes, including conjunctival, urethral, and genital, may be involved. Infection, malignancy, pulmonary fibrosis, and bone marrow failure are common, and death before age 40 years is typical. No effective treatment exists. Allogenic hemopoietic stem cell transplantation is curative treatment when bone marrow failure occurs.

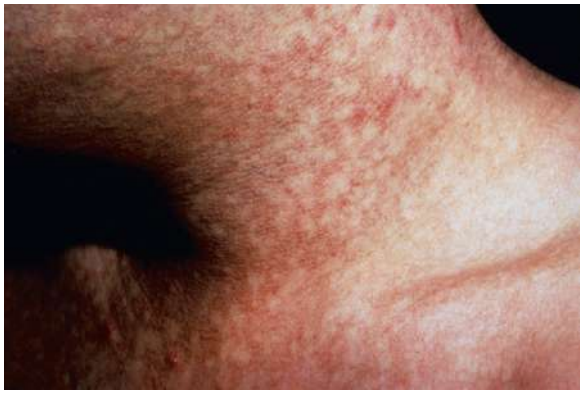

Fig. 689.4 Reticulated dyspigmentation on neck of patient with dyskeratosis congenita.

CUTIS VERTICIS GYRATA

Cutis verticis gyrata, an unusual alteration of the scalp that is more common in males, may be present from birth or may develop during adolescence. The scalp is characterized by convoluted elevated folds, 1-2 cm in thickness, usually in the fronto-occipital axis. Unlike the lax skin of other disorders, the convolutions cannot generally be flattened by traction. **Primary cutis gyrata** may be associated with intellectual disability, retinitis pigmentosa, sensorineural deafness, and thyroid aplasia. **Secondary cutis gyrata** may be the result of chronic inflammatory diseases, tumors, nevi, and acromegaly.

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Chapter 690

Ectodermal Dysplasias

Kari L. Martin

Ectodermal dysplasia (ED) is a heterogeneous group of disorders characterized by a constellation of findings involving defects of two or more of the following: teeth, skin, and appendageal structures, including hair, nails, and eccrine and sebaceous glands. Although more than 150 EDs have been described, the majority are rare, with an estimated incidence of 3.5 in 10,000 individuals.

Individuals presenting with a constellation of abnormalities involving the teeth, skin, and nails should raise suspicion for a diagnosis of ED. Table 690.1 provides a general list of abnormalities that may be seen in patients with EDs. Further specifying the specific type of ED can be challenging because there are a large number of subtypes and most are extremely rare (Table 690.2). Exome sequencing may enhance the identification of these rare subtypes.

Table 690.1 Clinical Abnormalities in Ectodermal Dysplasia

Teeth	Small primary teeth, anodontia or hypodontia of secondary teeth, conical or peg teeth, premature loss of teeth, delayed eruption of teeth, defective enamel, small widely spaced teeth, elongated pulp chamber in teeth
Skin	Atopic dermatitis, xerosis, photosensitivity, palmoplantar keratoderma, facial telangiectasias
Hair	Abnormal quantity, structure and quality: thin, brittle, slow-growing, kinky or wooly, fragile, dry, and lusterless hair. Often involves scalp, eyebrows and eyelashes.
Nails	Brittle, dystrophic, absent, ridging, pitting
Sweat	Hypohidrosis, hyperhidrosis of palms and soles
Other	Recurrent sinus infection, nasal congestion, hoarse voice, wheezing

Normal phenotype is also possible for any of these categories.

Table 690.2 Classification for Ectodermal Dysplasias*

DISORDER†	INHERITANCE	GENE	PROTEIN	FUNCTION
EDA/NF-κB PATHWAY				
Hypohidrotic ectodermal dysplasia	XLR	*EDA1*	Ectodysplasin (EDA)	Membrane ligand
Hypohidrotic ectodermal dysplasia	AD	*EDAR*	EDA receptor (EDAR)	Receptor of EDA
		EDARADD	EDAR-associated death domain	Adaptor molecule
Hypohidrotic ectodermal dysplasia	AR	*EDAR*	EDAR	Receptor of EDA
		EDARADD	EDAR-associated death domain	Adaptor molecule
		TRAF6	TNF receptor–associated factor 6	Activates IKK
Hypohidrotic ectodermal dysplasia with immune deficiency (males) ± osteopetrosis (males) ± lymphedema	XLR	*NEMO/IKBKG*	NF-kB essential modulator	NF-kB activation
Incontinentia pigmenti (females)	XLD	*NEMO/IKKγ*	NF-κB essential modulator	NF-κB activation
Hypohidrotic ectodermal dysplasia with immune deficiency	AR	*IkBα*	IkBα	NF-kB activation
P63 PATHWAY				
Ectrodactyly-ectodermal dysplasia-clefting syndrome	AD	*p63*	p63	Transcription factor
Rapp-Hodgkin syndrome	AD	*p63*	p63	Transcription factor
Ankyloblepharon-ectodermal dysplasia-clefting syndrome (AEC)	AD	*p63*	p63	Transcription factor
Acrodermatoungual-lacrimal-tooth (ADULT)	AD	*p63*	p63	Transcription factor
Limb-mammary syndrome	AD	*p63*	p63	Transcription factor
Curly hair, ankyloblepharon, and nail dystrophy (CHAND) syndrome	AR	*RIPK4*	RIPK4	Serine/threonine protein kinase
Popliteal pterygium syndromes (spectrum)	AR, AD	*IRF6*	IRF6	Transcription factor
Popliteal pterygium	AR	*RIPK4*	RIPK4	Kinase
Bartsocas-Papas (Cocoon syndrome)	AR	*CHUK*	CHUK	Kinase
Ectodermal dysplasia	AD	*KDF1*	KDF1	Keratinocyte differentiation factor
Trichodentoosseous syndrome (TDO)	AD	*DLX3*	DLX3	Transcription factor
Clefting-ectodermal dysplasia	AR	*PVRL1*	Nectin 1	Interacts with cadherins, especially at adherens junctions
Ectodermal dysplasia-syndactyly syndrome	AR	*PVRL4*	Nectin 4	Interacts with cadherins, especially at adherens junctions
Hypotrichosis with juvenile macular dystrophy ± ectrodactyly/other ectodermal defects	AR	*CDH3*	Cadherin 3/P-cadherin	Adhesion molecule for cell-cell binding
WNT PATHWAY				
Witkop syndrome	AD	*MSX1*	MSX1	Transcription factor
Focal dermal hypoplasia	X-linked dominant	*PORCN*	PORCN	Regulates Wnt signaling
Oculodentodigital dysplasia (ODDD)	AD	*WNT10A*	Wnt10A	Wnt pathway
Hypohidrotic ectodermal dysplasia	AR, AD	*WNT10A*	Wnt10A	β-catenin-mediated signaling
Schöpf-Schulz-Passarge syndrome	AR	*WNT10A*	Wnt10A	β-catenin-mediated signaling

Table 690.2 Classification for Ectodermal Dysplasias*—cont'd

DISORDER†	INHERITANCE	GENE	PROTEIN	FUNCTION
Ectodermal dysplasia	AR	*KREMEN1*	KREMEN1	Receptor involved in Wnt regulation
STRUCTURAL ELEMENT				
Clouston syndrome	AD	*GJB6*	Connexin 30	Intercellular junctions
Ectodermal dysplasia	AR	*GRHL2*	Grainyhead-like 2	Transcription factor
Oculodentodigital dysplasia (ODDD)	AR	*GJA1*	Connexin 43	Intercellular junctions
Ellis van Creveld syndrome	AR	*EVC, EVC2*	EVC, EVC2	Ciliopathy
Ectodermal dysplasia 4, hair/nail type (ECTD4)	AR	*KRT85*	KRT85	Keratin
Keratitis-ichthyosis-deafness syndrome, autosomal dominant (KID)	AR	*GJB2*	Connexin 26	Intercellular junctions
Ectodermal dysplasia: skin fragility syndrome	AR	*PKP1*	Plakophilin 1	Desmosomal plaque/ stability
Naegeli- Franceschetti-Jadassohn syndrome	AD	*KRT14*	KRT14	Keratin
Pachyonychia congenita	AD	*KRT 6a, 6b, 6c, 16, 17*	KRT 6a, 6b, 6c, 16, 17	Keratin

*Many forms of ectodermal dysplasia remain unclassified.
†Some more recently described forms of ectodermal dysplasia are not yet named.
AD, Autosomal dominant; AR, autosomal recessive; IKK, inhibitor of kappa light polypeptide gene enhancer in B-cell kinase; TNF, tumor necrosis factor; XLD, X-linked dominant; XLR, X-linked recessive.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 6th ed. Philadelphia: Elsevier; 2022: Table 7.1, p. 165.

HYPOHIDROTIC ECTODERMAL DYSPLASIA

The syndrome known as hypohidrotic ectodermal dysplasia (HED) manifests as a triad of defects: partial or complete absence of sweat glands, anomalous dentition, and hypotrichosis. There are many recognized types of HED; HED-1 (X-linked recessive) is most common, with a frequency of 1 per 17,000 live births.

In HED, affected patients are unable to sweat and may experience episodes of high fever in warm environments, which may be mistakenly considered to be **fevers of unknown origin**. This error is particularly common in infancy when the facial changes are not easily appreciated. Diagnosis at this time may be made using the starch-iodine test or palmar or scalp biopsy. Scalp biopsy is the most sensitive and is 100% specific. It shows a complete lack of eccrine structures. Infants and older children must be protected from high temperatures given their inability to sweat. Cooling devices and clothing can be helpful to increase participation in activities and sports. Aside from patients with *WNT10A* pathogenic variants—who do not have facial dysmorphism—the typical facies are characterized by frontal bossing; malar hypoplasia; a flattened nasal bridge; recessed columella; thick, everted lips; wrinkled, hyperpigmented periorbital skin; and prominent, low-set ears (Fig. 690.1). The skin over the entire body is dry, finely wrinkled, and hypopigmented, often with a prominent venous pattern. Extensive peeling of the skin is a clinical clue to diagnosis in the newborn period. The paucity of sebaceous glands may account for the dry skin. The scalp hair is sparse, fine, and lightly pigmented, and eyebrows and lashes are sparse or absent. Other body hair is also sparse or absent. Sexual hair growth is normal. Anodontia or hypodontia with widely spaced, conical teeth is a consistent feature (see Fig. 690.1). *Co-management with pediatric dentistry familiar with ectodermal dysplasias is critical for oral health, nutrition, and maintenance of the facial bones.* Otolaryngic and ophthalmologic abnormalities secondary to decreased saliva and tear production are seen. The incidence of atopic diseases in children with HED is high. Gastroesophageal reflux is common and may play a role in failure to thrive, which is seen in 20% of cases. Sexual development is usually normal. Historically, the infant mortality rate has been 30%. Carrier females of X-linked HED may have no or less severe clinical manifestations.

Prenatal therapy of X-linked HED with a recombinant protein containing the EDA receptor binding domain has been successful in three patients.

Hypohidrotic ED with immune deficiencies causes similar findings in sweating and hair and nail development, in association with a dysgammaglobulinemia. Significant mortality is seen from recurrent infections. A variety of pathogenic variants of the genes encoding the tumor necrosis factor α (TNFα)–related signaling pathway proteins—key in signal transduction from ectoderm to mesoderm during development—are the molecular basis for this disorder (see Table 690.2).

Treatment of children with HED includes protecting them from exposure to high ambient temperatures. Early dental evaluation is necessary so that prostheses can be provided for cosmetic reasons and for adequate nutrition. The use of artificial tears prevents damage to the cornea in patients with defective lacrimation. Alopecia may necessitate the wearing of a wig to improve appearance.

HIDROTIC ECTODERMAL DYSPLASIA (CLOUSTON SYNDROME)

The salient features of the autosomal dominant disorder hidrotic ED are dystrophic, hypoplastic, or absent nails; sparse hair; and hyperkeratosis of the palms and soles (Table 690.3). Conjunctivitis and blepharitis are common. The dentition and sweating are always normal. Absence of eyebrows and eyelashes, clubbing of the fingers, and hyperpigmentation over the knees, elbows, and knuckles have been noted in some affected individuals. Pathogenic variants in the *GJB6* gene encoding the gap junction protein connexin 30 are responsible for this disorder. A similar disorder associated with deafness has been described with pathogenic variants in the *GJB2* gene encoding the connexin 26 protein. Pathogenic variants in *GJB1* have also been implicated.

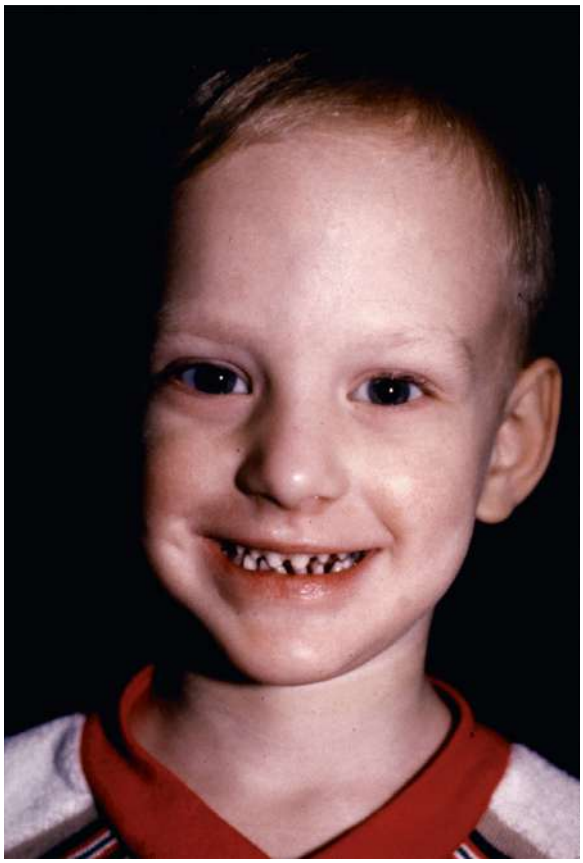

Fig. 690.1 Hypohidrotic ectodermal dysplasia is characterized by pointed ears, fine hair, periorbital hyperpigmentation, midfacial hypoplasia, and pegged teeth. *(Courtesy the Fitzsimons Army Medical Center teaching file.)*

Table 690.3 Common Ectodermal Dysplasias: Inheritance and Characteristic Clinical Findings

TYPE	INHERITANCE(S)	CHARACTERISTIC CLINICAL FINDINGS
Hypohidrotic ED	XLR, AD, AR	Distinctive facies: prominent forehead, thick lips and flattened nasal bridge; collodion-like membrane; eczema Hypotrichosis of scalp and trunk, light/brittle/slow-growing hair Hypodontia, conical teeth Hypohidrosis
Hypohidrotic ED-immune deficiency (EDA-ID)	XLR, AD	Seborrheic dermatitis–like rash, intertrigo Hypotrichosis Hypodontia, pointed teeth Hypohidrosis/anhidrosis Recurrent infections Decreased immunoglobulin levels
Hidrotic ED (Clouston)	AD	Hyperpigmented skin over joints; palmoplantar keratoderma, conjunctivitis, blepharitis Milky-white nails in early childhood, nail dystrophy, clubbing Sparse, wiry, brittle, pale scalp hair to total alopecia Normal sweating
Witkop tooth and nail syndrome	AD	Usually normal hair, rarely sparse or fine Normal sweating Small primary teeth, hypodontia causing lower lip eversion ("pouting lower lip") Thin, slow growing hypoplastic nails (toes > fingers), koilonychia
EEC	AD	Dry skin, aplasia or hypoplasia of skin Normal sweating Coarse, lightly pigmented hair; thick eyebrows Hypodontia (reduced number), taurodontia, premature loss of teeth, dental enamel abnormalities Ectrodactyly more common than syndactyly Nail dystrophy, transverse ridging and pitting Corneal erosion, lacrimal duct abnormality, blepharitis, GU defects, cleft lip or palate

Continued

Table 690.3 Common Ectodermal Dysplasias: Inheritance and Characteristic Clinical Findings—cont'd

TYPE	INHERITANCE(S)	CHARACTERISTIC CLINICAL FINDINGS
AEC (Hay-Wells syndrome) and RHS	AD	Erosive dermatitis, neonatal erythroderma (e.g., scalp, hands), dyspigmentation of skin Coarse, wiry, lightly pigmented hair, patchy alopecia ± Hypohidrosis Hypodontia, conical teeth Nail absence or dystrophy with thickened nails Ectrodactyly more common than syndactyly Lacrimal duct abnormality, hearing loss, cleft lip/palate, ankyloblepharon, reflux
Limb-mammary	AD	Normal hair Hypodontia ± Hypohidrosis Nail dystrophy Ectrodactyly more common than syndactyly Bifid uvula, hypoplastic nipples, joint contracture of hand, lacrimal duct atresia, cleft palate
ADULT	AD	Dry skin, photosensitivity, lentigines Hypodontia, premature loss of teeth Normal sweating Pitting and longitudinal ridging of nails Ectrodactyly and syndactyly No cleft palate or lip Hypoplastic nipples, lacrimal duct atresia,

AD, Autosomal dominant; ADULT, acro-dermato-ungal-lacrimal-tooth; AEC, ankyloblepharon-ectodermal dysplasia-clefting; AR, autosomal recessive; ED, ectodermal dysplasia; EEC, ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome; RHS, Rapp-Hodgkin syndrome; XLR, X-linked recessive.

Table 690.4 Disorders Associated with Decreased Sweat Production

CUTANEOUS LESIONS
Congenital absence of sweat glands without ectodermal dysplasia
Incontinentia pigmenti
Burns
MULTISYSTEM DISORDERS
Fabry disease
Crisponi syndrome
Chronic graft-versus-host disease
Sjögren syndrome
NEUROLOGIC DISORDERS
Spinal cord injury
Guillain-Barré syndrome
Hereditary sensory autonomic neuropathy type I, II, IV
Complex regional pain syndrome
Multiple sclerosis
Multiple system atrophy
Ross syndrome
Shy-Drager syndrome
MEDICATIONS
Anticholinergic drugs
Opioids
Botulism toxin
Clonidine
Barbiturate overdose
α_2-Receptor antagonists
OTHER
Idiopathic acquired generalized anhidrosis
Hypothyroidism
Conversion disorder
Heat shock
Sympathectomy

In addition to the EDs, other disorders are associated with absent or decreased sweat production (Table 690.4).

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Chapter 691

Vascular Anomalies

Kari L. Martin

Nearly all vascular lesions of childhood may be divided into vascular malformations and vascular tumors (Table 691.1). Vascular malformations are developmental disorders of blood vessel formation. Malformations do not regress, but slowly enlarge. They should be named after the predominant vessel(s) forming the lesion: arterial, capillary, lymph, venous, or combinations of these. Vascular tumors exhibit endothelial cell hyperplasia and proliferation. The International Society for the Study of Vascular Anomalies (ISSVA) continues to update the classification structure for vascular disorders as new disorders are identified and as the biology and genetic causes for established disorders are found. The complete classification, associated syndromes, and causative pathogenic variants can be found at www.issva.org.

VASCULAR MALFORMATIONS

Capillary Malformation (Port-Wine Stain)

Capillary malformations (CMs) are present at birth. These vascular malformations consist of mature dilated dermal capillaries. The lesions are macular, sharply circumscribed, pink to purple, and tremendously varied in size (Fig. 691.1). The head and neck region is the most common site of predilection; most lesions are unilateral. The mucous membranes can be involved. As a child matures into adulthood, the CM may become darker in color and pebbly in consistency; it may occasionally develop papules that bleed spontaneously. CM may occur in isolation or in combination with other vessel malformations.

True CM should be distinguished from **nevus simplex**, which, in contrast, is a relatively transient lesion often located in the midline (see Chapter 688). When a CM is lateral and localized to the forehead and upper eyelid, the diagnosis of **Sturge-Weber syndrome** (glaucoma, leptomeningeal venous angioma, seizures, hemiparesis contralateral to the facial lesion, intracranial calcification) must be considered (see Chapter 636.3). Early screening for glaucoma is important to

Table 691.1 Contemporary Classification of Vascular Anomalies (ISSVA 2014 Classification)

VASCULAR TUMORS
Benign
Infantile hemangioma/hemangioma of infancy
Congenital hemangiomas (RICH, NICH, PICH)
Tufted angioma
Spindle cell hemangioma
Epithelioid hemangioma
Pyogenic granuloma
Locally Aggressive or Borderline
Kaposiform hemangioendothelioma
Retiform hemangioendothelioma
Papillary intralymphatic angioendothelioma (Dabska tumor)
Composite hemangioendothelioma
Kaposi sarcoma
Malignant
Angiosarcoma
Epithelioid hemangioendothelioma
VASCULAR MALFORMATIONS
Simple
Capillary (CM) (e.g., port-wine stain, telangiectasia, CMTC, salmon patch/nevus simplex)
Venous (VM) (includes common, familial, glomuvenous, others)
Lymphatic (LM) (includes macrocystic, microcystic, primary lymphedema, others)
Arteriovenous (AVM) and arteriovenous fistula (sporadic or syndromal)
Combined
CM + VM, CM + LM, CM + AVM
LM + VM
CM + LM + VM
CM + LM + AVM, CM + VM + AVM
CM + LM + VM + AVM
Of major named vessels
Affect veins, arteries or lymphatics; usually of large caliber
Associated with other anomalies
Associated with anomalies of bone, soft tissue (usually overgrowth, rarely undergrowth) or viscera

CMTC, Cutis marmorata telangiectatica congenita; *NICH*, noninvoluting congenital hemangioma; *PICH*, partially involuting congenital hemangioma; *RICH*, rapidly involuting congenital hemangioma.

From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Box 12.1, p. 327. Created with data from Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: Recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics.* 2015;136(1):e203–e214.

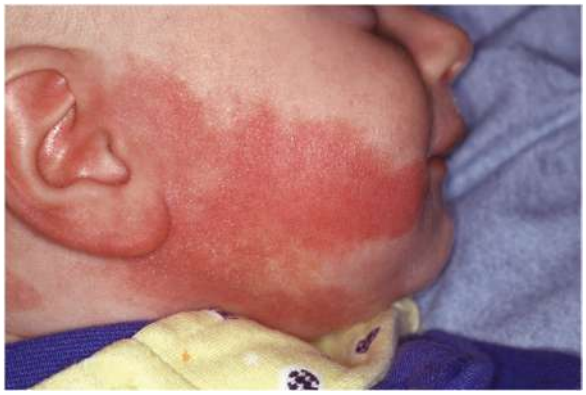

Fig. 691.1 Capillary malformation. Pink macule on the cheek of an infant.

Table 691.2 Port-Wine Stain–Associated Syndromes

- Sturge-Weber syndrome
- Klippel-Trenaunay syndrome
- Parkes-Weber syndrome
- Phakomatosis pigmentovascularis
- Macrocephaly–capillary malformation (M-CM) syndrome
- Capillary malformation–arteriovenous malformation (CM-AVM) syndrome
- Diffuse capillary malformation with overgrowth (DCMO)
- Bannayan-Riley-Ruvalcaba syndrome
- Von Hippel-Lindau disease
- Rubinstein-Taybi syndrome
- Wyburn-Mason syndrome
- Roberts syndrome
- Coat disease

Modified from Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Elsevier: Philadelphia; 2022: Box 12.4, p. 347.

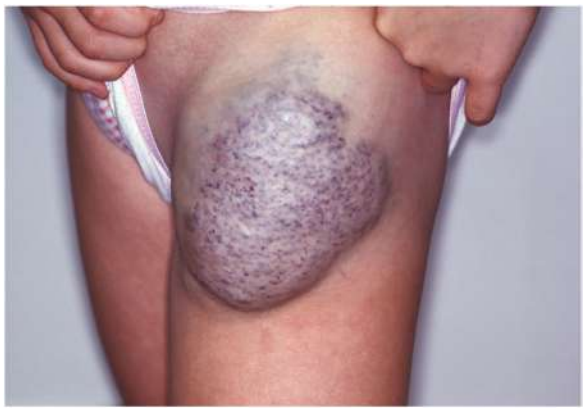

Fig. 691.2 Nodular venous malformation on the leg of an adolescent.

prevent additional damage to the eye. CMs also occur as a component of **Klippel-Trenaunay syndrome** and with moderate frequency in other syndromes, including megalencephaly, capillary malformation, polymicrogyria (MCAP), Cobb (spinal arteriovenous malformation [AVM], port-wine stain), congenital lipomatous, overgrowth, vascular malformations, epidermal nevi, skeletal anomalies (CLOVES), Proteus, Beckwith-Wiedemann, and Bonnet-Dechaume-Blanc syndromes, and others (Table 691.2). In the absence of associated anomalies, morbidity from these lesions may include a poor self-image, hypertrophy of underlying structures, and traumatic bleeding.

The most effective treatment for CM is with the pulsed-dye laser. This therapy is targeted to hemoglobin within the lesion and minimizes thermal injury to the surrounding normal tissue. After such treatment, the texture and pigmentation of the skin are generally improved with low risks of scarring. Therapy can begin in infancy when the surface area of involvement is smaller. There may be advantages to treating within the first year of life. Although this approach is quite effective, redarkening of the stain may occur over time, making ongoing treatments useful. Camouflaging cosmetics may also be used.

Venous Malformation

Venous malformations include vein-only malformations and combination malformations. Malformations consisting of veins only range from nodules containing a mass of venules (Fig. 691.2) to diffuse large vein abnormalities that may consist of either a superficial component resembling varicose veins, deeper venous malformations, or both. Most venous malformations are sporadic, although inherited forms exist as well. Inherited forms and up to 40% of sporadic venous malformations are caused by *TIE2* pathogenic variants. Treatment is reserved for painful or symptomatic lesions. Surgical excision is best for small

or superficial nodular lesions; sclerotherapy or laser ablation is used for larger, diffuse lesions. Localized intravascular coagulopathy can be problematic in these lesions because of the chronic slow flow. This leads to both painful thrombotic episodes and the risk of progression to systemic disseminated intravascular coagulopathy. Pulmonary embolus has been reported in patients with large venous malformations.

LYMPHATIC MALFORMATIONS

See Chapter 538.

ARTERIOVENOUS MALFORMATION

AVMs are direct connections of artery to vein that bypass the capillary bed (Fig. 691.3). AVMs of the skin are very rare. Skin changes are often noted at birth, but they tend to be very subtle, presenting as a red-pink patch. Over time the lesions deepen in color and often result in thickening of the skin and surrounding tissue. They are diagnosed from their obvious arterial palpation. Some AVMs are progressive and can lead to significant morbidity and even mortality, so early diagnosis and evaluation by an experienced multidisciplinary team are essential.

KLIPPEL-TRENAUNAY AND PARKES-WEBER SYNDROMES

Klippel-Trenaunay syndrome is a term historically used to describe complex mixed vascular malformation with overgrowth of bone and soft tissue (Figs. 691.4 and 691.5). The anomaly is present at birth and usually involves a lower limb but may involve more than one limb, as well as portions of the trunk or face. Enlargement of the soft tissues may be gradual and may involve the entire extremity, a portion of it, or selected digits. The vascular lesion most often is a capillary malformation, generally localized to the hypertrophied area. The deep venous system may be absent or hypoplastic. Venous blebs and/or vesicular lymphatic lesions may be present on the malformation's surface. Thick-walled venous varicosities typically become apparent ipsilateral to the vascular malformation after the child begins to ambulate. If there is an associated AVM, the disorder is called **Parkes-Weber syndrome**.

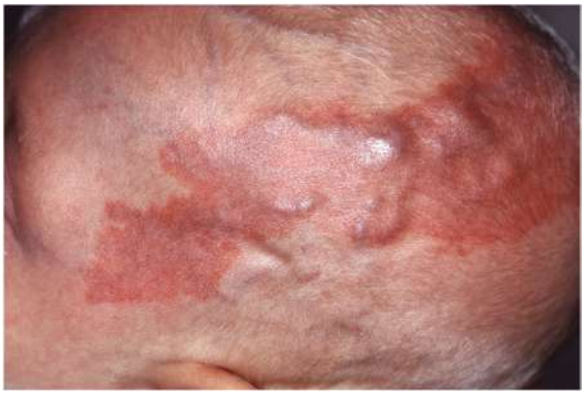

Fig. 691.3 Arteriovenous malformation in conjunction with a port-wine stain of the scalp of a newborn.

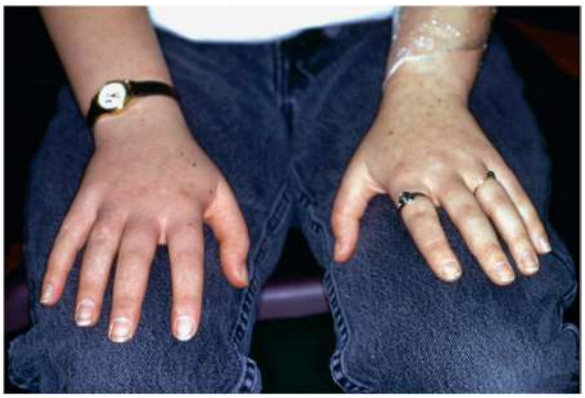

Fig. 691.4 Overgrowth of the right arm and hand in an adolescent with Klippel-Trenaunay syndrome.

Somatic pathogenic activating variants in multiple genes have been associated with vascular malformations and limb overgrowth (Fig. 691.6 and Table 691.3).

These disorders can be confused with Maffucci syndrome or, if the surface vascular lesion is minimal, with Milroy disease. Pain, limb swelling, and cellulitis may occur. Thrombophlebitis, dislocations of joints, hematuria secondary to angiomatous involvement of the urinary tract, rectal bleeding from lesions of the gastrointestinal tract, pulmonary lesions, and malformations of the lymphatic vessels are infrequent complications. MRI may delineate the extent of the anomaly, but surgical correction or palliation is often difficult. Sclerotherapy or endovenous laser ablation may be of benefit when a venous component is the dominant vessel in the malformation. The indications for radiologic studies of viscera and bones are best determined by clinical evaluation. Supportive care includes compression bandages for varicosities; surgical treatment may help carefully selected patients. Leg-length differences should be treated with orthotic devices to prevent the development of spinal deformities. Corrective bone surgery may eventually be needed to treat significant leg-length discrepancy.

Angiokeratoma Circumscriptum

Several forms of angiokeratoma have been described. Angiokeratomas are characterized by ectasia of superficial lymphatic vessels and capillaries with hyperkeratosis of the overlying epidermis. Angiokeratoma circumscriptum is a rare disorder consisting of a solitary lesion or multiple lesions that manifest as a plaque or plaques of blue-red crusted papules or nodules. The limbs are the sites of predilection. **If therapy is desired, surgical excision is the treatment of choice.**

Cutis Marmorata Telangiectatica Congenita

Cutis marmorata telangiectatica congenita, a benign vascular anomaly apparent at birth, is composed of dilated superficial capillaries and veins. Involved areas of skin have a reticulated red or purple hue that resembles physiologic cutis marmorata but is more pronounced and relatively unvarying (Fig. 691.7). The lesions may be restricted to a single limb and a portion of the trunk or may be more widespread. The lesions become more pronounced during changes in environmental temperature, physical activity, or crying. In some cases, the underlying subcutaneous tissue is atrophic, and ulceration may occur within the reticulated bands. Rarely, defective growth of bone and other congenital abnormalities may be present. No specific therapy is indicated. Mild vascular-only cases may show gradual improvement. Cutis marmorata telangiectatica congenita may be associated with CM, Adams-Oliver syndrome, patent ductus arteriosus, and a variety of other anomalies. It must be differentiated from reticulate CM and physiologic cutis marmorata.

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus is a rare syndrome consisting of numerous venous malformations of the skin, mucous membranes, and gastrointestinal tract caused by somatic pathogenic variants in *TEK* in some patients. Typical lesions are blue-purple and rubbery in consistency; they vary in size from a few millimeters to a few centimeters in diameter. They are sometimes painful or tender. The compressible nodules may be present at birth but usually are progressive during childhood. New lesions may continue to develop throughout life. Large disfiguring and irregular blue marks may also occur. The lesions, which can rarely be located in the liver, spleen, and central nervous system in addition to the skin and gastrointestinal tract, do not involute spontaneously. Recurrent gastrointestinal hemorrhage caused by lesions in the gastrointestinal tract may lead to severe anemia. Palliation can be achieved by excision of involved bowel.

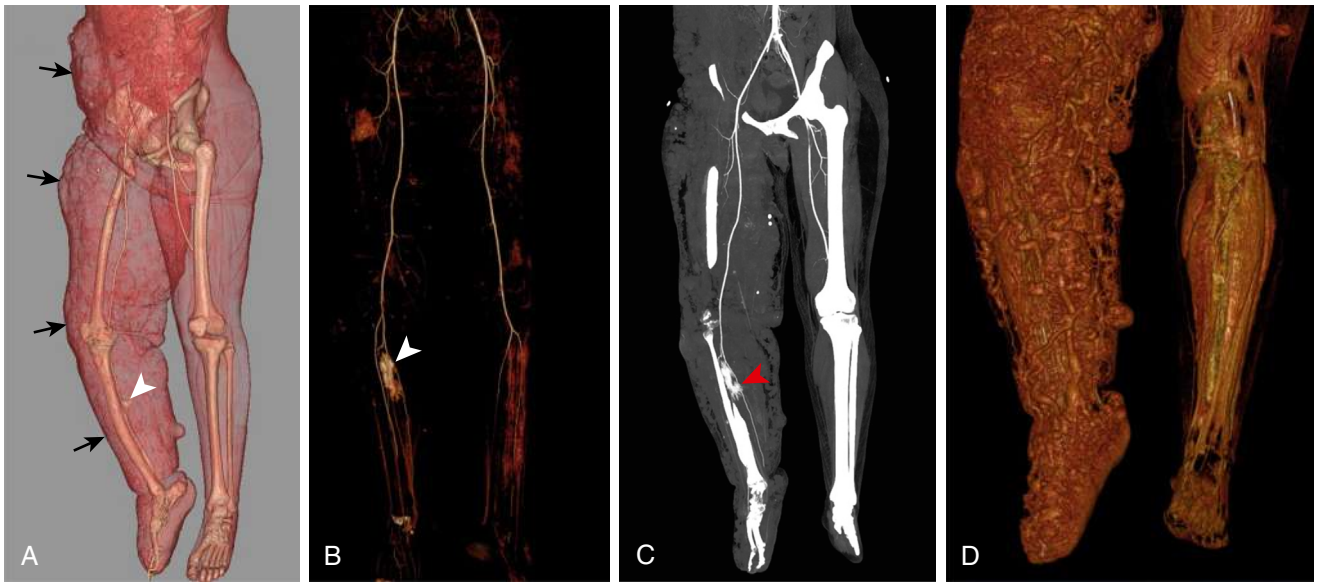

Fig. 691.5 Parkes-Weber syndrome. **A**, Three-dimensional volume-rendering CT angiography image of the limbs shows overgrowth of the right limb *(arrows)* with an arterial blush adjacent to the posterior tibial artery (*arrowhead*), consistent with a high-flow vascular malformation. **B**, Three-dimensional volume-rendering CT angiography image of the limbs shows arterial blush adjacent to the posterior tibial artery *(arrowhead)*. **C**, Coronal CT angiography image of the limb shows arterial blush adjacent to the posterior tibial artery *(arrowhead)*. **D**, Venous phase CT of the limb reveals varicose veins in the right limb. *(From Ufuk F. Limb overgrowth with vascular anomalies. J Pediatr. 2020;240:308–309, Fig, p. 309)*

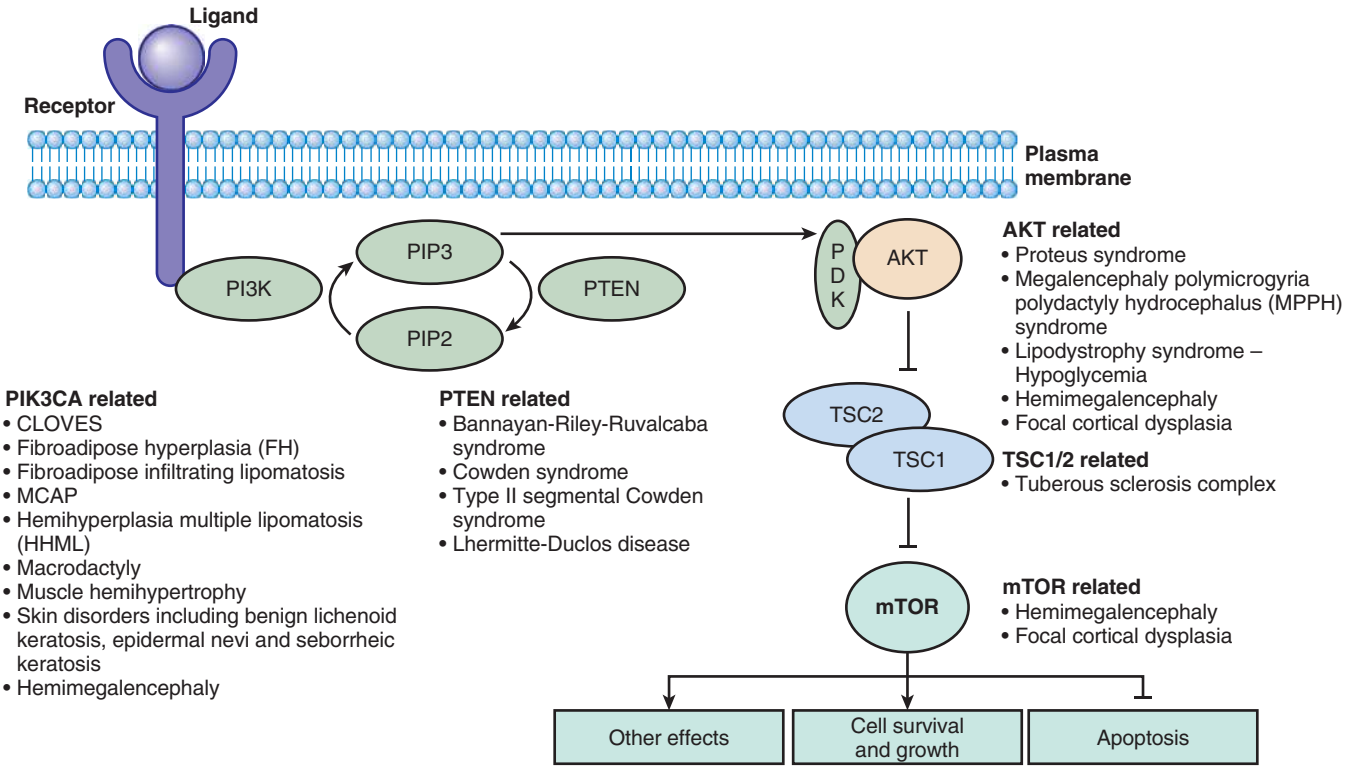

Fig. 691.6 Simplified PIK3CA-AKT-mTOR pathway and associated clinical overgrowth disorders. PIP, Phosphatidylinositol polyphosphate; PTEN, phosphatase and tensin homolog; PDK, phosphatidylinositol-dependent kinase. *(From Kang HC, Baek ST, Song S, Gleeson JG. Clinical and genetic aspects of the segmental overgrowth spectrum due to somatic mutations in PIK3CA. J Pediatr. 2015;167[5]:957–962, Fig, p. 959)*

PHAKOMATOSIS PIGMENTOVASCULARIS

Phakomatosis pigmentovascularis is a rare disorder characterized by the association of a capillary malformation and melanocytic lesions. Typically, the capillary malformation is extensive, and associated pigmentary lesions may include dermal melanocytosis, café-au-lait macules, or a nevus spilus (speckled nevus). Nonpigmented skin lesions that may occur in this setting include nevus anemicus and epidermal nevi. Systemic anomalies are seen in rare cases.

NEVUS ANEMICUS

Although present at birth, nevus anemicus may not be detectable until early childhood. The nevus consists of solitary or numerous sharply

Table 691.3 Clinical Diagnostic Criteria for *PIK3CA*-Related Overgrowth Spectrum (PROS)

REQUIRED CRITERIA

1. The presence of somatic *PIK3CA* pathogenic variant (if the pathogenic variant cannot be defined, then the disease is regarded as a presumptive PROS disorder)
2. Congenital or early childhood onset
3. Sporadic, without family history and mosaic distribution
4. Affected patients can have one or more findings from category A or B

CATEGORY A (MORE THAN 2 FEATURES)*	CATEGORY B (ISOLATED FEATURES)
1. Adipose, muscle, nerve, and skeletal overgrowth	1. Large, isolated LM
2. Capillary, venous, arteriovenous, and/or LMs	2. Isolated macrodactyly,† overgrown and splayed feet/hands, or overgrown limbs
3. Epidermal nevus	3. Truncal adipose overgrowth
	4. Hemi- or bilateral dysplastic megalencephaly or focal cortical dysplasia type 2
	5. Epidermal nevus
	6. Seborrheic keratosis
	7. Benign lichenoid keratoses

*Typically progressive. Can manifest as scoliosis (kyphosis), limb overgrowth, central nervous system (hydrocephalus, cerebellar tonsillar ectopia, Chiari, megalencephaly, mega corpus callosum), regional lipomatous undergrowth with overgrowth, infiltrating lipomatosis, or Wilms tumor/ovarian cystadenoma.

†Other terms include macrodystrophia lipomatosa, macrodactylia fibrolipomatosis, and gigantism.

From Kang HC, Baek ST, Song S, Gleeson JG. Clinical and genetic aspects of the segmental overgrowth spectrum due to somatic mutations in *PIK3CA*. *J Pediatr*. 2015;167(5):957–962, Table 1.

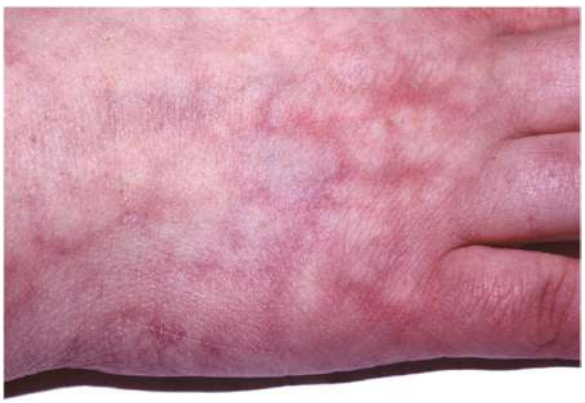

Fig. 691.7 Mottled pattern of cutis marmorata telangiectatica congenita on the right hand.

delineated, pale macules or patches that are most often on the trunk but may also occur on the neck or limbs. These nevi may simulate plaques of vitiligo, leukoderma, or nevoid pigmentary defects, but they can be readily distinguished because of their response to firm stroking. Stroking evokes an erythematous line and flare in normal surrounding skin, but the skin of a nevus anemicus does not redden. They can also be diagnosed by diascopy, in which pressure of the skin with a glass slide will obscure the borders of a nevus anemicus. Although the cutaneous vasculature appears normal histologically, the blood vessels within the nevus do not respond to injection of vasodilators. It has been postulated that the persistent pallor may represent a sustained localized adrenergic vasoconstriction.

VASCULAR TUMORS

Vascular tumors include infantile hemangiomas (IHs), tufted angiomas, kaposiform hemangioendotheliomas (KHEs), congenital hemangiomas, and additional more rare entities.

Infantile Hemangioma

IHs are proliferative benign vascular tumors of vascular endothelium that may be present at birth or, more commonly, may become apparent in the first or second week of life, predictably enlarge, and then spontaneously involute. IHs are the most common tumor of infancy, occurring in 5% of newborns. Risk factors include prematurity, low birthweight, female gender, and White race. IHs should be classified as superficial, deep, or mixed (Fig. 691.8). The terms *strawberry* and *cavernous* should not be used to describe hemangiomas. The immunohistochemical marker GLUT-1 is specifically expressed in an IH, which helps distinguish it histologically from other vascular anomalies. Superficial IHs are bright red, protuberant, compressible, sharply demarcated lesions that may occur on any area of the body (Fig. 691.9, see also Fig. 691.8). Although sometimes present at birth, they more often appear in the first or second month of life and are heralded by an erythematous or blue mark or an area of pallor, which subsequently develops a fine telangiectatic pattern before the growth phase (see Fig. 691.9). The presenting sign may occasionally be an ulceration of the perineum or lip. Favored sites are the face, scalp, back, and anterior chest; lesions may be solitary or multiple. Patterns of facial involvement include frontotemporal, maxillary, mandibular, and frontonasal regions. IHs that are more deeply situated are more diffuse and are less defined than superficial IHs. The lesions are cystic, firm, or compressible, and the overlying skin may appear normal in color or may have a bluish hue (Fig. 691.10).

Most IHs are mixed, having both superficial and deep components. IHs undergo a phase of rapid expansion, followed by a stationary period and finally by spontaneous involution (Fig. 691.11). Regression may be anticipated when the lesion develops pale gray areas centrally. The course of a particular lesion is unpredictable, but approximately 60% of these lesions reach maximal involution by 5 years of age and 90–95% by 9 years. Spontaneous involution cannot be correlated with size or site of involvement, but lip lesions seem to persist most often. Complications include impairment of a vital function, ulceration, secondary infection, and permanent disfigurement. The location of a lesion may interfere with a vital function (e.g., on an eyelid interfering with vision, on the urethra with urination, on the airway with respiration). IHs in a "beard" distribution may be associated with upper airway or subglottic involvement. Stridor should suggest a tracheobronchial lesion. Large visceral (hepatic) IHs may be complicated by coexistent hypothyroidism because of type 3 iodothyronine deiodinase; symptoms may be difficult to detect in this age-group. Table 691.4 lists other concerning features.

In the usual patient with an IH who has no serious complications or extensive growth resulting in tissue destruction and severe disfigurement, treatment consists of expectant observation. Because almost all lesions regress spontaneously, therapy is rarely indicated. Parents require repeated reassurance and support. After spontaneous involution, many patients are left with small cosmetic defects, such as telangiectasia, hypopigmentation, fibrofatty deposits, and scars if the lesion has ulcerated. Residual telangiectasias may be treated with pulsed dye laser therapy. Other defects can be treated or minimized by judicious surgical repair if desired.

In the rare case in which intervention is required, topical timolol solution (1 drop of 0.5% gel-forming solution applied twice each day) is effective, especially in small, superficial, nonulcerating, and nonmucosal IH. Topical timolol treatment is a very safe alternative to observation alone for a superficial IH. Timolol solution may also be used with caution in the treatment of an ulcerated IH, with or without occlusion.

In a disfiguring, life- or vision-threatening, or ulcerated IH that is not responding to other treatment, oral propranolol is the first-line treatment. IHs typically respond with growth arrest and often early signs of involution within a couple of weeks of treatment initiation. Dosing varies ranging from 1 to 3 mg/kg/day, though best outcomes occur at 3 mg/kg/day with no increase in side effects. Some recommend inpatient initiation of propranolol for infants younger than 8 weeks gestational age or those with comorbid conditions. The dose is initiated at 1 mg/kg/day divided into three doses with heart rate and blood pressure monitoring at 1 and 2 hours after each dose. If that dose is tolerated, the dose is increased to 2 mg/kg/day divided

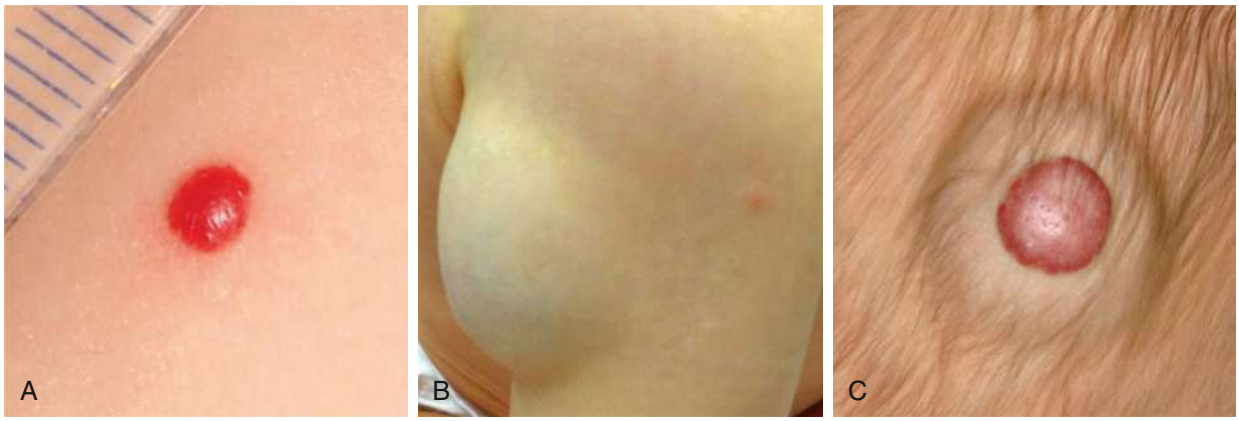

Fig. 691.8 Types of infantile hemangiomas according to anatomic location. **A,** Bright red, superficial hemangioma. **B,** Bluish, deep hemangioma. **C,** Mixed type. *(From Léaute-Labréze C, Harper JI, Hieger PH. Infantile haemangioma. Lancet. 2017;390:85–94, Fig. 4, p. 88.)*

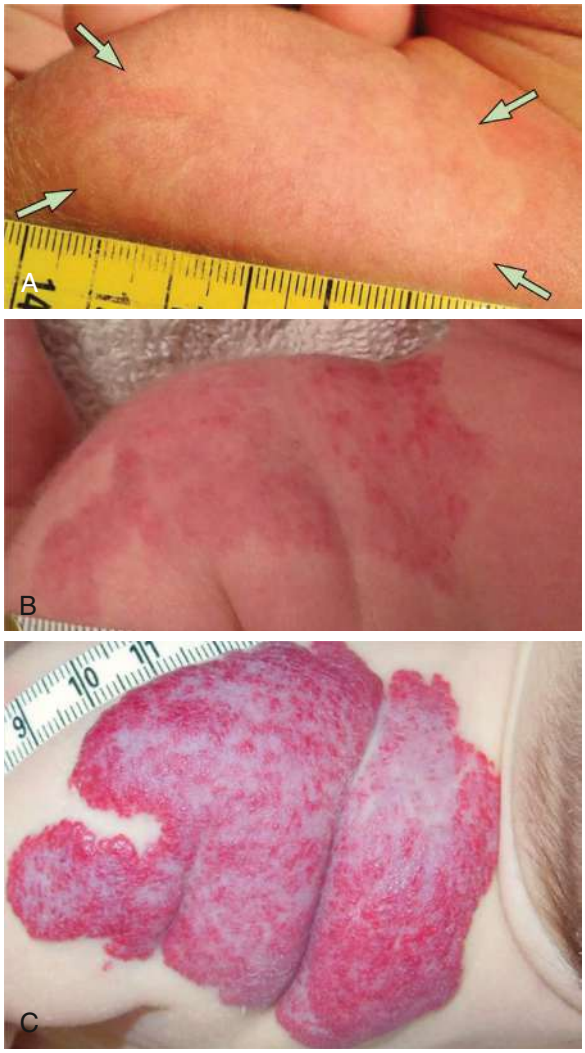

Fig. 691.9 Precursor lesions of infantile hemangioma. Figure shows a sharply demarcated, so-called anemic spot on the left shoulder. **A,** Day 3. **B,** Day 21. **C,** Day 90. *(From Léaute-Labréze C, Harper JI, Hieger PH. Infantile haemangioma. Lancet. 2017;390:85–94, Fig. 3, p. 87.)*

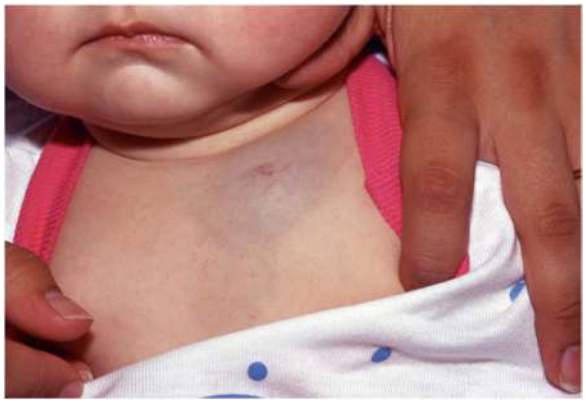

Fig. 691.10 Deep infantile hemangioma of the chest.

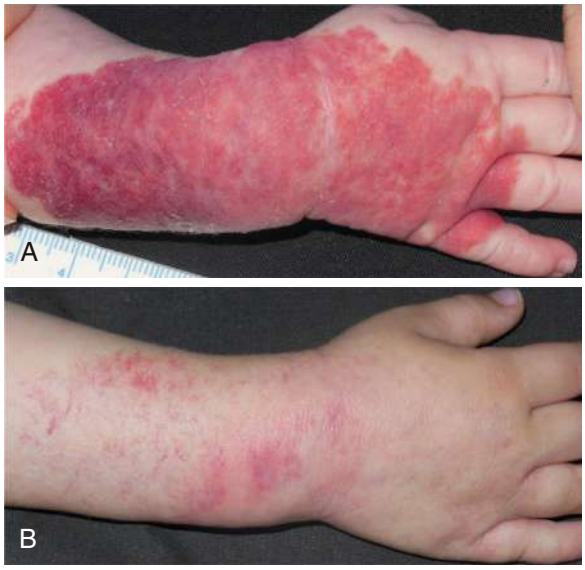

Fig. 691.11 Spontaneous regression of infantile hemangioma. **A,** Hemangioma on right lower arm, age 14 wk. **B,** Residual telangiectasia at age 23 mo. *(From Léaute-Labréze C, Harper JI, Hieger PH. Infantile haemangioma. Lancet. 2017;390:85–94, Fig. 5, p. 88.)*

into three doses. The outpatient initiation assumes good social support and access to the hospital. The initial dose and monitoring are similar to the inpatient plan; if the dose is tolerated for 3-7 days, the dose is increased to 1.5 mg/kg/day. If the latter dose is tolerated after 3-7 days, the dose is increased to 2 mg/kg/day. In all situations, propranolol must be given a minimum of 6 hours after the last dose. Risks of propranolol treatment include hypoglycemia, bradycardia, hypotension, gastroesophageal reflux disease or

Table 691.4 Clinical "Red Flags" Associated with Hemangiomas

CLINICAL FINDING	RECOMMENDED EVALUATION
Facial hemangioma involving significant area of face (>5 cm)	Evaluate for PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities): MRI and MRA of brain, neck, orbit
	Cardiac, ophthalmologic evaluation
	Evaluate for midline abnormality: supraumbilical raphe, sternal atresia, cleft palate, thyroid abnormality
Cutaneous hemangiomas in beard distribution	Evaluate for airway hemangioma, especially if manifesting with stridor
Periocular hemangioma	MRI of orbit Ophthalmologic evaluation
Paraspinal midline vascular lesion	Ultrasonography or MRI to evaluate for occult spinal dysraphism
Multifocal infantile hemangiomas (>5 cm)	Evaluate for parenchymal hemangiomas, especially hepatic/central nervous system Guaiac stool test, liver ultrasound
Large hemangioma, especially hepatic	Ultrasonography with Doppler flow study
	MRI
	TSH to detect associated hypothyroidism
Thrill and/or bruit associated with hemangioma	Consider cardiac evaluation and echocardiography to rule out diastolic reversal of flow in aorta
	MRI to evaluate extent and flow characteristics
Perineal segmental hemangioma	MRI of spine, kidneys to detect LUMBAR/PELVIS/SACRAL syndrome

LUMBAR, Lower body infantile hemangiomas and other skin defects, urogenital anomalies and ulceration, myelopathy, bony deformities, anorectal malformations and arterial anomalies, renal anomalies; PELVIS, perineal hemangioma, external genital malformations, lipomyelomeningocele, vesicorenal anomalies, imperforate anus, skin tag; SACRAL, spinal dysraphism, anogenital anomalies, cutaneous anomalies, renal/urologic anomalies, angioma in lumbosacral location.
Modified from Blei F. Vascular anomalies: from bedside to bench and back again. *Curr Probl Pediatr Adolesc Health*. 2002;32:67–102.

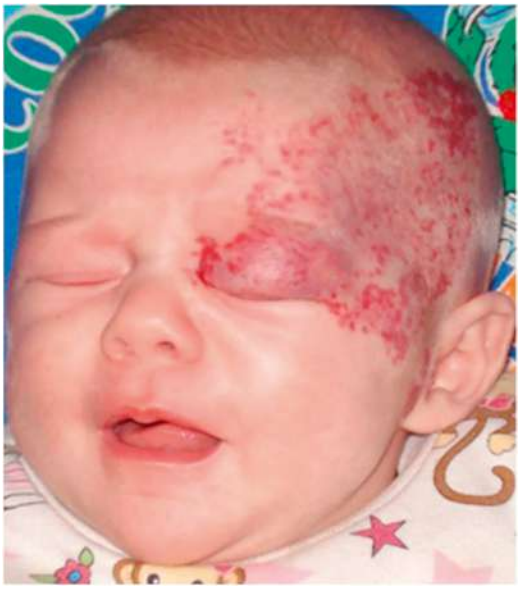

Fig. 691.12 Large segmental infantile hemangioma of the face in a 2-mo-old infant with definite PHACE. *(From Garzon MC, Epstein LG, Heyer GL, et al. PHACE syndrome: consensus-derived diagnosis and care recommendations. J Pediatr. 2016;178:24–33, Fig. 1, p. 25.)*

worsening of existing disease, hyperkalemia, and bronchospasm/wheezing. Nonetheless, reports of side effects of propranolol used for IH treatment are rare. Increased propranolol levels occur with inhibitors of CYP2D6 (cimetidine, amiodarone, fluoxetine, quinidine, ritonavir) and CPY1A2 (cimetidine, ciprofloxacin, isoniazid, ritonavir, theophylline); decreased blood levels occur with inducers of hepatic drug metabolism (rifampin, phenytoin, phenobarbital).

In patients unable to tolerate propranolol, or if the IH has not responded after a couple of weeks of treatment, systemic oral corticosteroids may be used. Termination of growth and sometimes regression may be evident after 2-4 weeks of therapy. When a response is obtained, the dose should be decreased gradually, though most patients will require treatment until about 1 year of age.

Intralesional corticosteroid injection by an experienced physician can also induce rapid involution of a localized IH but has risks of ulceration, tissue atrophy, and blindness if used near the orbit. Vincristine is used by some oncologists to treat significant IH. Interferon-α therapy may also be effective, but spastic diplegia is seen in 10% of cases. Use of these therapies has become less necessary since the introduction of propranolol.

In patients with large segmental IH of the face, **PHACES** syndrome should be considered (Fig. 691.12 and Table 691.5). PHACES stands for **p**osterior fossa brain defects such as Dandy-Walker malformation or cerebellar hypoplasia, large segmental facial infantile **h**emangioma, **a**rterial cerebrovascular abnormalities such as aneurysms and stroke, **c**oarctation of the aorta, and **e**ye abnormalities. **S**ternal raphe defects such as pits, scars, or **s**upraumbilical raphe are infrequently observed. Evaluation of children at risk for PHACES is important both to detect any underlying abnormalities and before starting systemic therapy, which may be indicated given the size and location of the IH typically associated with this syndrome. PHACES children with cervical and intracranial arterial abnormalities are at increased risk of cerebrovascular accidents, and specialized care by an experienced multidisciplinary team is essential.

Multifocal Infantile Hemangioma

Diffuse neonatal hemangiomatosis (or benign neonatal hemangiomatosis) is a historical term to describe a condition in which numerous or multifocal vascular lesions are widely distributed (Fig. 691.13). Several distinct diagnoses have been previously lumped together under this clinical phenotype with mortality cited as high as 60–80%. Upon further analysis, this group of disorders has been found to comprise several distinct entities, which are important to distinguish from one another, given their varying prognoses and management strategies. Therefore the term *multifocal IH* is more accurate and leads to correct treatments and prognosis for these patients with more than one cutaneous (and/or visceral) IH.

Multifocal IHs may occur in the skin and visceral organs, but remain GLUT-1–positive when biopsied, have a relatively good prognosis with low morbidity, and respond to systemic propranolol just as solitary cutaneous IH. Patients with more than five cutaneous IH should undergo an abdominal physical exam and possibly liver ultrasound to detect liver IH, which can grow quite large (Fig. 691.14).

Multifocal lymphangioendotheliomatosis (also known as cutaneovisceral angiomatosis) also presents with many vascular tumors in the skin and visceral organs but is GLUT-1–negative and complicated by

Table 691.5 PHACES Diagnostic Criteria: Revised

ORGAN SYSTEMS	MAJOR CRITERIA	MINOR CRITERIA
Arterial anomalies	Anomaly of major cerebral or cervical arteries* Dysplasia† of the large cerebral arteries Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate-severe hypoplasia of the large cerebral and cervical arteries Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries)	Aneurysm of any of the cerebral arteries
Structural brain	Posterior fossa brain anomalies Dandy-Walker complex Other hypoplasia/dysplasia of the mid and/or hind brain	Midline brain anomalies Malformation of cortical development
Cardiovascular	Aortic arch anomalies Coarctation of the aorta Dysplasia* Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch/double aortic arch Systemic venous anomalies
Ocular	Posterior segment abnormalities Persistent hyperplastic primary vitreous Persistent fetal vasculature Retinal vascular anomalies Morning glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma	Anterior segment abnormalities Microphthalmia Sclerocornea Coloboma Cataracts
Ventral/midline	Anomaly of the midline chest and abdomen • Sternal defect • Sternal pit • Sternal cleft • Supraumbilical raphe	Ectopic thyroid hypopituitarism Midline sternal papule/hamartoma

DEFINITE PHACE

Hemangioma >5 cm in diameter of the head including scalp PLUS one major criteria or two minor criteria	Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS two major criteria

POSSIBLE PHACE

Hemangioma >5 cm in diameter of the head including scalp PLUS one minor criteria	Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS one major or two minor criteria	No hemangioma PLUS two major criteria

*Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
†Includes kinking, looping, tortuosity, and/or dolichoectasia.
From Garzon MC, Epstein LG, Heyer GL, et al. PHACE syndrome: consensus-derived diagnosis and care recommendations. *J Pediatr.* 2016;178:24–33, Table II.

severe thrombocytopenia and gastrointestinal bleeding with high mortality. Accurate diagnosis in patients who present with multifocal vascular tumors is critical so early, appropriate management may be initiated.

Congenital Hemangioma

Congenital hemangiomas are benign vascular tumors that are present typically at birth. They are most often red or blue hued with telangiectasia and may have a ring of pallor. They do not undergo further growth after delivery as IHs do. Changes after delivery occur along a spectrum, and the lesion may stay stable **(noninvoluting congenital hemangiomas [NICH])**, partially involute (**partially involuting congenital hemangiomas [PICH]**), or decrease rapidly in size, leaving fibrofatty residual tissue behind **(rapidly involuting congenital hemangiomas [RICH])**. They are distinguishable from IH because of their clinical course and negative GLUT-1 markers on histopathology. It is also important to note the difference because CH do not respond to propranolol.

Kaposiform Hemangioendothelioma

KHE is a rare and potentially life-threatening vascular tumor. KHE classically presents as a red to purple firm plaque on the lateral neck, axilla, trunk, or extremities. Visceral tumors occur as well. Lesions may occasionally get smaller over time but rarely resolve completely. Tufted angioma, once thought to be a separate tumor on the same clinical spectrum as KHE, is considered under the umbrella term of KHE (Fig. 691.15). The main complication of these tumors is the development of **Kasabach-Merritt phenomenon (KMP)**, which may be fatal; therefore early diagnosis and treatment are important. Oral sirolimus may be helpful to stabilize and sometimes shrink these tumors. Retroperitoneal or intrathoracic lesions in the absence of cutaneous lesions are uncommon but are often associated with KMP.

Kasabach-Merritt Phenomenon

KMP is a life-threatening combination of a rapidly enlarging KHE, thrombocytopenia, microangiopathic hemolytic anemia, and an acute

or chronic consumption coagulopathy. The clinical manifestations are usually evident during early infancy. The vascular lesion is usually cutaneous and is only rarely located in viscera. The associated thrombocytopenia may lead to precipitous hemorrhage accompanied by ecchymoses, petechiae, and a rapid increase in the size of the vascular lesion. Severe anemia from hemorrhage or microangiopathic hemolysis may ensue. Thrombocytopenia is present, but the bone marrow contains increased numbers of normal or immature megakaryocytes. The thrombocytopenia has been attributed to sequestration or increased destruction of platelets within the lesion. Hypofibrinogenemia and decreased levels of consumable clotting factors are relatively common (see Chapter 533.6).

Treatment includes surgical excision of small lesions, although this is often difficult because of coagulopathy. Additional pharmacologic treatments include systemic steroids with or without vincristine as first-line therapy in most cases. Antiplatelet, antifibrinolytic, and other chemotherapeutic agents have been used with mixed results. Initial studies of sirolimus therapy have been promising. The mortality rate overall once patients have KMP is significant.

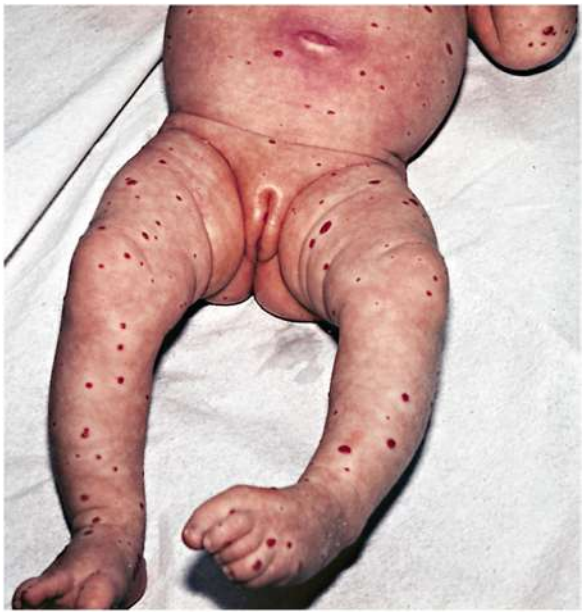

Fig. 691.13 Multifocal cutaneous and systemic (liver) infantile hemangiomas. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology, 2nd ed. Philadelphia: Saunders; 2008:359.)*

Pyogenic Granuloma (Lobular Capillary Hemangioma)

A pyogenic granuloma (PG) is a small, red, glistening, sessile, or pedunculated papule that often has a discernible epithelial collarette (Fig. 691.16). The surface may be weeping and crusted or completely epithelialized. PGs initially grow rapidly, may ulcerate, and bleed easily

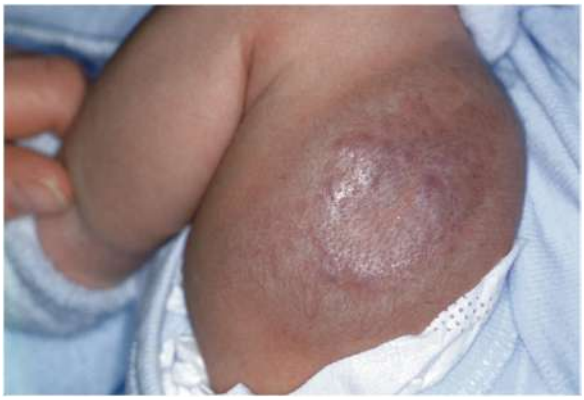

Fig. 691.15 Nodular tufted angioma on the left thigh.

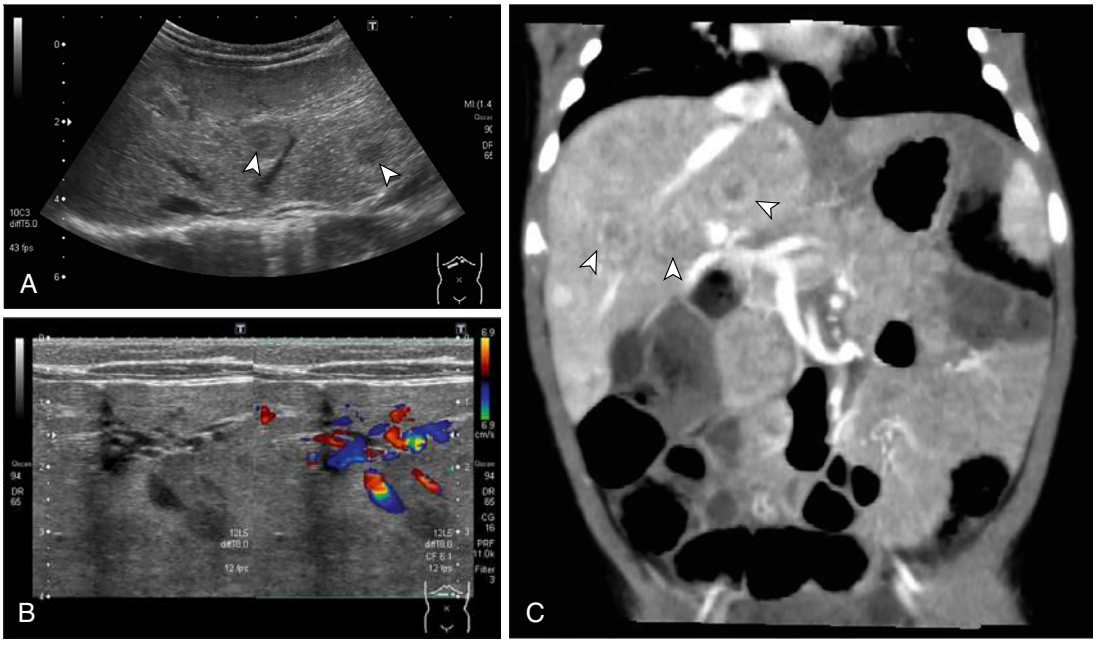

Fig. 691.14 Multifocal infantile hemangioma. **A,** Multiple hypoechoic lesions *(arrowheads)*. **B,** Arteriovenous shunting on ultrasound. **C,** Multiple hypervascular masses in the liver on computed tomography *(arrowheads)*. *(From Uda K, Okubo Y, Matushima T, et al. Multifocal infantile hemangioma. J Pediatr. 2019;210:238, Fig. 2, p. 238.e1.)*

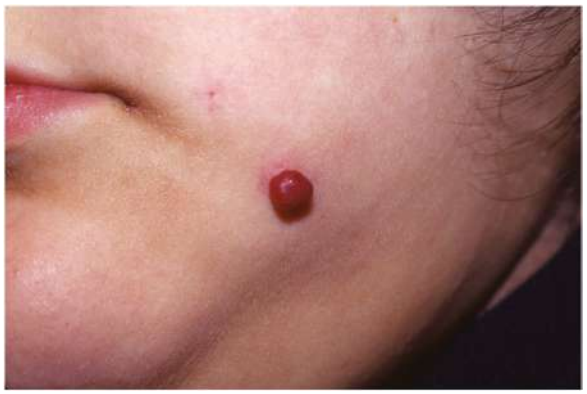

Fig. 691.16 Pyogenic granuloma on the left cheek.

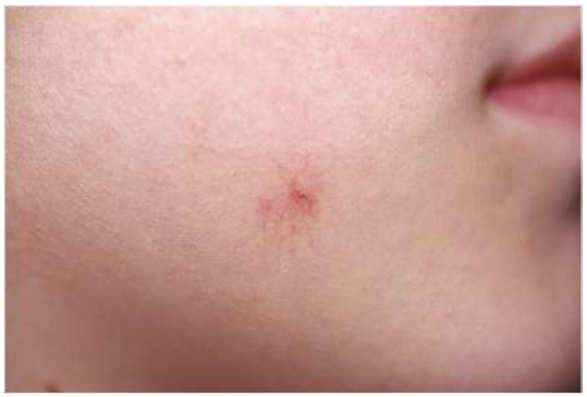

Fig. 691.17 Spider angioma with visible central arteriole component.

when traumatized because they consist of exuberant granulation tissue. They are relatively common in children, particularly on the face, arms, and hands. Such a lesion located on a finger or hand may appear as a subcutaneous nodule. PGs may arise at sites of injury, but a history of trauma often cannot be elicited.

PGs are benign but a nuisance because they bleed easily with trauma and may recur if incompletely removed. Numerous satellite papules have developed after surgical excision of PGs from the back, particularly in the interscapular region. Small lesions may regress after cauterization with silver nitrate; larger lesions require excision and electrodesiccation of the base of the granuloma. Small (<5 mm) lesions may be treated successfully with pulsed dye laser therapy.

Angiokeratoma of Mibelli

Angiokeratoma of Mibelli is characterized by 1- to 8-mm red, purple, or black scaly, verrucous, occasionally crusted papules and nodules that appear on the dorsum of the fingers and toes and on the knees and the elbows. Less commonly, palms, soles, and ears may be affected. In many patients, onset has followed frostbite or chilblains. These nodules bleed freely after injury and may involute in response to trauma. They may be effectively eradicated by cryotherapy, electrofulguration, excision, or laser ablation.

Spider Angioma

A vascular spider (nevus araneus) consists of a central feeder artery with many dilated radiating vessels and a surrounding erythematous flush, varying from a few millimeters to several centimeters in diameter (Fig. 691.17). Pressure over the central vessel causes blanching; pulsations visible in larger nevi are evidence for the arterial source of the lesion. Spider angiomas are associated with conditions in which there are increased levels of circulating estrogens, such as cirrhosis and pregnancy, but they also occur in up to 15% of normal preschool-age children and 45% of school-age children. Sites of predilection in children are the dorsum of the hand, forearm, nose, infraocular region, lips, and ears. Lesions often regress spontaneously after puberty. If removal is desired, pulsed dye laser therapy is the mode of choice; resolution is achieved in 90% of cases with a single treatment.

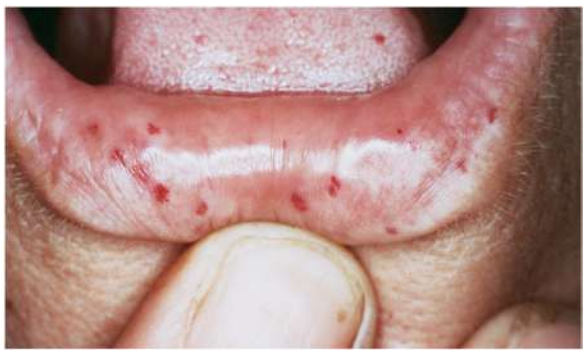

Fig. 691.18 Hereditary hemorrhagic telangiectasia. Telangiectases are found on the lips, oral mucosa, nasal mucosa, skin, and conjunctiva. Epistaxis is the most common manifestation of the disease. Blood transfusions may be required. *(From Habif TP. Clinical Dermatology: A Color Guide to Diagnosis and Therapy, 4th ed. Philadelphia: Mosby; 2004: Fig. 23.22, p. 831.)*

Maffucci Syndrome

The association of spindle cell hemangiomas with nodular enchondromas in the metaphyseal or diaphyseal cartilaginous portion of long bones is known as *Maffucci syndrome.* Maffucci syndrome is caused by somatic mosaic pathogenic variants in the *IDH1* and *IDH2* genes. Vascular lesions are typically soft, compressible, asymptomatic, blue to purple subcutaneous masses that grow in proportion to a child's growth and stabilize by adulthood. Mucous membranes or viscera may also be involved. Onset occurs during childhood. Bone lesions may produce limb deformities and pathologic fractures. Malignant transformation of enchondromas (chondrosarcoma, angiosarcoma) or primary malignancies (ovarian, fibrosarcoma, glioma, pancreatic) may be a complication (see Chapter 550).

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Hereditary hemorrhagic telangiectasia (HHT), which is inherited as an autosomal dominant trait, occurs in two types. The gene in **HHT-1** encodes *ENG,* a membrane glycoprotein on endothelial cells that binds transforming growth factor-β. **HHT-2** is caused by pathogenic variants in the *ACVRL1* gene and is associated with increased risk for hepatic involvement and pulmonary hypertension. **HHT-juvenile polyposis syndrome** is caused by a pathogenic variant in *SMAD4.*

Affected children usually experience recurrent epistaxis before detection of the characteristic skin and mucous membrane lesions. The mucocutaneous lesions, which usually develop at puberty, are 1- to 4-mm, sharply demarcated, red to purple macules, papules, or spider-like projections, each composed of a tightly woven mat of tortuous telangiectatic vessels (Fig. 691.18). The nasal mucosa, lips, and tongue are usually involved; less commonly, cutaneous lesions occur on the face, ears, palms, and nail beds. Vascular ectasias may also arise in the conjunctivae, larynx, pharynx, gastrointestinal tract, bladder, vagina, bronchi, brain, and liver. Diagnostic criteria include spontaneous recurrent epistaxis, telangiectasias (oral, nose, fingers), visceral lesions (gastrointestinal telangiectasias,

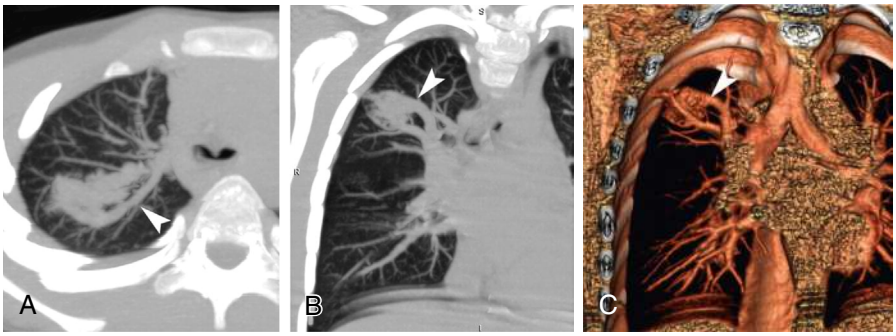

Fig. 691.19 Chest multislice spiral CT in a patient showing a large pulmonary arteriovenous malformation in the posterior segment of right upper lobe *(arrowhead)*. **A**, Axial maximum intensity projection image. **B**, Coronal maximum intensity projection image. **C**, Three-dimensional volume rendering. *(From Giordano P, Lenato GM, Suppressa P, et al. Hereditary hemorrhagic telangiectasia: arteriovenous malformations in children. J Pediatr. 2013;163:179–186, Fig. 1, p. 182.)*

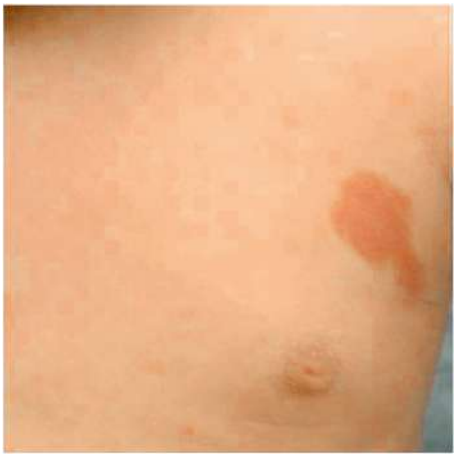

Fig. 691.20 Infant with CM-AVM syndrome and a typical-appearing CM-AVM stain of the left chest. This lesion demonstrates high flow on Doppler evaluation, differentiating it from classic CM. In CM-AVM syndrome, the lesions tend to be multifocal, with more arising over time. *(From Eichenfield LF, Frieden IJ, eds. Neonatal and Infant Dermatology, 3rd ed. Philadelphia: Elsevier; 2015: Fig. 22.14, p. 363.)*

pulmonary or hepatic or cerebral AVMs), and first-degree relative with HHT.

Massive hemorrhage is the most serious complication of HHT and may result in severe anemia. Bleeding may occur from the nose, mouth, gastrointestinal tract, genitourinary tract, or lungs; epistaxis is often the only complaint, occurring in 80% of patients. Approximately 15–20% of patients with AVMs in the lungs present with stroke due to embolic abscesses (Fig. 691.19). Hepatic encephalopathy in the presence of normal liver function may occur with a hepatic AVM. Persons with HHT have normal levels of clotting factors and an intact clotting mechanism. In the absence of serious complications, the life span of a person with HHT is normal. Local lesions may be ablated temporarily with chemical cautery or electrocoagulation. More drastic surgical measures may be required for lesions in critical sites, such as the lung or gastrointestinal tract. Bevacizumab, an anti–vascular endothelial growth factor agent, has been effective in treating affected patients with HHT who have high cardiac output secondary to hepatic AVMs. The nasal spray form of bevacizumab may be beneficial therapy for epistaxis.

Capillary Malformation–Arteriovenous Malformation Syndrome (CM-AVM)

CM-AVM is an autosomal dominant disorder caused by pathogenic variants in *RASA1* (CM-AVM-1) or *EPHB4* (CM-AVM-2) and is characterized by multiple atypical-appearing macules or patches that are present at birth, suggestive of microcutaneous AVMs that look like capillary malformations (Fig. 691.20). Lesions that are present at birth will enlarge and darken with increasing age. Some lesions have peripheral pallor (**halo effect**). In addition, associated high-flow AVMs may be present in the brain, spinal cord, or skin. Arteriovenous fistulas have also been reported. Pulse dye laser treatment may be effective for cutaneous lesions, whereas embolization is indicated for AVMs.

Ataxia-Telangiectasia

See Chapter 637.1.

Ataxia-telangiectasia is transmitted as an autosomal recessive trait because of a pathogenic variant in the *ATM* gene. The characteristic telangiectasias develop at approximately 3 years of age, first on the bulbar conjunctivae and later on the nasal bridge, malar areas, external ears, hard palate, upper anterior chest, and antecubital and popliteal fossae. Additional cutaneous stigmata include café-au-lait spots, premature graying of the hair, and sclerodermatous changes. Progressive cerebellar ataxia, neurologic deterioration, sinopulmonary infections, and malignancies are also seen.

Angiokeratoma Corporis Diffusum (Fabry Disease)

See Chapter 106.4.

An inborn error of glycolipid metabolism (α-galactosidase), angiokeratoma corporis diffusum is an X-linked recessive disorder that is fully penetrant in males and is of variable penetrance in carrier females. Angiokeratomas appear before puberty and occur in profusion over the genitalia, hips, buttocks, and thighs and in the umbilical and inguinal regions. They consist of 0.1- to 3.0-mm, red to blue-black papules that may have a hyperkeratotic surface. Telangiectasias are seen in the mucosa and conjunctiva. On light microscopy, these angiokeratomas appear as blood-filled, dilated, endothelium-lined vascular spaces. Granular lipid deposits are demonstrable in dermal macrophages, fibrocytes, and endothelial cells.

Additional clinical manifestations include recurrent episodes of fever and agonizing pain, cyanosis and flushing of the acral limb areas, paresthesias of the hands and feet, corneal opacities detectable on slit-lamp examination, and hypohidrosis. Renal involvement and cardiac involvement are the usual causes of death. The biochemical defect is a deficiency of the lysosomal enzyme α-galactosidase, with accumulation of ceramide trihexoside in tissues, particularly vascular endothelium, and excretion in urine (see Chapter 106.4 for therapy). Similar cutaneous lesions have also been described in another lysosomal enzyme disorder, α-L-fucosidase deficiency, and in sialidosis, a storage disease with neuraminidase deficiency.

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Chapter 692

Cutaneous Nevi

Kari L. Martin

Nevus skin lesions are characterized histopathologically by collections of well-differentiated cell types normally found in the skin. Vascular nevi are described in Chapter 691. Melanocytic nevi are subdivided into two broad categories: those that appear after birth (acquired nevi) and those that are present at birth (congenital nevi).

ACQUIRED MELANOCYTIC NEVUS

Melanocytic nevi are benign clusters of melanocytic nevus cells that arise as a result of alteration and proliferation of melanocytes at the epidermal-dermal junction.

Epidemiology

The number of *acquired* melanocytic nevi increases gradually during childhood and more slowly in early adulthood. The number reaches a plateau in the third or fourth decade and then slowly decreases thereafter. The mean number of melanocytic nevi in an adult varies depending on genetics, skin color, and sun exposure. The greater the number of nevi present, the greater the risk for development of melanoma, though the majority of melanomas arise de novo. Sun exposure during childhood, particularly intermittent, intense exposure of an individual with light skin, and a propensity to burn and freckle rather than tan are important determinants of the number of melanocytic nevi that develop. Red-haired children, despite their light skin and propensity to freckle and sunburn, have fewer nevi than other children. Increased numbers of nevi are also associated with immunosuppression and administration of chemotherapy.

Clinical Manifestations

Melanocytic nevi have a well-defined life history and are classified as junctional, compound, or dermal in accordance with the location of the nevus cells in the skin. In childhood, >90% of nevi are junctional; melanocyte proliferation occurs at the junction of the epidermis and dermis to form nests of cells. Junctional nevi appear anywhere on the body in various shades of brown; they are relatively small, discrete, flat, and variable in shape. Although some nevi, particularly those on the palms, soles, and genitalia, remain junctional throughout life, most become compound as melanocytes migrate into the papillary dermis to form nests at both the epidermal-dermal junction and within the dermis. If the junctional melanocytes stop proliferating, nests of melanocytes remain only within the dermis, forming an intradermal nevus. With maturation, compound and intradermal nevi may become raised, dome-shaped, verrucous, or pedunculated. Slightly elevated lesions are usually compound. Distinctly elevated lesions are usually intradermal. With age, the dermal melanocytic nests regress and nevi gradually disappear.

Prognosis and Treatment

Acquired pigmented nevi are benign, but a very small percentage undergo malignant transformation. Suspicious changes are indications for excision and histopathologic evaluation. This includes rapid increase in size; unusual colors such as red, black, varying shades of brown, gray, and white; bleeding; textures such as scaling, erosion, ulceration, and induration; and regional lymphadenopathy. Most of these changes are from irritation, infection, or maturation; darkening and gradual increase in size and elevation normally occur during adolescence and should not be cause for concern. Two common benign changes are clonal nevi (fried-egg moles) and eclipse nevi. A **clonal nevus** is light brown with a dark, raised center representing a clonal change of a subset of nevus cells within the lesion. **Eclipse nevi** are flat and light brown with dark brown rims. They are seen primarily in the scalp (Fig. 692.1). Consideration should be given to the presence of risk factors for development of melanoma and the patient's parents' wishes about removal of the nevus. If doubt remains about the benign nature of a nevus, excision is a safe and simple outpatient procedure that may be justified to allay anxiety.

ATYPICAL MELANOCYTIC NEVUS

Atypical melanocytic nevi occur both in an autosomal dominant familial melanoma-prone setting (familial mole–melanoma syndrome, dysplastic nevus syndrome, BK mole syndrome) and as a sporadic event. Only 2% of all pediatric melanomas occur in individuals with a familial syndrome; melanoma develops before age 20 years in 10% of individuals with the syndrome. Malignant melanoma has been reported in children with dysplastic nevus syndrome as young as 10 years old. Risk for development of melanoma is essentially 100% in individuals with dysplastic nevus syndrome who have two family members who have had melanomas. The term *atypical mole syndrome* describes lesions in those individuals without an autosomal dominant familial history of melanoma but with more than 50 nevi, some of which are atypical. The lifetime risk of melanoma associated with dysplastic nevi in this context is estimated to be 5–10%.

Atypical nevi tend to be large (5-15 mm) and round to oval. They have irregular margins and variegated color, and portions of them are elevated. These nevi are most common on the posterior trunk, suggesting that intermittent, intense sun exposure has a role in their genesis. They may also occur in sun-protected areas such as the breasts, buttocks, and scalp. Atypical nevi do not usually develop until puberty, although scalp lesions may be present earlier. Atypical nevi demonstrate disordered proliferation of atypical intraepidermal melanocytes, lymphocytic infiltration, fibroplasia, and angiogenesis. It may be helpful to obtain histopathologic documentation of dysplastic change by biopsy to identify these individuals. It is prudent to excise borderline atypical nevi in immunocompromised children or in those treated with irradiation or chemotherapeutic agents. Although chemotherapy is associated with the development of a greater number of melanocytic nevi, it has not been directly linked to increased risk for development of melanoma. The threshold for removal of clinically atypical nevi is also lower at sites that are difficult to observe, such as the scalp. Children with atypical nevi should undergo a complete skin examination every 6-12 months. In these children, photographic mole mapping serves as a useful adjunct in following nevus change. Parents must be counseled about the importance of sun protection and avoidance and should be instructed to look for early signs of melanoma on a regular basis, approximately every 3-4 months.

CONGENITAL MELANOCYTIC NEVUS

Congenital melanocytic nevi are present in 2–3% of newborn infants. These nevi have been categorized by size: giant congenital nevi are >40 cm in diameter (adult size) or >5% of the body surface; large nevi are 20-40 cm, medium nevi are 1.5-20 cm, and small nevi are <1.5 cm in diameter (Fig. 692.2). Congenital nevi are characterized by the

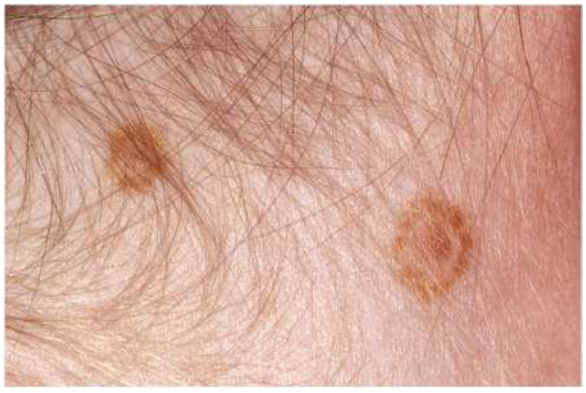

Fig. 692.1 Eclipse nevi (rim moles) in the scalp.

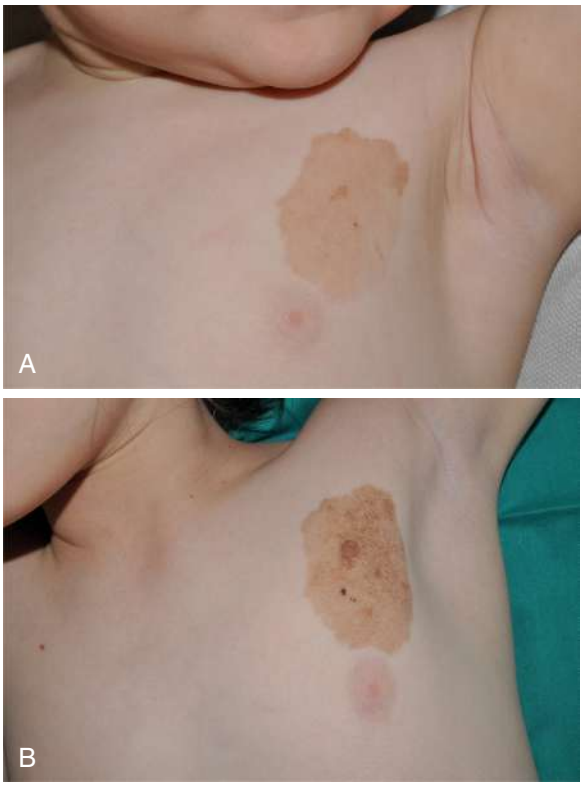

Fig. 692.2 Congenital melanocytic nevus. Changing appearance with time of a congenital melanocytic nevus of small-to-medium size on the trunk when the patient was 9 months old (A) and 10 years old (B). *(From Anderson-Vildosola J, Hernandez-Martin A. Addressing frequently asked questions and dispelling myths about melanocytic nevi in children. Dermatol Clin. 2022;40:51–59, Fig. 5)*

presence of nevus cells in the lower reticular dermis; between collagen bundles; surrounding cutaneous appendages, nerves, and vessels in the lower dermis; and occasionally extending to the subcuticular fat. Large and giant congenital nevi often harbor *NRAS* pathogenic variants, and *BRAF* pathogenic variants typically seen in regular melanocytic nevi are most common in small or medium congenital nevi. Identification is often uncertain, however, because they may have the histologic features of ordinary junctional, compound, or intradermal nevi. Some nevi that were not present at birth display histopathologic features of congenital nevi; these should not be considered congenital, but may be called congenital nevus–like nevi (CNLN). Furthermore, congenital nevi may be difficult to distinguish clinically from other types of pigmented lesions, adding to the difficulty that parents may have in identifying nevi that were present at birth. The clinical differential diagnosis includes dermal melanocytosis, café-au-lait macules, and smooth muscle hamartomas.

Sites of predilection for small congenital nevi are the lower trunk, upper back, shoulders, chest, and proximal limbs. The lesions may be flat, elevated, verrucous, or nodular and may be various shades of brown, blue, or black. Given the difficulty in identifying small congenital nevi with certainty, data regarding their malignant potential are controversial and likely overstated. The true incidence of melanoma in congenital nevi, especially small and medium-sized lesions, is unknown. Removal of all small congenital nevi is not warranted because the development of melanoma in a small congenital nevus is an exceedingly rare event before puberty. A number of factors must be weighed in the decision about whether or not to remove a nevus, including its location, the ability to monitor it clinically, the potential for scarring, the presence of other risk factors for melanoma, and the presence of atypical clinical features.

Giant congenital pigmented nevi (<1 in 20,000 births) occur most commonly on the posterior trunk (Fig. 692.3) but may also appear on the head or extremities. These nevi are of special significance because

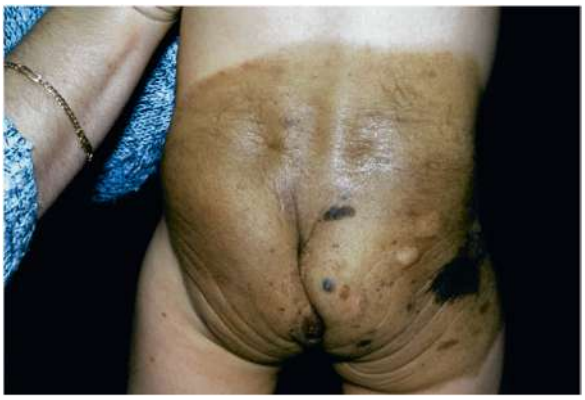

Fig. 692.3 "Bathing suit" large congenital melanocytic nevus.

of their association with leptomeningeal melanocytosis (neurocutaneous melanocytosis) and their predisposition for development of malignant melanoma.

Leptomeningeal involvement occurs most often when the nevus is located on the head or midline on the trunk, particularly when associated with multiple "satellite" melanocytic nevi (>20 lesions). Nevus cells within the leptomeninges and brain parenchyma may cause increased intracranial pressure, hydrocephalus, seizures, intellectual disability, and motor deficits and may result in melanoma. Malignancy can be identified by careful cytologic examination of the cerebrospinal fluid for melanin-containing cells. MRI demonstrates asymptomatic leptomeningeal melanosis in 30% of individuals with giant congenital nevus of the type described earlier. The overall incidence of malignant melanoma arising in a giant congenital nevus is 1–2%. The median age at diagnosis of the melanomas that arise within a giant congenital nevus is 7 years. The mortality rate approaches 100%. The risk of melanoma is greater in patients in whom the predicted adult size of the nevus is >40 cm, lesions are on the trunk, and satellite lesions are present. Management of giant congenital nevi remains controversial and should involve the parents, pediatrician, dermatologist, and plastic surgeon. If the nevus lies over the head or spine, MRI may allow detection of neural melanosis**,** the presence of which makes gross removal of a nevus from the skin a futile effort. In the absence of neural melanosis, early excision and repair aided by tissue expanders or grafting may reduce the burden of nevus cells and thus the potential for development of melanoma, but at the cost of many potentially disfiguring operations. Nevus cells deep within subcutaneous tissues may evade excision. Random biopsies of the nevus are not helpful, but biopsy of newly expanding nodules is indicated. Follow-up every 6 months for 5 years and every 12 months thereafter is recommended. Serial photographs of the nevus may aid in detecting changes.

MELANOMA

Malignant melanoma is the most common skin cancer in children, and approximately 1% of all melanomas occur before 20 years of age. An estimated 400 cases of pediatric melanoma are diagnosed each year. The incidence of melanoma in the pediatric population increases with age, from 1-2 cases per 1 million in children under age 10 to 16.9 cases in children age 15-19 years. The incidence of pediatric melanoma has increased by an average of 2% per year between 1973 and 2009. This increase was especially notable in females between the ages of 15 and 19. In this age-group, melanoma accounts for 6% of all childhood cancers. Melanoma develops primarily in White individuals, on the head and trunk in males, and on the extremities in females. In preadolescent patients, melanoma is more likely to present on the head and neck than in other locations. Risk factors for the development of melanoma include the presence of familial atypical mole–melanoma syndrome or xeroderma pigmentosum; an increased number of acquired melanocytic nevi, or atypical nevi; fair complexion; excessive sun exposure, especially intermittent exposure to intense sunlight; a personal or family (first-degree relative) history of a previous melanoma; giant

congenital nevus; and immunosuppression (Table 692.1). In previously well children, UV radiation is responsible for most melanomas. Less than 5% of childhood melanomas develop within giant congenital nevi or in individuals with familial atypical mole–melanoma syndrome. Approximately 40–50% of the time, melanoma develops at a site where there was no apparent nevus. The mortality rate from melanoma is related primarily to tumor thickness and the level of invasion into the skin. About 75% of pediatric cases are localized and have an excellent outcome. Ninety percent of pediatric patients diagnosed with melanoma are expected to be alive in 5 years. In patients with nodal disease, the outcomes are intermediate, with about 60% expected to survive long-term.

There is variability in prognosis depending on the age of diagnosis in pediatric patients. Children younger than 10 with melanoma often have poor prognostic features. They are more often non-White, have head and neck primary tumors, thicker primary lesions, a higher incidence of spitzoid morphology, vascular invasion and nodal metastases, and more often have syndromes that predispose them to melanoma. The treatment of melanomas, as in adult patients, is surgical excision with 1-cm margins for tumors <1 mm deep, 1- to 2-cm margins for tumors >1 mm and <2 mm deep, and 2-cm margins for tumors >2 mm deep. Sentinel lymph node biopsy has become a widespread practice in pediatric melanoma. It should be considered in lesions >1 mm and in thin lesions with ulceration, mitotic rate greater than 1 mm^2, and young age. Though pediatric patients are more likely to have nodal metastases than their adolescent counterparts, this has not been associated with a decrease in overall survival. Alternatively, in adolescents, nodal disease is a significant negative prognostic factor. Increased tumor thickness and ulceration are associated with lymph node positivity. If the sentinel node is positive, a lymph node dissection can be considered. Patients with regional lymph node involvement can be offered treatment with interferon alfa-2b or ipilimumab (FDA approved for 12 years of age and older). *BRAF* and *MEK* inhibitors are not currently available for pediatric patients; however, phase 1 and 2 clinical trials are currently ongoing for adolescent patients.

Given the lack of effective therapy for melanoma, prevention and early detection are the most effective measures. Emphasis should be given to avoidance of intense midday sun exposure between 10 AM and 3 PM; wearing of protective clothing such as a hat, long sleeves, and pants; and use of sunscreen. Adolescents should be counseled not to use tanning booths. Early detection includes frequent clinical and photographic examinations of patients at risk (dysplastic nevus syndrome) and prompt response to rapid changes in nevi (size, shape, color, inflammation, bleeding or crusting, and sensation). The ABCDE rule (asymmetry, border irregularities, color variability, diameter >6 mm, evolving), which is a useful screening tool for adults, may not be as effective for children. Unlike adult melanomas, which are usually pigmented, pediatric melanomas are often amelanotic and can mimic benign lesions such as warts and pyogenic granulomas. They are also more likely to have regular borders and to be less than 6 mm in diameter. They often present as papules or papulonodules. To highlight these differences from adult melanomas, an **ABCDE rule for pediatric melanoma** has been proposed: **A**melanotic, **B**leeding, **B**umps, uniform **C**olor, small **D**iameter, **D**e novo, and in **E**volution.

HALO NEVUS

Halo nevi occur primarily in children and young adults, most commonly on the back (Fig. 692.4). Development of the lesion may coincide with puberty or pregnancy. Several pigmented nevi frequently develop halos simultaneously. Subsequent disappearance of the central nevus over several months is the usual outcome, and the depigmented area usually repigments. Excision and histopathologic examination of the lesion is indicated only when the nature of the central lesion is in question. An acquired melanocytic nevus occasionally develops a peripheral zone of depigmentation over a period of days to weeks. There is a dense inflammatory infiltrate of lymphocytes and histiocytes in addition to the nevus cells. The pale halo reflects disappearance of the melanocytes. This phenomenon is associated with congenital nevi, blue nevi, Spitz nevi, dysplastic nevi, neurofibromas, primary and secondary malignant melanoma, and occasionally with poliosis, **Vogt-Koyanagi-Harada** syndrome, and pernicious anemia. Patients with vitiligo have an increased incidence of halo nevi. Individuals with halo nevi have circulating antibodies against the cytoplasm of melanocytes and nevus cells.

SPITZ NEVUS (SPINDLE AND EPITHELIOID CELL NEVUS)

Spitz nevus manifests most commonly in the first 2 decades of life as a pink to red, smooth, dome-shaped, firm, hairless papule on the face, shoulder, or upper limb (Fig. 692.5). Most are <1 cm in diameter, but they can achieve a size of 3 cm. Rarely, they occur as numerous grouped lesions. Visually similar lesions include pyogenic granuloma, hemangioma, nevocellular nevus, juvenile xanthogranuloma, and basal cell carcinoma, but these entities are histologically distinguishable. Classic-appearing Spitz nevi can be monitored with regular clinical and dermoscopic examination, and multiple dermoscopy studies

Table 692.1 Summary of Clinical and Histologic Features by Subtypes of Pediatric Melanoma

	SPITZOID MELANOMA	MELANOMA ARISING IN CMN	CONVENTIONAL MELANOMA
Clinical	Papule or nodule; frequently amelanotic, but can be any color (e.g., pink-red to blue-black); distribution is not limited to sun-exposed skin	New, rapidly growing nodule arising in the deep dermis or subcutaneous tissues of a CMN; commonly solitary and ulcerated; by comparison, proliferative nodules commonly occur in multiples and are not ulcerated	Children: typically papules or nodules of any color, but often amelanotic; most do not follow ABCD criteria; nodular subtype most common Adolescents: similar to presentation in adults with lesions having ABCD criteria
Histologic	Primary differential diagnosis is Spitz nevus vs atypical Spitz tumor; most cells have abundant eosinophilic cytoplasm and characteristic spitzoid cytomorphology; nuclear atypia is typically high grade; growth in the form of expansile nodules or sheets; ulceration, epidermal consumption, brisk deep mitotic activity, and poor maturation are often seen; epidermal hyperplasia might be seen on the surface, but Kamino bodies are relatively uncommon	The primary differential diagnosis is benign proliferative nodules arising in congenital nevi; compared with benign proliferative nodules, melanomas typically have epithelioid or small, blue cell, tumor-like morphology, with sheets of melanocytes with high-grade nuclear atypia; mitotic activity is high (often >3/mm^2); zones of necrosis or ulceration can be helpful in establishing a diagnosis	Nodular melanoma: similar to adult nodular melanoma; no horizontal growth phase present; superficial spreading melanoma: similar to superficial spreading melanoma in adults with a preceding horizontal growth phase, pagetosis, lentiginous growth, and junctional confluence with frequent alteration of the epidermal contour; precursor nevus is common

CMN, Congenital melanocytic nevi; ABCD, asymmetry, border irregularity, color variegation, diameter >6 mm.
From Merkel EA, Mohan LS, Shi K, et al. Paediatric melanoma: clinical update, genetic basis, and advances in diagnosis. *Lancet Child Adoles.* 2019;3:646–654, Table 1).

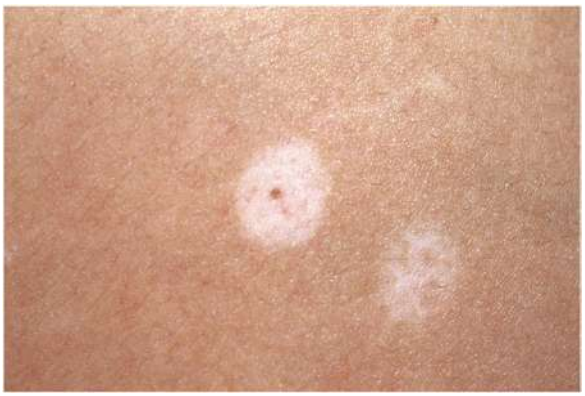

Fig. 692.4 Well-developed halo nevus.

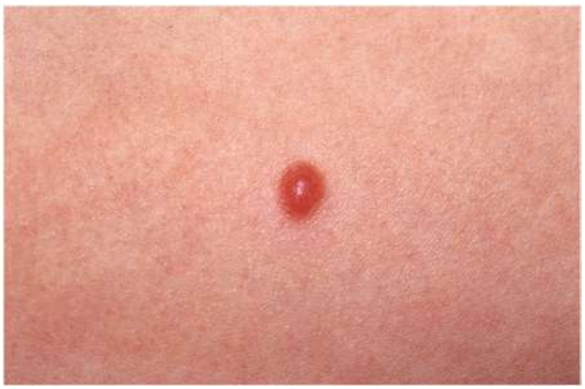

Fig. 692.5 Dome-shaped red Spitz nevus.

have demonstrated a tendency for these benign lesions to develop a reticular or homogeneous pattern and/or regress over time. Guidelines recommend excision be reserved for suspicious lesions (>8-10 mm, with excessive growth, asymmetry, or ulceration) in children over 12 years of age and for suspicious lesions in all ages when melanoma cannot be excluded. If a nevus arouses clinical suspicion that it may be a melanoma, an excisional biopsy of the entire lesion is recommended. If the margins of excision of a Spitz nevus are positive but the biopsy sample suggested a typical Spitz nevus, reexcision of the site is no longer routinely recommended. Because Spitz nevi may be difficult to distinguish histopathologically from malignant melanoma, immunohistochemistry and genomic alteration studies can be useful adjunct tools. Atypical Spitz tumors are Spitz nevi with atypical histologic features or unknown malignant potential. Management for these tumors is not clearly defined and may range from clinical monitoring to yearly nodal ultrasonography to potentially sentinel lymph node biopsy and lymphadenectomy. Improving genetic profiling of these tumors may provide better prognostic information soon. Prognostic implication of positive sentinel lymph node biopsy has not been established, and given the potential morbidity of the procedure, it is often avoided.

ZOSTERIFORM LENTIGINOUS NEVUS (AGMINATED LENTIGINES)

Zosteriform lentiginous nevus is a unilateral, linear, bandlike collection of numerous 2- to 10-mm brown or black macules on the face, trunk, or limbs. The nevus may be present at birth or may develop during childhood. There are higher numbers of melanocytes in elongated rete ridges of the epidermis.

NEVUS SPILUS (SPECKLED LENTIGINOUS NEVUS)

Nevus spilus is a flat brown patch within which are darker flat or raised brown melanocytic elements with a prevalence of 2–3% (Fig. 692.6). It varies considerably in size and can occur anywhere on the body. The color of the macular component may vary from light to dark brown,

Fig. 692.6 Nevus spilus.

and the number of darker lesions may be low or high. Nevus spilus is rare at birth and is commonly acquired in late infancy or early childhood. Dark elements within the nevus are usually present initially and tend to increase in number gradually over time. The darker macules represent nevus cells in a junctional or dermal location; the patch has increased numbers of melanocytes in a lentiginous epidermal pattern. The malignant potential of these nevi is uncertain; nevus spilus is found more commonly in individuals with melanoma than in matched control subjects. Like congenital melanocytic nevi, the risk of melanoma developing within a nevus spilus is thought to be proportionate to the size of the lesion as a whole. The nevi need not be excised unless atypical features or recent clinical changes are noted.

NEVUS OF OTA AND NEVUS OF ITO

Nevus of Ota is more common among females and Asian and Black patients. This nevus consists of a permanent patch composed of partially confluent blue, black, and brown macules. Enlargement and darkening may occur with time. Occasionally, some areas of the nevus are raised. The macular nevi resemble the more common dermal melanocytosis of the lower back and buttocks in color and occur unilaterally in the areas supplied by the first and second divisions of the trigeminal nerve. Nevus of Ota differs from a more common dermal melanocytosis patch not only by its distribution but also by having a speckled rather than a uniform appearance. Both are forms of mid-dermal melanocytosis. Nevus of Ota also has a greater concentration of elongated, dendritic dermal melanocytes located in the upper rather than the lower portion of the dermis. This nevus is sometimes present at birth; in other cases, it may arise during the first or second decade of life. Patchy involvement of the conjunctiva, hard palate, pharynx, nasal mucosa, buccal mucosa, or tympanic membrane occurs in some patients. Malignant change is exceedingly rare. Laser therapy may effectively decrease the pigmentation but can be unpredictable.

Nevus of Ito is localized to the supraclavicular, scapular, and deltoid regions. This nevus tends to be more diffuse in its distribution and less mottled than nevus of Ota. It is also a form of mid-dermal melanocytosis. The only available treatments are masking with cosmetics and laser therapy.

BLUE NEVI

The common blue nevus is a solitary, asymptomatic, smooth, dome-shaped, blue to blue-gray papule <10 mm in diameter on the dorsal aspect of the hands and feet. Rarely, common blue nevi form large plaques. Blue nevus is nearly always acquired, often during childhood and more commonly in females. Microscopically, it is characterized by groups of intensely pigmented, spindle-shaped melanocytes in the dermis. This nevus is benign.

The cellular blue nevus is typically 1-3 cm in diameter and occurs most frequently on the buttocks and in the sacrococcygeal area. In addition to collections of deeply pigmented dermal dendritic melanocytes, cellular islands composed of large spindle-shaped cells are noted in the dermis and may extend into the subcutaneous fat. A histologic continuum may be seen from blue nevi to cellular blue nevi. A combined nevus is the association of a blue nevus with an overlying melanocytic nevus.

The blue-gray color that is characteristic of these nevi is an optical effect caused by dermal melanin. Longer wavelengths of visible light penetrate to the deep dermis and are absorbed there by melanin; shorter-wavelength blue light cannot penetrate deeply but instead is reflected back to the observer.

NEVUS DEPIGMENTOSUS (ACHROMIC NEVUS)

Nevi depigmentosi are usually present at birth; they are localized macular hypopigmented patches or streaks, often with irregular borders (Fig. 692.7). They can resemble hypomelanosis of Ito clinically, except that they are more localized and often unilateral. Small lesions may also resemble the ash leaf macules of tuberous sclerosis. Nevi depigmentosi appear to represent a focal defect in transfer of melanosomes to keratinocytes.

EPIDERMAL NEVI

Epidermal nevi may be visible at birth or may develop in the first few months or years of life. They affect both sexes equally and usually occur sporadically. Epidermal nevi are hamartomatous lesions characterized by hyperplasia of the epidermis and/or adnexal structures in a focal area of the skin.

Epidermal nevi are classified into a number of variants, depending on the morphology and extent of the individual nevus and the predominant epidermal structure (Table 692.2). An epidermal nevus may appear initially as a discolored, slightly scaly patch that, with maturation, becomes more linear, thickened, verrucous, and hyperpigmented. *Systematized* refers to a diffuse or extensive distribution of lesions, and *ichthyosis hystrix* indicates that the distribution is extensive and bilateral (Fig. 692.8). Morphologic types include pigmented papillomas, often in a linear distribution; unilateral hyperkeratotic streaks involving a limb and perhaps a portion of the trunk; velvety hyperpigmented plaques; and whorled or marbled hyperkeratotic lesions in localized plaques or over extensive areas of the body along Blaschko lines. An inflammatory linear verrucous variant is markedly pruritic and tends to become erythematous, scaling, and crusted. Many have *RAS* pathogenic variants.

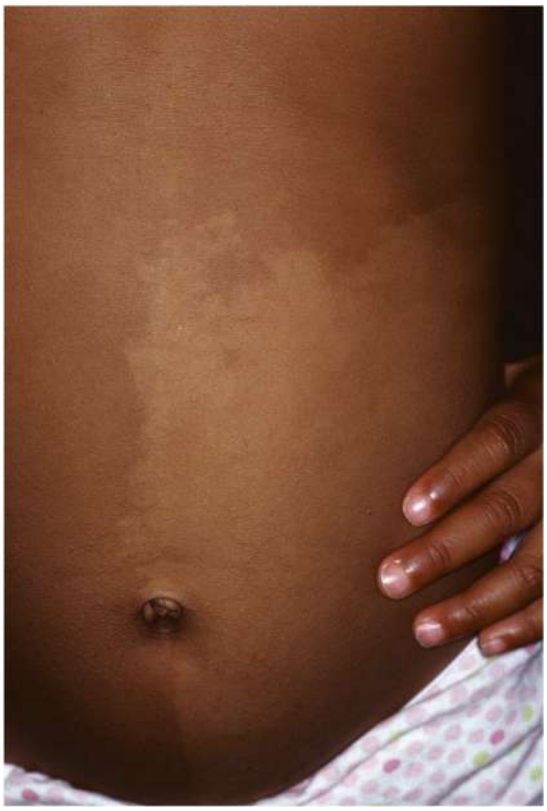

Fig. 692.7 Large nevus depigmentosus of the abdomen.

The histologic pattern evolves as an epidermal nevus matures, but epidermal hyperplasia of some degree is apparent in all stages of development. One or another dermal appendage may predominate in a particular lesion. These nevi must be distinguished from lichen striatus, lymphangioma circumscriptum, shagreen patch of tuberous sclerosis, congenital hairy nevi, linear porokeratosis, linear lichen planus, linear psoriasis, the verrucous stage of incontinentia pigmenti, and nevus sebaceus (Jadassohn). Keratolytic agents such as retinoic acid and salicylic acid may be moderately effective in reducing scaling and controlling pruritus, but definitive treatment requires full-thickness excision; recurrence is usual if more superficial removal is attempted. Alternatively, the nevus may be left intact. Epidermal nevi are occasionally associated with other abnormalities of the skin and soft tissues; eyes; and nervous, cardiovascular, musculoskeletal, and urogenital systems. In these instances, the disorder is referred to as epidermal nevus syndrome. This syndrome, however, is not a distinct clinical entity.

Nevus Sebaceus (Jadassohn)

A relatively small, sharply demarcated, oval or linear, elevated, yellow-orange plaque that is usually devoid of hair, nevus sebaceus occurs on the head and neck of infants (Fig. 692.9). Although the lesion is characterized histopathologically by an abundance of sebaceous glands, all elements of the skin are represented. It is frequently flat and inconspicuous in early childhood. With maturity, usually during adolescence, the lesions become verrucous and studded with large rubbery nodules. The changing clinical appearance reflects the histologic pattern, which is characterized by a variable degree of hyperkeratosis, hyperplasia of the epidermis, malformed hair follicles, and often a profusion of sebaceous glands and

Table 692.2 Epidermal Nevi and Their Associated Genetic Syndromes

LESION	PATHOGENIC GENE VARIANT
KERATINOCYTIC NEVI	
Epidermal nevus	*FGFR3* *FGFR2* *HRAS* *KRAS* *NRAS* *PIK3CA*
Epidermolytic ichthyosis	*KRT1* *KRT10* *KRT2*
CHILD syndrome	*NSDHL*
PTEN nevus	*PTEN*
Proteus syndrome and epidermal nevi	*AKT1*
PIK3CA-related overgrowth spectrum/ CLOVES	*PIK3CA*
Acantholytic dyskeratotic epidermal nevus	*ATP2A2* *GJB2*
Inflammatory linear verrucous epidermal nevus	*Not identified to date*
ADNEXAL NEVI	
Nevus sebaceous/nevus sebaceous syndrome	*FGFR2* *HRAS* *KRAS* *NRAS*
Porokeratotic adnexal ostial nevus	*GJB2 (connexin 26)*
Nevus comedonicus/nevus comedonicus syndrome	*NEK9* *FGFR2*
Becker nevus/Becker nevus syndrome	*ACTB (beta-actin)*

CHILD, Congenital hemidysplasia with ichthyosiform erythroderma and limb defects; CLOVES, congenital lipomatous overgrowth and vascular and skeletal anomalies.

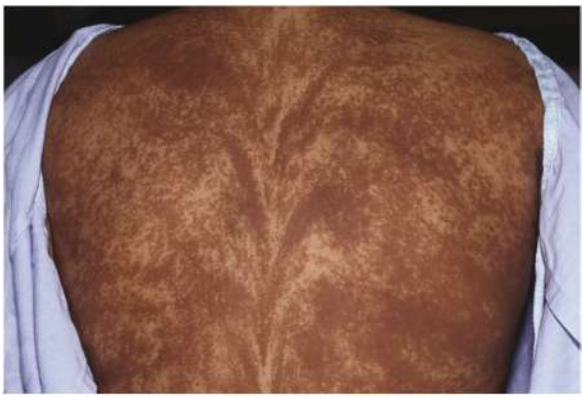

Fig. 692.8 Epidermal nevus (ichthyosis hystrix type).

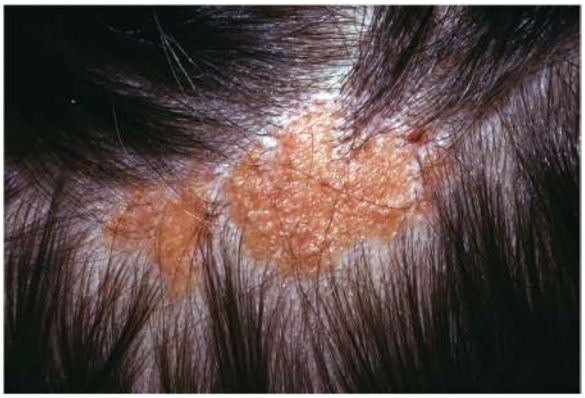

Fig. 692.9 Orange-yellow nevus sebaceus of the scalp.

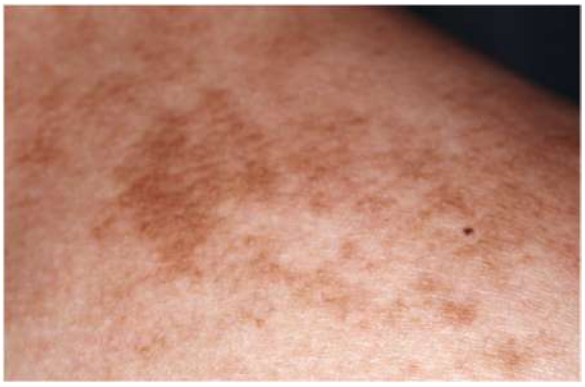

Fig. 692.10 Becker nevus on the shoulder of an adolescent male.

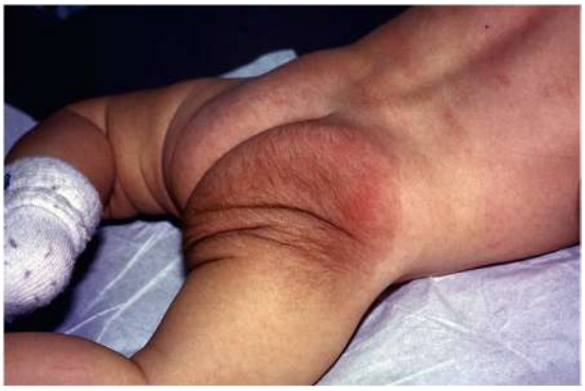

Fig. 692.11 Large smooth muscle hamartoma of the buttock.

the presence of ectopic apocrine glands. Sebaceous nevi are caused by somatic mosaic pathogenic variants in *HRAS* and *KRAS*. The disruption of these oncogenes helps explain the 14% incidence of these lesions developing tumors throughout a patient's lifetime. Most tumors are benign (trichoblastomas, syringocystadenoma papilliferum, trichilemmomas), but basal cell carcinoma can occur as well. Lesions may be monitored or excised if the family is unable to or uncomfortable with monitoring alone. Sebaceous nevi associated with central nervous system, skeletal, and ocular defects represent a variant of the epidermal nevus syndrome.

Becker Nevus (Becker Melanosis)

Becker nevus develops predominantly in males, during childhood or adolescence, initially as a hyperpigmented patch. The lesion commonly develops hypertrichosis, limited to the area of hyperpigmentation, and evolves into a unilateral, slightly thickened, irregular, hyperpigmented plaque. The most common sites are the upper torso and upper arm (Fig. 692.10). The nevus shows an increased number of basal melanocytes and variable epidermal hyperplasia. Becker melanosis is commonly associated with a smooth muscle hamartoma, which may appear as slight perifollicular papular elevations or slight induration. Stroking of such a lesion may induce smooth muscle contraction and make the hairs stand up **(pseudo-Darier sign)**. The nevus is benign, has no risk for malignant change, and is rarely associated with other anomalies.

NEVUS COMEDONICUS

An uncommon organoid nevus of epithelial origin, nevus comedonicus consists of linear plaques of plugged follicles that simulate comedones; they may be present at birth or may appear during childhood. The horny plugs represent keratinous debris within dilated, malformed pilosebaceous follicles. The lesions are most often unilateral and may develop at any site. Rarely, they are associated with other congenital malformations, including skeletal defects, cerebral anomalies, and cataracts. Although these lesions are often asymptomatic, some affected individuals experience recurrent inflammation, resulting in cyst formation, fistulas, and scarring. There is no effective treatment except full-thickness excision; palliation of larger lesions may be achieved by regular applications of a retinoic acid preparation.

CONNECTIVE TISSUE NEVUS

Connective tissue nevus is a hamartoma of collagen, elastin, and/or glycosaminoglycans of the dermal extracellular matrix. It may occur as a solitary defect or as a manifestation of an associated disorder. These nevi may occur at any site but are most common on the back, buttocks, arms, and thighs. They are skin-colored, ivory, or yellow plaques, 2-15 cm in diameter, composed of many tiny papules or grouped nodules that are frequently difficult to appreciate visually because of the subtle color changes. The plaques have a rubbery or cobblestone consistency on palpation. Biopsy findings are variable and include increased amounts and/or degeneration or fragmentation of dermal collagen, elastic tissue, or ground substance. Similar lesions occurring with tuberous sclerosis are called shagreen patches; however, shagreen patches consist only of excessive amounts of collagen. The association of many small papular connective tissue nevi with osteopoikilosis is called *dermatofibrosis lenticularis disseminata* **(Buschke-Ollendorff syndrome)**.

SMOOTH MUSCLE HAMARTOMA

Smooth muscle hamartoma is a developmental anomaly resulting from hyperplasia of the smooth muscle (arrector pili) associated with hair follicles. It is usually evident at birth or shortly thereafter as a flesh-colored or lightly pigmented plaque with overlying hypertrichosis on the trunk or limbs (Fig. 692.11). Transient elevation or a rippling movement of the lesion, caused by contraction of the muscle bundles, can sometimes be elicited by stroking of the surface (pseudo-Darier sign). Smooth muscle hamartoma can be mistaken for congenital pigmented nevus, but the distinction is important because the former has no risk for malignant melanoma and need not be removed.

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Chapter 693

Hyperpigmented Lesions

Joel C. Joyce

DISORDERS OF PIGMENTATION

Pigmentation of the skin requires migration of melanoblasts from the neural crest to the dermal-epidermal junction, enzymatic processes to form pigment, structural components to contain the pigment (melanosomes), and transfer of pigment to the surrounding keratinocytes. Increased skin color may be generalized or localized and may result from various defects in any of these requirements. Some of these aberrations are a manifestation of systemic disease, others represent generalized or focal developmental or genetic defects, and still others may be nonspecific and the result of cutaneous inflammation.

EPHELIDES (FRECKLES)

Ephelides (freckles) are well-demarcated macules—light or dark brown, round, oval, or irregularly shaped—that occur in sun-exposed areas such as the face, upper back, arms, and hands. They are usually less than 3 mm in diameter and are induced by exposure to sun, particularly during the summer, and may fade or disappear during the winter. They are a result of increased sun-induced melanogenesis and melanosome transport from melanocytes to keratinocytes and not from increased numbers of melanocytes. They are more common in redheads and fair-haired individuals and first appear in the preschool years. Histologically, they are marked by increased melanin pigment in epidermal basal cells, which have more numerous and larger dendritic processes than the melanocytes of the surrounding paler skin. The lack of melanocytic proliferation or elongation of epidermal rete ridges distinguishes them from **lentigines**. Ephelides have been identified as a marker for increased risk for ultraviolet (UV)-induced neoplasia and hence melanoma independent of melanocytic nevi. Treatment is not required, but regular and consistent sun protection can slow ephelis development.

LENTIGINES

Lentigines, often mistaken for ephelides or junctional nevi, are small (usually <5 mm but occasionally 1-2 cm), round, dark-brown macules that can appear anywhere on the body. They can be solitary or grouped. Onset can be at an early age, particularly when associated with genetic syndromes, but can appear at any age. They are more common in darkly pigmented than in lightly pigmented individuals. They do not vary in coloration seasonally and remain permanently. Histologically they have elongated, club-shaped epidermal rete ridges with increased numbers of melanocytes and dense epidermal deposits of melanin. No nests of melanocytes are found. Lentigines are benign and, when few, may be viewed as a normal occurrence. They are seen most commonly on the lower lip and sun-exposed skin but may occur elsewhere, particularly when associated with syndromes, inadvertent or therapeutic radiation exposure, or patterned (inherited-tendency).

Eruptive/generalized lentiginosis (lentiginosis profusa) involves innumerable small pigmented macules that are present at birth or appear during childhood. There are no associated abnormalities, and mucous membranes are spared. Carney complex is an autosomal dominant syndrome characterized by multiple lentigines and neoplasms, including myxomas of the skin, heart (atrial), and breast; psammomatous melanotic schwannomas; epithelioid blue nevi of skin and mucosae; growth hormone–producing pituitary adenomas; and testicular Sertoli cell tumors. Components of the Carney complex have been described previously as the NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides) and LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) syndromes. The complex is inherited in an autosomal dominant pattern and caused by an inactivating pathogenic variant of the *PRKAR1A* gene.

Multiple lentigines syndrome (formerly LEOPARD) is an autosomal dominant entity consisting of a generalized, symmetric distribution of *l*entigines (Fig. 693.1) in association with *e*lectrocardiographic *a*bnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals (cryptorchidism, hypogonadism, hypospadias), growth *r*etardation, and sensorineural *d*eafness (type 1, *PTPN11* gene; type 2, *RAF1* gene). Other features include hypertrophic obstructive cardiomyopathy and pectus excavatum or carinatum.

Peutz-Jeghers syndrome is characterized by melanotic macules on the lips and mucous membranes and by gastrointestinal (GI) polyposis. It is inherited as an autosomal dominant trait caused by pathogenic variants of *STK11*. Onset is noted in infancy and early childhood when pigmented macules appear on the lips and buccal mucosa. The macules are usually a few millimeters in size but may be as large as 1-2 cm. Macules also occasionally appear on the palate, gums, tongue, and vaginal mucosa. Cutaneous macules may develop on the nose, hands, and feet; around the mouth, eyes, and umbilicus; and as longitudinal bands or diffuse hyperpigmentation of the nails. Pigmented macules often fade from the lips and skin during puberty and adulthood but generally do not disappear from mucosal surfaces. Buccal mucosal macules are the most constant feature of the disorder; in some families, occasional members may be affected only with the pigmentary changes. Indistinguishable pigmentary changes beginning in adult life, without intestinal involvement, also occur sporadically in individuals.

Polyposis usually involves the jejunum and ileum but may also occur in the stomach, duodenum, colon, and rectum (see Chapter 393). Episodic abdominal pain, diarrhea, melena, and intussusception are frequent complications. Patients have a significantly increased risk of GI tract and non–GI tract tumors at a young age. GI cancer has been reported in 2–3% of patients; the lifetime relative risk for GI malignancy is 13-15. The relative risk of non–GI tract malignancies, including ovarian, cervical, and testicular tumors, is 9. **Peutz-Jeghers syndrome** must be differentiated from other syndromes associated with multiple lentigines (Laugier-Hunziker syndrome), from ordinary freckling, from Gardner syndrome, and from Cronkhite-Canada syndrome, a disorder characterized by GI polyposis, alopecia, onychodystrophy, and diffuse pigmentation of the palms, volar aspects of the fingers, and dorsal hands. Treatment of Peutz-Jeghers melanotic macules is not required, but various lasers have been effective for cosmesis in some cases.

CAFÉ-AU-LAIT MACULES

Café-au-lait macules (CALMs) are uniformly hyperpigmented, sharply demarcated macular lesions, the hues of which vary with the normal degree of pigmentation of the individual: they are tan or light brown in White individuals and may be dark brown in Black children (Figs. 693.2 and 693.3). CALMs vary tremendously in size and may be large, covering a significant portion of the trunk or limb. The borders are usually

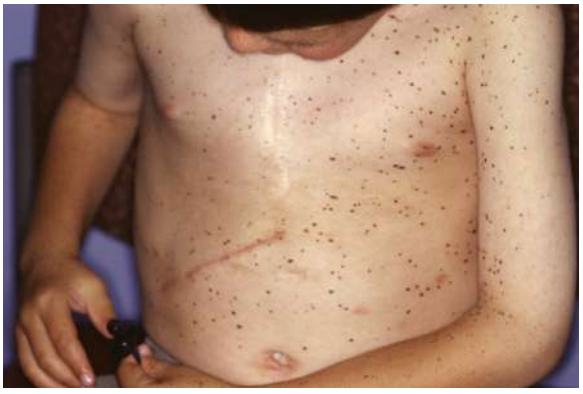

Fig. 693.1 Multiple lentigines in LEOPARD (*l*entigines in association with *e*lectrocardiographic *a*bnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals [cryptorchidism, hypogonadism, hypospadias], growth *r*etardation, and sensorineural *d*eafness) syndrome.

smooth (ovoid), but some have exceedingly irregular borders. They are characterized by increased numbers of melanocytes and melanin in the epidermis but lack the clubbed rete ridges that typify lentigines. One to three CALMs are common in the general population, and up to 27% of children have a solitary CALM, depending on ancestry. The spots may be present at birth or may develop during childhood. The spots themselves are benign and may fade with age.

Large, often asymmetric café-au-lait spots with irregular borders are characteristic of patients with **McCune-Albright syndrome** (*GNAS1* gene; see Chapter 600.6). This disorder includes polyostotic fibrous dysplasia of bone, leading to pathologic fractures; precocious puberty; and numerous hyperfunctional endocrinopathies. The macular hyperpigmentation has an irregular border and may be present at birth or may develop late in childhood (see Fig. 693.3). The lesions are often unilateral and migrate along the lines of Blaschko. Cutaneous pigmentation is typically most extensive on the side showing the most severe bone involvement.

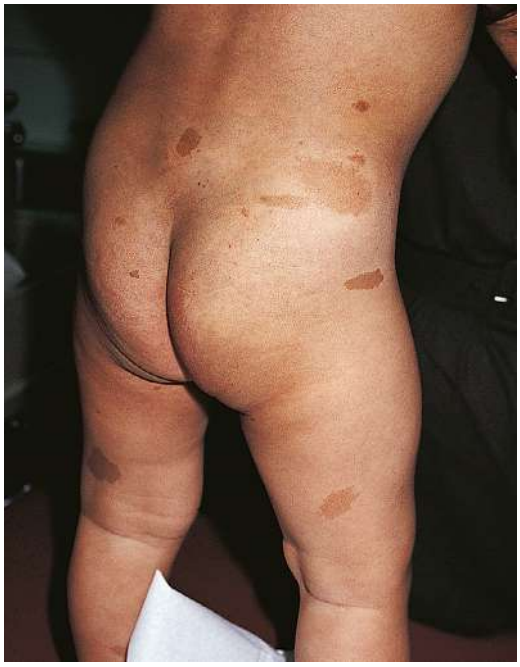

Fig. 693.2 Multiple café-au-lait macules on a child with neurofibromatosis type 1. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001:372.)*

Neurofibromatosis Type 1 (Von Recklinghausen Disease)

The CALM is the most familiar cutaneous hallmark of the autosomal dominant neurocutaneous syndrome known as **neurofibromatosis type 1** (*NF1*, see Fig. 693.2 and Chapter 636.1). Included in the criteria for this diagnosis is the presence of six or more CALMs (>5 mm in diameter in prepubertal patients and >15 mm in diameter in postpubertal patients; Table 693.1). Multiple CALMs commonly produce a freckled appearance of non–sun-exposed areas such as the axillae (Crowe sign), the inguinal and inframammary regions, and under the chin. CALMs can also be seen in segmental NF1, which results from somatic mosaicism arising from postzygotic pathogenic genetic variants in the *NF1* gene such that the clinical manifestations of NF1 are present only in a localized body segment. Another variant of NF1 is hereditary spinal neurofibromatosis, which is a rare disorder that generally presents with multiple CALM and multiple symmetric spinal root neurofibromas, but other stigmata of NF1 are typically absent.

CALM may be seen in **Watson syndrome**, an NF1 allelic variant (CALM, pulmonic stenosis intellectual disability, short stature), mosaic NF1, and **Legius syndrome** *(SPRED1)*. Differentiation of these disorders is noted in Figure 693.4 and Table 693.2.

CALMs also occur with certain other disorders, including other types of neurofibromatosis, but in many of these disorders the CALMs are not the defining diagnostic feature (see Table 693.2).

INCONTINENTIA PIGMENTI (BLOCH-SULZBERGER DISEASE)

See Chapter 636.7.

POSTINFLAMMATORY PIGMENTARY CHANGES

Either hyperpigmentation or hypopigmentation can occur as a result of cutaneous inflammation. Alteration in pigmentation usually follows a severe inflammatory reaction but may result from mild dermatitis. Dark-skinned individuals are more likely than fair-skinned children to show these changes. Although altered pigmentation may persist for weeks to months, patients can be reassured that these lesions are usually temporary. Sun protection and treatment of the underlying dermatitis can shorten duration.

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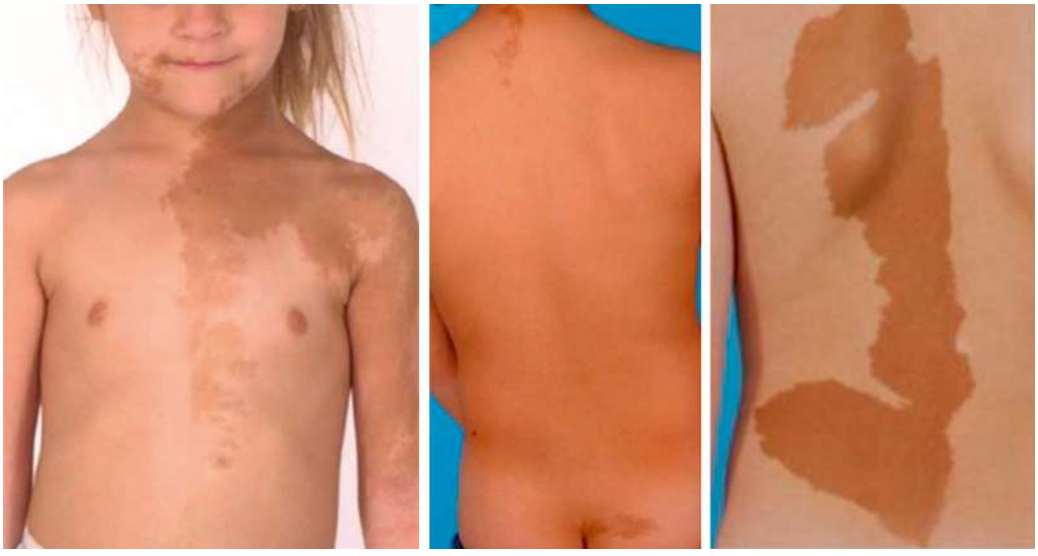

Fig. 693.3 Coast of Maine café-au-lait macules. Irregularly bordered café au lait macules that tend not to cross the midline are characteristic of McCune-Albright syndrome. *(Modified from Collins MT, Singer FR, Rugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 2012;7[Suppl. 1]:S4, Fig. 2.)*

Table 693.1 Previous and Recently Updated National Institutes of Health Diagnostic Criteria for Neurofibromatosis Type 1

CARDINAL CLINICAL FEATURES (ANY TWO OR MORE ARE REQUIRED FOR DIAGNOSIS)	NEW CHANGES
1. Six or more café-au-lait macules more than 5 mm in greatest diameter in prepubertal individuals and more than 15 mm in greatest diameter in postpubertal individuals	Must be bilateral (both sides of the body)*
2. Freckling in the axillary or inguinal regions	Must be bilateral (both sides of the body)*
3. Two or more neurofibromas of any type or one plexiform neurofibroma	No change
4. Two or more Lisch nodules	Or two or more choroidal abnormalities
5. Optic pathway glioma	No change
6. A distinctive osseous lesion such as sphenoid wing dysplasia	Added anterolateral bowing of tibia (tibial dysplasia) or pseudarthrosis of a long bone
7. First-degree relative (e.g., mother, father, sister, brother) with NF1	Changed to a parent with NF1 by the aforementioned criteria
	New criteria: A pathogenic NF1 variant

*If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1, but exceptionally, the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
NIH, National Institutes of Health.
From Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. *Dermatol Clin.* 2022;40:9–23, Table 1.

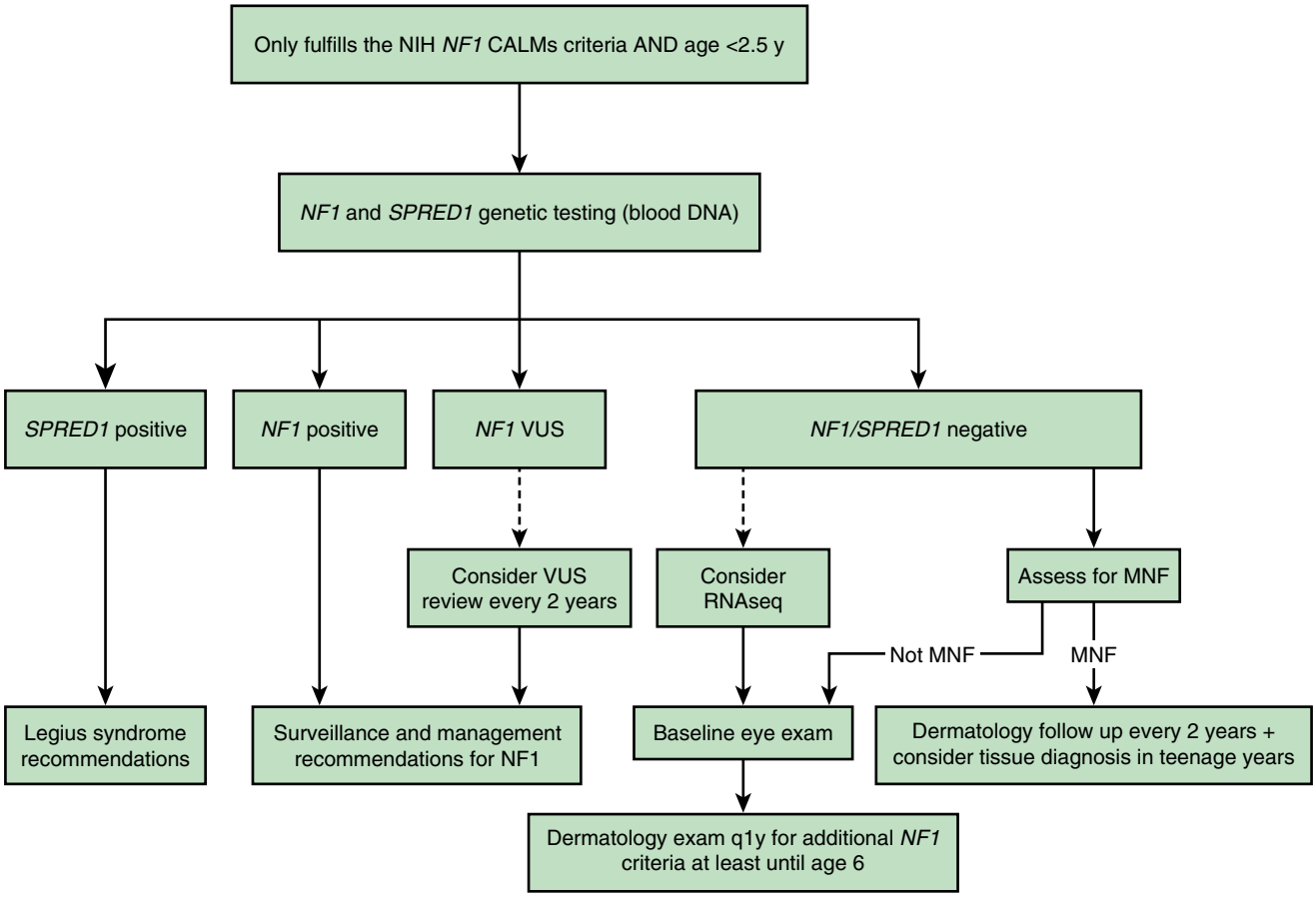

Fig. 693.4 Approach to the genetic diagnosis of young children who solely meet the CALM NIH criteria. MNF, Mosaic neurofibromatosis; NFI, neurofibromatosis; RNAseq, RNA sequencing; SPRED1, sprouty-related EVH1 domain-containing 1; VUS, variant of unknown significance. *(From Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. Dermatol Clin. 2022;40:9–23, Fig. 7.)*

Table 693.2 Conditions Featuring Café au Lait Macules

CONDITION	GENE (INHERITANCE)	ASSOCIATED FEATURES*	ADDITIONAL TESTING TO CONSIDER
Ataxia telangiectasia	*ATM* (AR)	Progeric changes in skin and hair, hypopigmented macules, progressive neurologic impairment, cerebellar ataxia, radiosensitivity, malignancy, immunocompromise, premature aging, and oculocutaneous telangiectasia	Karyotype* Serum AFP*
Cardiofaciocutaneous syndrome	*BRAF, MAP2K1/2* (AD)	Follicular hyperkeratosis, sparse, slow-growing, curly hair, ulerythema ophryogenes, melanocytic nevi, infantile hemangiomas, distinctive craniofacial features, cardiac anomalies, psychomotor delay, failure to thrive, and skin abnormalities	Gene panel for RASopathies
Constitutional mismatch repair deficiency syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM* (AR)	Adenomatous colonic polyps, multiple malignancies including colonic adenocarcinoma, glioblastoma, medulloblastoma, lymphoma, and a positive family history of Lynch syndrome–associated malignancies on both sides of the family	Gene panel for Lynch syndrome genes
Multiple café-au-lait spots	N/A (AD)	Six or more CALMs in multiple generations without NF1-associated features	No genetic testing available
Familial progressive hyperpigmentation and hypopigmentation syndrome	*KITLG* (AR)	Progressive, diffuse, partly blotchy, hyperpigmented lesions with scattered hypopigmented spots and lentigines	*KITLG* gene testing
Fanconi anemia	*FANCA* and other genes (AR)	Faint, ill-defined CALMs "shadow spots," hypopigmented macules, skinfold freckle-like macules, progressive bone marrow failure, short stature, hypogonadism, thumb or other radial ray abnormalities, and skeletal malformations	DNA breakage studies Gene panel for bone marrow failure syndromes
Legius syndrome	*SPRED1* (AD)	Six or more CALMs, intertriginous freckling, lipomas, macrocephaly, and learning disabilities	*SPRED1* gene testing
Noonan syndrome with lentigines	*PTPN11* (AD)	Small brown lentigines, café noir spots, CALMs, dysmorphic facial features, obstructive cardiomyopathy, pulmonary stenosis, growth abnormalities, and sensorineural hearing loss	*PTPN11* gene testing
McCune-Albright syndrome	*GNAS* (sporadic)	Coast of Maine CALMs associated with the lines of Blaschko, fibrous dysplasia, and endocrinopathies	*GNAS* gene testing from affected tissue (not blood)
Neurofibromatosis type 1	*NF1* (AD)	Six or more CALMs, skinfold freckling, neurofibromas, plexiform neurofibromas, Lisch nodules, optic gliomas, skeletal dysplasia, macrocephaly, nevus anemicus, and juvenile xanthogranuloma	*NF1* gene testing (DNA) ± RNA sequencing
Neurofibromatosis type 2	*NF2* (AD)	Schwannomas, cutaneous plaques with hypertrichosis, light irregularly bordered CALMs, subcutaneous nodular tumors, peripheral neuropathy, and ophthalmologic lesions	*NF2* gene testing (DNA) ± RNA sequencing
Noonan syndrome	*PTPN11, SOS2,* and other genes (AD)	Skin hyperlaxity, easy bruising, keratosis pilaris, temporal alopecia, distinctive facial features, developmental delay, learning difficulties, short stature, congenital heart disease, renal anomalies, lymphatic malformations	Gene panel for RASopathies
Piebaldism	*KIT* (AD)	Hypopigmented patches of skin and hair, hyperpigmentation of skin, CALMs, and axillary/inguinal freckling	*KIT* gene testing
PTEN hamartoma tumor syndrome	*PTEN* (AD)	Hamartomas, trichilemmomas, papillomatous papule, acral and plantar keratoses, lipomas, autism spectrum disorder, and macrocephaly	*PTEN* gene testing
Ring chromosome syndrome 7, 11, 12, 15, and 17	Sporadic	Depends on which chromosome but may include CALMs, nevus flammeus, dark pigmented nevi, patchy hypopigmented areas, microcephaly, mental delay, short stature, and skeletal abnormalities	Karyotype

Continued

Table 693.2 Conditions Featuring Café au Lait Macules—cont'd

CONDITION	GENE (INHERITANCE)	ASSOCIATED FEATURES*	ADDITIONAL TESTING TO CONSIDER
RSS	11p15 locus Chromosome 7 (sporadic) *CDKN1C, IGF2, PLAGL2, HMGA2* (AD)	Growth restriction, relative macrocephaly, craniofacial abnormalities, mild cognitive impairment, and delay	Molecular and methylation testing of 11p15 and uniparental disomy 7 ± RSS gene panel testing
Tuberous sclerosis	*TSC1, TSC2* (AD)	Facial angiofibromas, ash leaf macules, thumbprint-like macules, confetti-like skin lesions, shagreen patch, Koenen tumors, hamartomas, multisystem lymphangioleiomyomatosis, epilepsy, cognitive deficits	*TSC1* and *TSC2* gene testing

*All disorders listed have had multiple CALMs associated with them.

AD, Autosomal dominant; AFP, alpha fetoprotein; AR, autosomal recessive; ATM, ataxia telangiectasia variant gene; BRAF, B-RAF proto-oncogene; CDKN1C, cyclin-dependent kinase inhibitor 1C; EPCAM, epithelial cell adhesion molecule; FANCA, FA complementation group A; GNAS, GNAS complex locus; HMGA2, high mobility group AT-hook 2; IFG2, insulin-like growth factor 2; KIT, KIT proto-oncogene receptor tyrosine kinase; KITLG, *KIT* ligand; MAP2K1/2; mitogen-activated protein kinase 1, MLH1; MutL, *Escherichia coli* homolog of 1; MSH2; MutS, *E. coli* homolog of 2; MSH6, MutS , *E. coli* homolog of 6; NF1, neurofibromin 1; NF2, neurofibromin 2; PLAGL2, PLAG1-like zinc finger 2; PTEN, phosphate and tensin homolog; *PMS2*, postmeiotic segregation increased *Saccharomyces cerevisiae* 2; PTPN11, protein tyrosine phosphatase nonreceptor type 11; RSS, Russel-Silver syndrome; SPRED 1, sprouty-related EVH1 domain-containing protein 1; SOS2, SOS RAS/RAC guanine nucleotide exchange factor 2; TSC1, TSC1 gene; TSC2, TSC2 gene.

From Albaghdadi M, Thibodeau ML, Lara-Corrales I. Updated approach to patients with multiple café au lait macules. *Dermatol Clin*. 2022;40:9–23, Table 2.

Chapter 694

Hypopigmented Lesions

Joel C. Joyce

ALBINISM

Congenital oculocutaneous albinism (OCA) consists of partial or complete failure of melanin production in the skin, hair, and eyes despite the presence of normal number, structure, and distribution of melanocytes. These disorders are autosomal recessive in inheritance and result from pathogenic variants in genes related to melanin synthesis or the transport and storage of melanin within cells (Table 694.1). Tyrosinase is the copper-containing enzyme that catalyzes multiple steps in melanin biosynthesis (see Chapter 105.2), and gene variants resulting in abnormal function of tyrosinase and associated transporter proteins result in various OCA phenotypes. Gene variants resulting in abnormal structure and function of several cellular organelles may result in OCA with other extracutaneous complications.

Oculocutaneous Albinism with Abnormal Melanin Production

Oculocutaneous albinism type 1 (OCA1) is characterized by great reduction in or absence of tyrosinase activity caused by pathogenic gene variants in *TYR*. OCA1-A, the most severe form, is characterized by a lack of visible pigment in hair, skin, and eyes (Fig. 694.1). This manifests as photophobia, nystagmus, defective visual acuity, white hair, and white skin. The irises are blue-gray in oblique light and prominent pink in reflected light. OCA1-B, or yellow **albinism**, manifests at birth as white hair, pink skin, and gray eyes. This type is particularly prevalent in Amish communities. Progressively the hair becomes yellow-red, the skin tans lightly on exposure to the sun, and the irises may accumulate some brown pigment, with a resultant improvement in visual acuity. Photophobia and nystagmus are present but mild. OCA-TS is a temperature-sensitive type of albinism. The abnormal tyrosinase has decreased activity at 35–37°C (95–98.6°F). Therefore cooler regions of the body such as the limbs and head pigment to some degree, whereas other areas remain depigmented.

Oculocutaneous albinism type 2 (OCA2) ranges from nearly normal to closely resembling type 1 albinism. This is the most common form of albinism seen worldwide. Little or no melanin is present at birth, but pigment, particularly red-yellow pigment, may accumulate during childhood to produce straw-colored or light brown skin in White individuals. Pigmented nevi may develop. Progressive improvement in visual acuity and nystagmus occurs with aging. Black individuals may have yellow-brown skin, dark-brown freckles in sun-exposed areas, and brown coloration of the irises. Brown OCA is an allelic variant of OCA2. Prader-Willi and Angelman syndromes, which include hypopigmentation, have deletions that include the gene *(OCA2)* involved in OCA2.

Oculocutaneous albinism type 3 (OCA3), also known as *rufous albinism,* is seen predominantly in patients of African descent. It is characterized by red hair, reddish-brown skin, pigmented nevi, freckles, reddish-brown to brown eyes, nystagmus, photophobia, and decreased visual acuity. Vision abnormalities tend to be milder than in other forms of OCA. Abnormal gene variants in *TYRP1* are typically associated with development of OCA3.

Oculocutaneous albinism type 4 (OCA4) is a rare OCA with clinical findings similar to those in OCA2. Gene variants in *SLC45A2* are known to cause OCA4.

Additional rare variants of OCA exist that may present with similar clinical features to those noted earlier. See Table 694.1.

Cross-McKusick-Breen syndrome consists of tyrosinase-positive albinism with ocular abnormalities, cognitive impairment, spasticity, and athetosis. The genetic defect is unidentified.

Because of the absence of normal protection by adequate amounts of epidermal melanin, persons with albinism are predisposed to development of actinic keratoses and cutaneous carcinoma secondary to skin damage by ultraviolet light. Protective clothing and a broad-spectrum sunscreen (see Chapter 697) should be worn during exposure to sunlight.

Oculocutaneous Albinism with Organelle Dysfunction

Hermansky-Pudlak syndrome is a collection of autosomal recessive genetic disorders characterized by OCA, ceroid accumulation in lysosomes, and platelet dysfunction, resulting in prolonged bleeding time (Table 694.2). Ceroid accumulation over time can cause damage to the lung, kidneys, and gastrointestinal tract, with risk of development of granulomatous colitis and/or pulmonary fibrosis. Abnormalities in the development of platelet-dense granules lead to platelet dysfunction.

Table 693.2 Conditions Featuring Café au Lait Macules—cont'd

CONDITION	GENE (INHERITANCE)	ASSOCIATED FEATURES*	ADDITIONAL TESTING TO CONSIDER
RSS	11p15 locus Chromosome 7 (sporadic) *CDKN1C, IGF2, PLAGL2, HMGA2* (AD)	Growth restriction, relative macrocephaly, craniofacial abnormalities, mild cognitive impairment, and delay	Molecular and methylation testing of 11p15 and uniparental disomy 7 ± RSS gene panel testing
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Chapter 694

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Table 694.1 Forms of Oculocutaneous Albinism

TYPE	PERCENTAGE OF PATIENTS WORLDWIDE	GENETIC VARIANT	FUNCTION OF AFFECTED GENE	COMMENTS
OCA1A	50%	TYR (absence) = tyrosinase negative	Rate-limiting steps in melanin formation; hydroxylates L-tyrosine to L-DOPA and L-DOPA to DOPA-quinone	1:40,000; most severe cutaneous and ocular defects; highest risk of skin cancer; most common type in Whites
OCA1B		TYR (decreased)	Critical enzyme in melanin formation	Subtypes: yellow (yellow hair); platinum (metallic tinge); minimal pigment (only eyes darken)
OCA1-TS		TYR (variant site functions at higher temperatures)	Temperature sensitive	Melanin at cooler sites (arms, legs) Occurs in Siamese cats
OCA2	30%	P protein	Transmembrane protein that is key for melanosome biogenesis and normal processing and transport of TYR and *TRYP1*	1:36,000 (Whites); TYR-positive; includes brown albinism (1:3,900-1:10,000; most common form in patients of African origin; more pigment with advancing age); also includes red OCA2 with concomitant *MC1R* pathogenic variant and red hair
OCA3 (Rufous)	3%	*TRYP1*	Catalyzes oxidation of 5,6-dihydroxyindole-2-carboxylic acid monomers into melanin and stabilizes TYR so it can leave endoplasmic reticulum for incorporation into melanosomes	1:8,500 Africans; reddish-bronze color to skin and hair
OCA4	17%	*MATP/SLC45A2*	Membrane transporter in melanosomes and regulates pH	Rare (Whites); 27% of OCA in Japan; resembles OCA2
OCA5		Unknown (4q24)	—	One Pakistani family
OCA6		*SLC24A5*	$Na^+/K^+/Ca^+$ + solute carrier protein involved in melanosome maturation and melanin biosynthesis	Heterogeneous extent of pigmentation
OCA7		*LRMDA*	Melanocyte differentiation	Rare; skin color lighter only when compared with relatives

LRMDA, Leucine-rich melanocyte differentiation associated protein; MATP, membrane-associated transporter protein; OCA, oculocutaneous albinism; P protein, pink-eyed dilution protein; TS, temperature sensitive; TYR, tyrosinase; TRYP1, tyrosinase-related protein 1.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 11.1, p. 291.

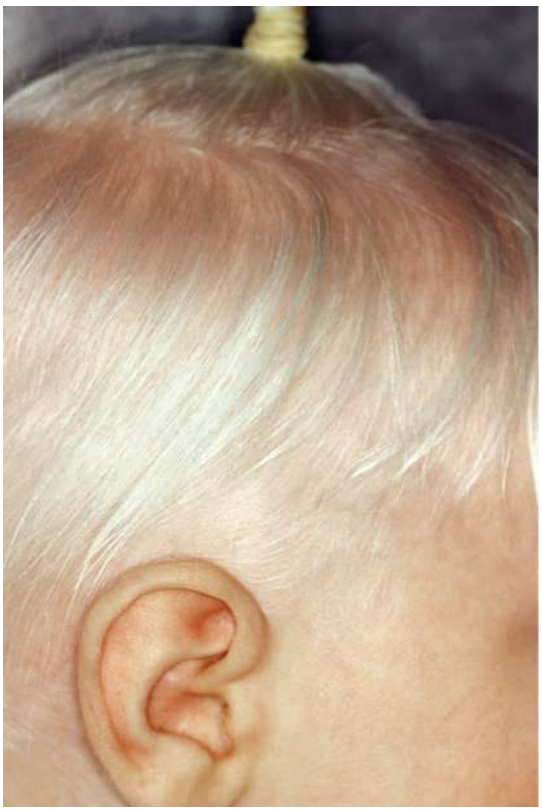

Fig. 694.1 White hair and skin in oculocutaneous albinism type 1 (OCA1).

Chédiak-Higashi syndrome (see Chapter 170) is another genetic abnormality associated with dysfunction of lysosome-related organelles. Patients with Chédiak-Higashi syndrome have hypopigmentation of the skin, eyes, and hair; prolonged bleeding times and easy bruising; recurrent infections; abnormal natural killer cell function; and peripheral neuropathy. Chédiak-Higashi syndrome is caused by pathogenic gene variants in the *CHS1/LYST* gene, which is a lysosomal trafficking regulatory gene.

MELANOBLAST MIGRATION ABNORMALITIES

Piebaldism

A congenital autosomal dominant disorder, piebaldism is characterized by sharply demarcated amelanotic patches that occur most frequently on the forehead, anterior scalp (producing a white forelock), ventral trunk, elbows, and knees. Islands of normal or darker-than-normal pigmentation may be present within the amelanotic areas (Fig. 694.2). The plaques are a result of a permanent localized absence of melanocytes as a result of a defect in the *KIT* protooncogene, which encodes the cell surface receptor transmembrane tyrosine kinase. The pattern of depigmentation arises from defective melanoblast migration from the neural crest during development. The reason that piebaldism is a localized and not a generalized process remains unknown. Piebaldism must be differentiated from vitiligo, which may be progressive and is not usually congenital, nevus depigmentosus, and Waardenburg syndrome.

Waardenburg Syndrome

Waardenburg syndrome also manifests at birth as localized areas of depigmented skin and hair. There are four main types of Waardenburg syndrome with additional subtypes identified. The hallmark of **Waardenburg type 1** (WS1) is the white forelock, which is seen in

Table 694.2 Clinical Features of Hermansky-Pudlak Syndrome

TYPE	PATHOGENIC VARIANT	UNDERLYING CAUSE	FINDINGS ASSOCIATED WITH THE CUTANEOUS PIGMENT DILUTION
HPS-1 HPS-4	*HPS1* (82% of HPS in Puerto Ricans; 37% in non–Puerto Ricans) *HPS4*	BLOC-3 deficiency: HPS1 and HPS4 associate in a complex (BLOC-3) that regulates biogenesis of melanosomes, platelet-dense bodies, and the lung lamellar body	Nystagmus, decreased visual acuity; prolonged bleeding; pulmonary fibrosis (typical onset in young adults); granulomatous colitis (up to one third of patients)
HPS-2 HPS-10	*AP3B1* (~10% of non–Puerto Ricans) and *AP3D1* (rare)	AP-3 deficiency: *AP3B1* and APSD1 encode subunits of AP-3, which mediates protein trafficking into transport vesicles of the lysosome (and is thus also involved in immune function)	Nystagmus, decreased visual acuity; prolonged bleeding; congenital neutropenia and impaired NK cell cytotoxicity; recurrent bacterial and viral infections; conductive hearing loss; fibrosing lung disease (30–50%) beginning during childhood; seizures in HPS-10
HPS-3 HPS-5 HPS-6	*HPS3* (~20% in Puerto Ricans and ~12% in non–Puerto Ricans) *HPS5* (~9% in non–Puerto Ricans) *HPS6* (~16% in non–Puerto Ricans)	BLOC-2 deficiency: HPS3, HPS5, and HPS6 are associated in a complex (BLOC-2) that localizes tyrosinase and *TRYP1*, allowing them to function normally	Nystagmus, decreased visual acuity; mild extraocular manifestations (bleeding, skin pigmentation)
HPS-7 HPS-8 HPS-9	*DTNBP1* *BLOC1S3* *BLOC1S6/PLDN*	BLOC-1 deficiency: Dysbindin, BLOC1S3, and BLOC1S6 are subunits of BLOC-1 and also involved in skin melanosome biogenesis and platelet function	Nystagmus, decreased visual acuity; prolonged bleeding (may not be a feature with *BLOC1S6* pathogenic variant)

BLOC, Biogenesis of lysosome-related organelles complex; DTNBP1, dystrobrevin binding protein 1; HPS, Hermansky-Pudlak syndrome.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*, 6th ed. Philadelphia: Elsevier; 2022: Table 11.2, p. 295.

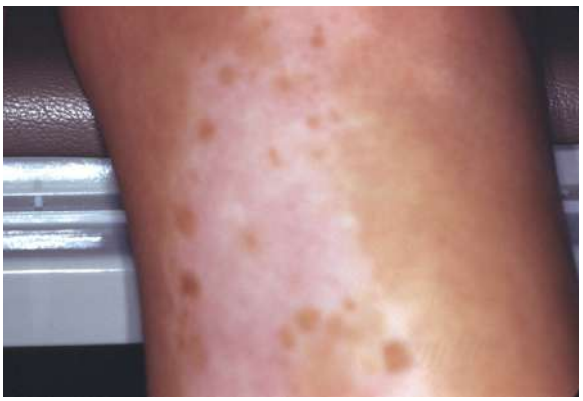

Fig. 694.2 Depigmented macule with islands of hyperpigmentation in piebaldism.

20–60% of patients. Only 15% of patients have areas of depigmented skin. Deafness occurs in 9–37%, heterochromia irides in 20%, and unibrow (synophrys) in 17–69% of those affected. Dystopia canthorum (i.e., telecanthus) is seen in all patients with WS1. **Waardenburg type 2** is similar to type 1, except that patients with type 2 lack dystopia canthorum, but they also have a higher incidence of deafness. **Waardenburg type 3** is similar to WS1, except that patients also have limb abnormalities. It is also called *Klein-Waardenburg syndrome.* **Waardenburg type 4** is also called *Shah-Waardenburg syndrome.* Patients with this type all have Hirschsprung disease. Dystopia canthorum is seldom seen in these patients. Multiple pathogenic variants in multiple genes have been identified as causative of the various types of **Waardenburg syndrome** (Table 694.3).

Tuberous Sclerosis Complex (*TSC1*, *TSC2* Genes)

See Chapter 636.2 for a discussion of this complex.

Hypomelanosis of Ito

Hypomelanosis of Ito is a rare congenital skin disorder affecting children that can have associated defects in several organ systems. There is no evidence for genetic transmission; chromosomal mosaicism and chromosomal translocations have been reported. Hypomelanosis of Ito is a descriptive diagnosis. Blaschkoid or mosaic hypomelanosis may be better descriptive terms. It is also known as *incontinentia pigmenti achromians.*

The skin lesions of hypomelanosis of Ito are generally present at birth but may be acquired in the first 2 years of life. The lesions are similar to a negative image of those present in incontinentia pigmenti, consisting of patterned, hypopigmented macules arranged over the body surface in sharply demarcated whorls, streaks, and patches that follow the lines of Blaschko (Fig. 694.3). The palms, soles, and mucous membranes are spared. The hypopigmentation remains unchanged throughout childhood but fades during adulthood. The degree of depigmentation varies from hypopigmented to achromic. Neither inflammatory nor vesicular lesions precede the development of the pigmentary changes as in incontinentia pigmenti. The hypopigmented areas demonstrate fewer and smaller melanocytes and a decreased number of melanin granules in the basal cell layer than normal. Inflammatory cells and pigment incontinence are lacking.

The majority of patients with hypomelanosis of Ito have no associated abnormalities, but involvement of other organ systems can rarely occur. The most commonly associated abnormalities involve the nervous system, including intellectual disability (70%), seizures (40%), microcephaly (25%), and muscular hypotonia (15%). The musculoskeletal system is the second most frequently involved system, affected by scoliosis and thoracic and limb deformities. Minor ophthalmologic defects (strabismus, nystagmus) are present in 25% of patients, and 10% have cardiac defects. These frequencies are likely to be overestimated because patients with isolated skin disease often do not seek further evaluation. The differential diagnosis includes systematized nevus depigmentosus, which is a stable leukoderma not associated with systemic manifestations. Differentiation from incontinentia pigmenti, particularly the hypopigmented fourth stage, is critical for genetic counseling because incontinentia pigmenti, unlike hypomelanosis of Ito, is inherited.

Table 694.3 Subtypes of Waardenburg Syndrome

DISORDER	INHERITANCE	GENE(S)	OTHER COMMENTS
WS1	AD	*PAX3*	Most common form; dystopia canthorum
WS2	AD	*MITF, SOX10, SLUG, KITLG, KIT*	No facial dysmorphism; high risk of hearing loss; iris heterochromia
WS3	AD/AR	*PAX3*	Associated limb abnormalities
WS4A	AD/AR	*EDNRB*	Aganglionic megacolon
WS4B	AD/AR	*EDN3*	Aganglionic megacolon
WS4C	AD	*SOX10*	Aganglionic megacolon
PCWH	AD	*SOX10*	Severe hypotonicity with central nervous system and peripheral nerve abnormalities

AD, Autosomal dominant; AR, autosomal recessive; EDN, endothelin; EDNRB, endothelin receptor beta; PCWH, peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 11.4, p. 298.

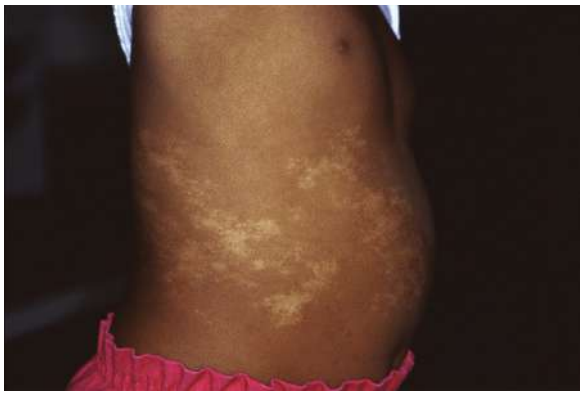

Fig. 694.3 Marbled hypopigmented streaks on the abdomen in hypomelanosis of Ito.

Vitiligo

Epidemiology and Etiology

Vitiligo is an *acquired* macular depigmentation disorder associated with the destruction of melanocytes. The disorder represents a clinical end-point resulting from a complex interaction of environmental, genetic, and immunologic factors. Autoimmune, genetic, autocytotoxic, and neural theories have been postulated. The prevalence is 0.5–2% of most populations.

There is an autoimmune component to vitiligo. Eighty percent of patients with active disease have anti-melanocyte antibodies to one of several antigens on melanocytes. These antibodies appear to be cytotoxic for melanocytes. There is also a correlation between disease activity and the titer of serum anti-melanocyte antibody. Melanocyte-specific $CD8^+$ T lymphocytes are also involved in the pathogenesis of vitiligo. These antibodies and T cells recognize a variety of melanocyte enzymatic and structural proteins.

The genetic epidemiology of vitiligo is part of a broader genetically determined autoimmune and autoinflammatory diathesis. Between 15 and 20% of patients with generalized vitiligo have one or more affected first-degree relatives. In these families the genetic pattern is suggestive of polygenic, multifactorial inheritance. In the other patients, the disease occurs sporadically. Genome-wide association studies in patients with vitiligo have identified a substantial number of associated genes, of which consistent association is seen with *DDR1, XBP1, NLRP1, PTPN22,* and *COMT,* although many other genes have been implicated.

Table 694.4 Vitiligo Subgroups

DERMATOMAL OR SEGMENTAL	NONDERMATOMAL OR NONSEGMENTAL
Onset in childhood	Can begin in childhood; 50% before 20 yr of age
Less common	More common
Rapid onset; stabilizes in ~1 yr	Progressive, with flare-ups; lifelong
Involves hair after onset	Involves hair in later stages
Autoimmune diseases uncommon	Personal or family history of autoimmunity* common
Often occurs on the face or upper extremities	Occurs at sites sensitive to pressure, friction, or trauma; Koebner phenomenon
Responsive to autologous grafting, with repigmentation	Relapses after autologous grafting
Difficult to distinguish from nevus depigmentosus	Associated with halo nevus formation

*Autoimmune thyroid diseases, type 1 diabetes, psoriasis, pernicious anemia, systemic lupus erythematosus, Addison disease, alopecia areata.

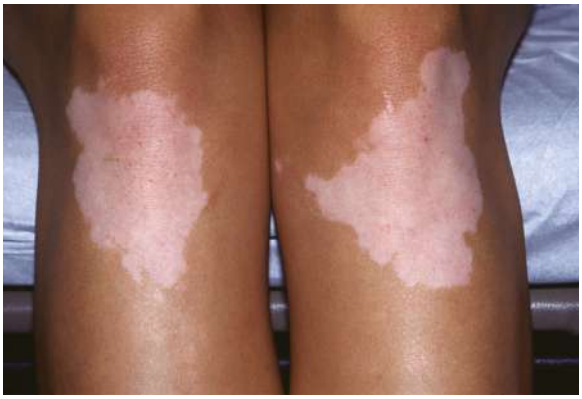

Fig. 694.4 Sharply demarcated, symmetric, depigmented areas of vitiligo.

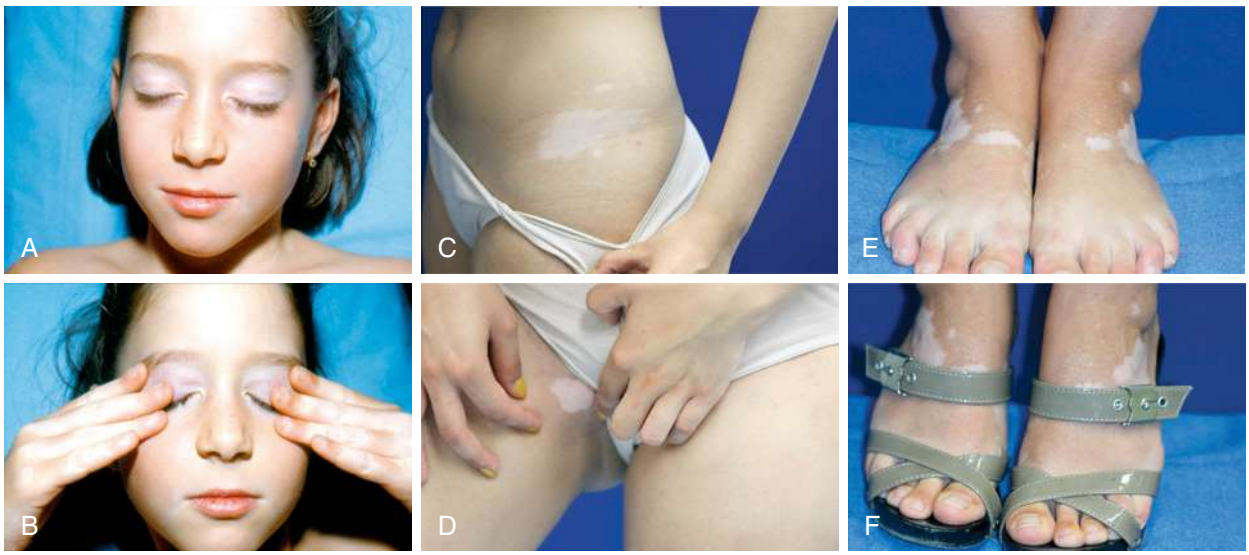

Fig. 694.5 Koebner phenomenon in relation to daily living activities. **A** and **B**, Eye rubbing. **C** and **D**, Underwear print. **E** and **F**, Shoe print. *(From Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. Lancet. 2015;386:74–82, Fig. 5.)*

Many authorities believe that the cause of melanocyte destruction in vitiligo is an interferon gamma–based immune destruction and melanocyte apoptosis. It has also been suggested that melanocytes are destroyed because of the accumulation of a toxic melanin synthesis intermediate and/or lack of protection from hydrogen peroxide and other oxygen radicals. There is in vitro evidence that some of these metabolites may be lethal to melanocytes.

Clinical Manifestations

There are two subtypes of vitiligo, generalized (nonsegmental) and segmental, which likely are distinctly different diseases (Table 694.4). Generalized vitiligo (85–90% of cases) may be divided into widespread (type A) and localized (type B). Approximately 50% of all patients with vitiligo have onset before 18 years of age, and 25% demonstrate depigmentation before age 8 years. Most children have the generalized form, but the segmental type is more common among children than among adults. Patients with the generalized form usually present with a remarkably symmetric pattern of white macules and patches (Fig. 694.4); the margins may be somewhat hyperpigmented. The patches tend to be acral and/or periorificial. Occasionally, almost the entire skin surface becomes depigmented. Vitiligo lesions may develop in areas of traumatized skin (Koebner phenomenon) (Fig. 694.5).

There are several varieties of localized vitiligo. One form is halo nevus phenomenon, whereby benign moles develop depigmented rings at the periphery (see Chapter 692). Premature graying of scalp hair (canities) has also been considered a form of localized vitiligo. In segmental vitiligo, depigmented areas are typically limited to a dermatomal distribution. This type of vitiligo has a rapid onset and progression in a localized area without the development of depigmentation in other areas.

A number of **autoimmune diseases** occur in up to 20% of patients with vitiligo, including Addison disease, Hashimoto thyroiditis, pernicious anemia, diabetes mellitus, hypoparathyroidism, and polyglandular autoimmune syndrome with selective immunoglobulin A deficiency. In addition, other diseases with possible immune defects, such as alopecia areata and morphea, have been seen in patients with vitiligo.

Vogt-Koyanagi-Harada syndrome is vitiligo associated with uveitis, dysacusia, meningoencephalitis, and depigmentation of the skin, scalp hair, eyebrows, and eyelashes. In **Alezzandrini syndrome**, vitiligo is associated with tapetoretinal degeneration and deafness. It is typically unilateral. Light microscopic examination of early lesions shows mild inflammatory change. Over time, degenerative changes occur in melanocytes, leading to their complete disappearance.

The differential diagnosis of vitiligo includes other causes of widespread acquired leukoderma. The two most common alternative diagnoses are pityriasis versicolor and postinflammatory hypopigmentation.

Treatment

Localized areas of vitiligo may respond to a potent topical steroid (class I or II) and/or topical calcineurin inhibitor (tacrolimus or pimecrolimus), depending on the location of involvement. Therapy with Janus kinase inhibitors has been effective in adults with vitiligo. In patients with more extensive involvement, narrow-band ultraviolet light B (NBUVB) [UVB311] is the treatment of choice. Treatment with NBUVB is often undertaken simultaneously with topical therapy. Systemic therapy and whole-body depigmentation are rarely used in children, although systemic corticosteroids can be given to slow the rate of change in rapidly progressive depigmentation. In all forms of vitiligo, response to therapy may be slow, taking many months to years. For those not interested in treatment, cover-up cosmetics may be used. All areas of vitiligo are susceptible to sun damage, and care should be taken to minimize sun exposure of affected areas. Spontaneous remission may be seen in a small percentage of cases.

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Chapter 695

Vesiculobullous Disorders

Joel C. Joyce

Many diseases are characterized by vesiculobullous lesions; they vary considerably in cause, age of onset, and pattern. The morphology and distribution of the blisters in these **blistering disorders** often provides a visual clue to the location of the lesion within the skin. Blisters localized to the epidermal layers are thin-walled, relatively flaccid, and easily ruptured. Subepidermal blisters are tense, thick-walled, and more durable. Biopsies of blisters can be diagnostic because the level of cleavage within the skin and associated findings, such as the nature of the inflammatory infiltrate, are characteristic for a particular disorder. Other diagnostic procedures, such as direct immunofluorescence on affected tissue and indirect immunofluorescence from a patient's serum to detect circulating antibodies, can often help to distinguish vesiculobullous disorders that have nearly identical histopathologic findings (Table 695.1).

695.1 Erythema Multiforme

Joel C. Joyce

ETIOLOGY

Among the numerous factors implicated in the etiology of erythema multiforme (EM), infection with herpes simplex virus (HSV) is the most common. Other viral infections, as well as vaccinations, have been implicated as triggers. Infection with *Mycoplasma pneumoniae* and other pathogens may produce a similar lesion, particularly in children and young adults; differentiation from Stevens-Johnson syndrome and reactive infectious mucocutaneous eruptions (RIMEs; see Chapter 695.2) can be difficult. HSV labialis and, less commonly, HSV genitalis are implicated in 60–70% of episodes of EM and are believed to trigger nearly all episodes of *recurrent* (six or more episodes per year) EM, frequently in association with sun exposure. HSV antigens and DNA are present in skin lesions of EM but are absent in nonlesional skin. The presence of the human leukocyte antigens A33, B62, B35, DQw3 (DQB1*0301 split), and DR53 is associated with an increased risk of HSV-induced EM, particularly the recurrent form. Most patients experience a single self-limited episode of EM. Lesions of HSV-induced recurrent EM typically develop 10-14 days after onset of recurrent HSV eruptions and have a similar appearance from episode to episode, but they may vary in frequency and duration in a given patient. Not all episodes of recurrent HSV evolve into EM in susceptible patients.

Drug-related EM is less common (<10% of patients) and may be associated with nonsteroidal antiinflammatory agents, including acetaminophen, sulfonamides, and other antibiotics. The differential diagnosis in drug-related EM should include severe cutaneous adverse reactions such as Stevens-Johnson syndrome (see Chapter 695.3) and drug hypersensitivity syndrome (sometimes called drug reaction [rash] with eosinophilia and systemic symptoms [DRESS] or drug-induced hypersensitivity syndrome [DIHS]) (see Chapter 686.2).

CLINICAL MANIFESTATIONS

EM has numerous morphologic manifestations on the skin, varying from erythematous macules, papules, vesicles, bullae, or urticarial plaques to patches of confluent erythema. The eruption appears most commonly in patients between the ages of 10 and 40 years (with highest incidence in males in the second decade) and usually is asymptomatic, although a burning sensation or pruritus may be present. The diagnosis of EM is established by finding the classic lesion: doughnut-shaped, **targetoid** (target-like, iris, or bull's-eye) papules with an erythematous outer border, an inner pale ring, and a dusky purple to necrotic center (which sometimes blisters and erodes; Figs. 695.1 and 695.2).

EM is characterized by an abrupt, symmetric cutaneous eruption, most commonly on the extensor upper extremities; lesions are relatively sparse on the face, trunk, and legs. Lesions can be seen on the palms and soles. The eruption often appears initially as red macules or urticarial plaques that evolve and expand centrifugally to form lesions up to 2 cm in diameter with a dusky to necrotic center. Lesions of a particular episode typically appear within 72 hours and remain fixed in place (average duration: 7 days). Oral lesions may occur with a predilection for the vermilion border of the lips and the buccal mucosa, but other mucosal surfaces are usually spared. EM may manifest initially as urticaria-like lesions, but in contrast to urticaria, a given lesion of EM does not fade within 24 hours. Prodromal symptoms are generally absent. Prognosis is favorable with limited long-term morbidity. Lesions typically resolve without sequelae in approximately 2 weeks, but in darker pigmented individuals, pigmentary alterations at the site of lesions can be long-standing. *Progression to Stevens-Johnson syndrome does not occur.* Many authors distinguish between **EM minor** (mainly cutaneous typical or atypical **targetoid** lesions affecting <10% body surface area plus no or limited mucosal involvement, often limited to one site, such as the mouth) and **EM major** (same cutaneous involvement pattern as EM minor plus two or more mucosal sites with more severe oral involvement). EM major and Stevens-Johnson syndrome are separate entities.

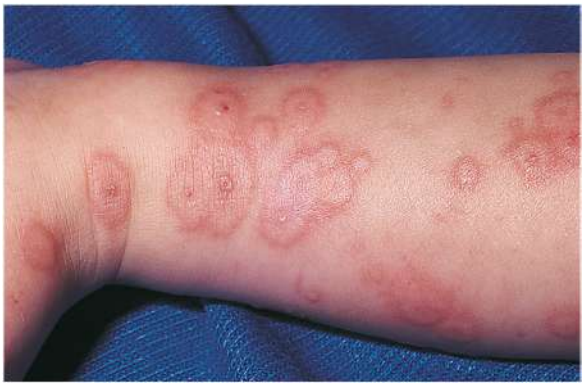

Fig. 695.1 Early fixed papules with a central dusky zone on the dorsum of the hand of a child with erythema multiforme caused by herpes simplex virus. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002:156.)*

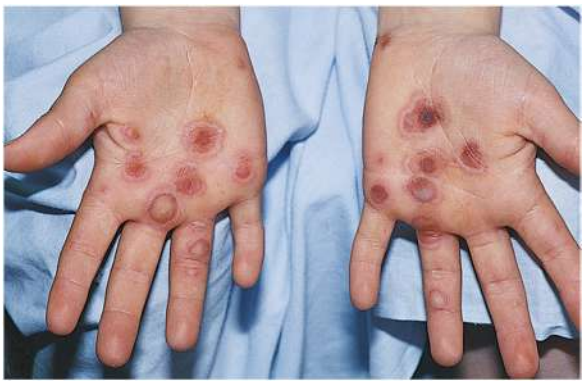

Fig. 695.2 "Target" or "iris" lesions with characteristic central dusky zone on palms of a child with erythema multiforme caused by herpes simplex virus. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002:156.)*

Table 695.1 Sites of Blister Formation and Diagnostic Studies for the Vesiculobullous Disorders

DISORDER	BLISTER CLEAVAGE SITE	DIAGNOSTIC STUDIES
Acrodermatitis enteropathica	IE	Serum zinc level
Bullous impetigo	GL	Smear, culture
Bullous pemphigoid	SE (junctional)	Direct and indirect immunofluorescence
Candidiasis	SC	KOH preparation, culture
Dermatitis herpetiformis	SE	Direct immunofluorescence
Dermatophytosis	IE	KOH preparation, culture
Dyshidrotic eczema	IE	Routine histopathology
EB simplex	IE	Electron microscopy, immunofluorescence mapping, genetic testing
Junctional EB	SE (junctional)	Electron microscopy, immunofluorescence mapping, genetic testing
Recessive dystrophic EB	SE	Electron microscopy, immunofluorescence mapping, genetic testing
Dominant dystrophic EB	SE	Electron microscopy, immunofluorescence mapping, genetic testing
Epidermolytic ichthyosis	IE	Routine histopathology
Erythema multiforme	SE	Routine histopathology
Erythema toxicum	SC, IE	Smear for eosinophils
Incontinentia pigmenti	IE	Smear for eosinophils Routine histopathology
Insect bites	IE	Routine histopathology
Kindler syndrome	IE, SE	Electron microscopy, immunofluorescence mapping, genetic testing
Linear IgA dermatosis	SE	Direct immunofluorescence
Mastocytosis	SE	Routine histopathology
Miliaria crystallina	IC	Routine histopathology
Neonatal pustular melanosis	SC, IE	Smear for neutrophils
Pemphigus foliaceus	GL	Direct and indirect immunofluorescence studies
		Tzanck smear
Pemphigus vulgaris	Suprabasal	Direct and indirect immunofluorescence studies
		Tzanck smear
Scabies	IE	Skin scraping
Staphylococcal scalded skin syndrome	GL	Routine histopathology
Toxic epidermal necrolysis	SE	Routine histopathology
Viral blisters	IE	Viral PCR (preferred) or direct immunofluorescence testing for HSV and VZV Routine histopathology

EB, Epidermolysis bullosa; GL, granular layer; HSV, herpes simplex virus; IC, intracorneal; IE, intraepidermal; KOH, potassium hydroxide; PCR, polymerase chain reaction; SC, subcorneal; SE, subepidermal; VZV, varicella-zoster virus.

Pathogenesis

The pathogenesis of EM is unclear, but it may be a host-specific, cell-mediated immune response to an antigenic stimulus, resulting in damage to keratinocytes. The HSV *Pol1* gene expressed in HSV-induced recurrent EM lesions upregulates/activates the transcription factor SP1 and inflammatory cytokines. These cytokines, released by activated mononuclear cells and keratinocytes, may contribute to epidermal cell death and constitutional symptoms.

Pathology

Microscopic findings in EM are variable but may aid in diagnosis. Early lesions typically have slight intercellular edema, rare dyskeratotic keratinocytes, and basal vacuolation in the epidermis, as well as a perivascular lymphohistiocytic infiltrate with edema in the upper dermis. More mature lesions demonstrate accentuation of these characteristics and the development of lymphocytic exocytosis, as well as an intense, perivascular, and interstitial mononuclear infiltrate in

the upper third of the dermis. In severe cases, the entire epidermis becomes necrotic.

Differential Diagnosis

The differential diagnosis of EM also includes RIME, bullous pemphigoid, pemphigus vulgaris, linear immunoglobulin (Ig) A dermatosis, graft-versus-host disease, fixed-drug eruption, bullous drug eruption, urticaria, viral infections such as HSV, reactive arthritis syndromes, Kawasaki disease, Sweet syndrome, Behçet disease, vasculitis, erythema annulare centrifugum, and polymorphous drug eruption. EM that primarily involves the oral mucosa may be confused with Stevens-Johnson syndrome, bullous pemphigoid, pemphigus vulgaris, vesiculobullous or erosive lichen planus, Behçet syndrome, recurrent aphthous stomatitis, and primary herpetic gingivostomatitis. In contrast to EM, Stevens-Johnson syndrome manifests with erythematous or purpuric macules (no papules) and usually begins on the trunk. Serum sickness–like reaction to cefaclor (or other antibiotics) may also manifest as EM-like lesions; the lesions may develop a dusky to purple center, but in most cases, the eruption of cefaclor-induced serum sickness–like reaction is pruritic, transient, and migratory and is probably urticarial rather than true EM.

Treatment

Treatment of EM is supportive. If secondary to underlying infection, the infection should be treated. Topical emollients, systemic antihistamines, and nonsteroidal antiinflammatory agents do not alter the course of the disease but may provide symptomatic relief. For individuals with severe mucosal disease, opioids can be used to control pain, and diligent oral hygiene is essential. No controlled, prospective studies support the use of corticosteroids in the management of EM. Prophylactic oral acyclovir given for 6 months may be effective in controlling *recurrent episodes of HSV-associated EM*. On discontinuation of acyclovir, both HSV and EM may recur, although episodes may be less frequent and milder. For recurrent cases not responsive to antiviral therapy, steroid-sparing agents used to decrease frequency of recurrence include azathioprine, mycophenolate mofetil, and dapsone. Appropriate laboratory monitoring is recommended. See Chapter 695.2.

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695.2 Reactive Infectious Mucocutaneous Eruption

Joel C. Joyce

Originally named *Mycoplasma*-induced rash and mucositis (MIRM), RIME may also be caused by other infectious agents such as *Chlamydophila,* enterovirus, COVID-19, and others. It is believed to be a distinct entity not classified as EM or Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN).

RIME presents 1-2 weeks after a prodrome characterized by fever, malaise, headache, and cough or features more characteristic of a specific infection (pneumonia secondary to *M. pneumoniae* or COVID-19). The dominant feature is severe mucositis (Fig. 695.3, Table 695.2) most often involving the oral (~95%), ocular (~80%), and urogenital mucosa. Rash may be absent in ~30%, but when present is sparse; lesions are vesiculobullous (~75%) or atypical targeted (~45%), papules, macules, or morbilliform. Lesions involve <10% of body surface area but rarely may be extensive in severe RIME.

The differential diagnosis includes EM, which manifests with an acral rash that evolves from macules to papules to plaques and target lesions. In addition, severe RIME may resemble SJS/TEN, which presents with macules, purpura, erythroderma, atypical target lesions, and extensive blistering.

Treatment includes mouth care and pain management. Azithromycin is used when there is evidence of *Mycoplasma* infection (positive PCR plus IgM) or *Chlamydophila* infection. Steroids have been used, as has etanercept, for more severe disease. In general, RIME is a self-limiting disease that heals without residua. Recurrences are rare.

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695.3 Stevens-Johnson Syndrome

Joel C. Joyce

ETIOLOGY

Drugs, particularly sulfonamides, nonsteroidal antiinflammatory agents, antibiotics (particularly β-lactams), and anticonvulsants, are the most common precipitants of the blistering drug rashes known as Stevens-Johnson syndrome (SJS) and toxic epidermal **necrolysis** (TEN). SJS and TEN exist along a spectrum: SJS is defined as affected body surface area <10%, SJS-TEN overlap syndrome as affected body surface area between 10% and 30%, and TEN as affected body surface area >30%. TEN is the most severe disorder in the clinical spectrum of the disease, involving considerable constitutional toxicity and extensive necrolysis of the mucous membranes and >30% of the body surface area. Approximately 80% of cases are classified as SJS. In children in the United States, the risk of death is 0.3–1.5%. Human leukocyte antigen (HLA)-B*1502 and HLA-B*5801 are implicated in the development of these two disorders in Han Chinese patients receiving carbamazepine and in Japanese patients receiving allopurinol, respectively. Current thinking defines most cases of classic SJS as secondary to medications.

Clinical Manifestations

Cutaneous lesions in SJS generally consist initially of erythematous macules that rapidly and variably develop central necrosis to form vesicles, bullae, and areas of denudation on the face, trunk, and extremities. The **Nikolsky sign** (denudation of the skin with gentle

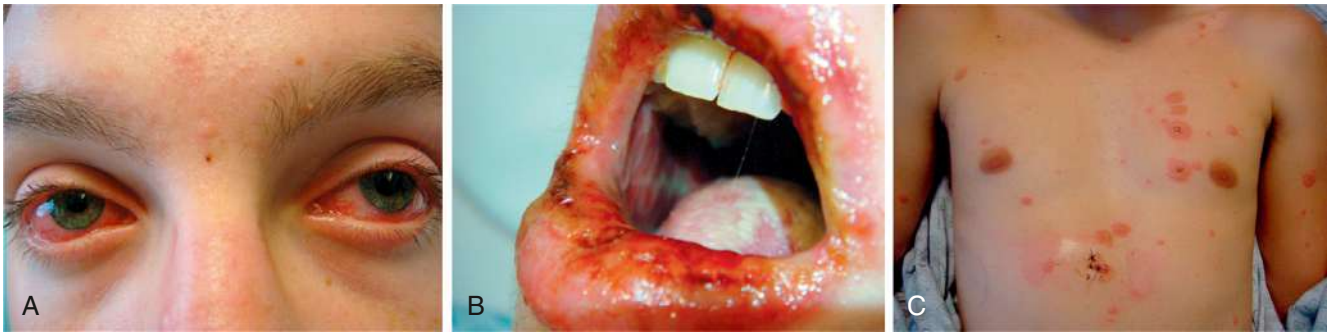

Fig. 695.3 Manifestations of mycoplasma-induced rash and mucositis. **A,** Bilateral conjunctivitis. **B,** Oral mucositis. **C,** Cutaneous targetoid vesicles; sutures are visible at sites where skin biopsy sample was taken. *(From Sandhu R, Mareddy C, Itskowitz M, et al. Mycoplasma-induced rash and mucositis in a young patient with red eyes, oral mucositis, and targetoid cutaneous vesicles. Lancet Infect Dis. 2017;17:562.)*

Table 695.2	Mucocutaneous Lesions of *Mycoplasma pneumoniae*–Induced Rash and Mucositis
ORAL	
Erosions	
Ulcers	
Vesiculobullae	
Denudation	
Hemorrhagic crusting	
OCULAR	
Conjunctival injection	
Conjunctivitis	
Photophobia	
Eyelid edema	
Lid margin ulceration	
Conjunctival pseudomembranes	
Corneal involvement (rare)	
UROGENITAL	
Erosions	
Ulcerations	
Vesiculobullae	
Oro-esophageal	
Mucositis	
ANAL	
Mucositis	
CUTANEOUS	
Vesiculobullae	
Targetoid	
Papules	
Macules	
Morbilliform	

From Ramien ML. Reactive infectious mucocutaneous eruption: Mycoplasma pneumoniae-induced rash and mucositis and other parainfectious eruptions. *Clin Exper Dermatol.* 2021;46:420–429.

tangential pressure) may be positive. The skin lesions are typically more widespread than in EM and are accompanied by involvement of two or more mucosal surfaces, namely the eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or anogenital mucosa (Fig. 695.4). A burning sensation, edema, and erythema of the lips and buccal mucosa are often the presenting signs, followed by development of bullae, ulceration, and hemorrhagic crusting. Lesions may be preceded by a flulike upper respiratory illness. Pain from mucosal ulceration is often severe, but skin tenderness is minimal to absent in SJS, in contrast to pain in TEN. Corneal ulceration, anterior uveitis, panophthalmitis, bronchitis, pneumonitis, myocarditis, hepatitis, enterocolitis, polyarthritis, hematuria, and acute tubular necrosis leading to renal failure may occur. Disseminated cutaneous bullae and erosions may result in increased insensible fluid loss and a high risk of bacterial superinfection and sepsis. New lesions occur in crops, and complete healing may take 4-6 weeks, and ocular scarring, visual impairment, and strictures of the esophagus, bronchi, vagina, urethra, or anus may remain. Nonspecific laboratory abnormalities in SJS include leukocytosis, elevated erythrocyte sedimentation rate, and, occasionally, increased liver transaminase levels and decreased serum albumin values.

Pathogenesis

Pathogenesis is related to drug-specific $CD8^+$ cytotoxic T cells, with perforin/granzyme B and granulysin triggering keratinocyte apoptosis. This process is followed by expanded enactment of apoptosis involving the interaction of soluble Fas ligand with Fas receptor. Consideration has been given to the role that macrophages/monocytes play in the development of SJS/TEN via tumor necrosis factor-α, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), and tumor necrosis factor–inducer of apoptosis weak (TWEAK) signaling pathways. It is likely that many affected individuals have yet unrecognized underlying genetic predispositions.

Fig. 695.4 Bullae are present on the conjunctivae (A) and in the mouth (B) with Stevens-Johnson syndrome. C, Sloughing, ulceration, and necrosis in the oral cavity interfere with eating. Genital lesions cause dysuria and interfere with voiding. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:631.)*

Differential Diagnosis

The differential diagnosis of SJS includes TEN, urticaria, RIME, DRESS (sometimes called DIHS; see Chapter 686), other drug eruptions, and viral exanthems, as well as Kawasaki disease. SJS has rarely been reported in patients with systemic lupus erythematosus.

Treatment

Management of SJS is supportive and symptomatic. Potentially offending drugs must be discontinued as soon as possible. *Ophthalmologic consultation is mandatory because ocular sequelae such as corneal scarring can lead to vision loss.* Application of cryopreserved amniotic membrane to the ocular surface during the acute phase of the disease limits the destructive and long-term sequelae. Early topical steroid treatment may also reduce ocular sequelae. Oral lesions should be managed with mouthwashes and glycerin swabs. Urogenital lesions should be observed closely and treated to prevent stricture or fusion. Topical (oral) anesthetics (diphenhydramine, dyclonine, viscous lidocaine) may provide relief from pain, particularly when applied before eating. Denuded skin lesions can be cleansed with saline or Burrow solution compresses. Treatment may require admission to an intensive care unit, IV fluids,

nutritional support, sheepskin or air-fluid bedding, daily saline or Burrow solution compresses, paraffin gauze or colloidal gel (Hydrogel) dressing of denuded areas, saline compresses on the eyelids, lips, or nose, analgesics, and urinary catheterization (when needed). A daily examination for infection and ocular lesions, which constitute the major cause of long-term morbidity, is essential. Systemic antibiotics are indicated for documented urinary or cutaneous infections and for suspected bacteremia (*Staphylococcus aureus* or *Pseudomonas aeruginosa*) because infection is the leading cause of death. Prophylactic systemic antibiotics are not necessary. Systemic antiinflammatory and immunosuppressive therapies have been controversial. A large systematic review concluded that patients who received IV immunoglobulin (IVIG) and systemic corticosteroids had better outcomes than supportive care alone. Other publications have found that these agents have not improved outcomes such as decreased time to healing or shortened hospital stay. Nevertheless, advocates for use remain, and IVIG (1.5-2.0 g/kg/day × 3 days) may be considered in early disease. Total dose >2 g/kg has shown improved but not statistically significant outcomes in children compared with adults. Case reports/series have demonstrated rapid efficacy with cyclosporine (3 mg/kg/day divided twice daily), as well as with infliximab (5 mg/kg intravenously for one dose) or with etanercept (0.8 mg/kg injection once and then a second dose 1 week later). Emerging evidence has supported the use of anti–tumor necrosis factor therapy in the acute setting, particularly in adults but also in children.

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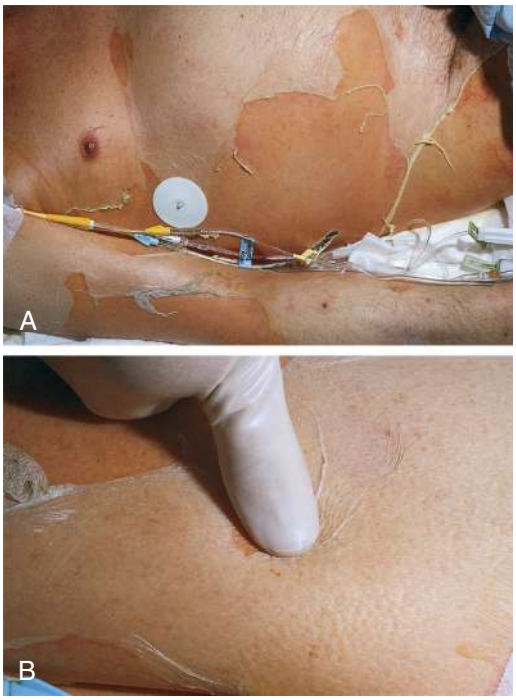

Fig. 695.5 A, Large sheets of full-thickness epidermis are shed. B, Toxic epidermal necrolysis begins with diffuse, hot erythema. In hours the skin becomes painful, and with slight thumb pressure, the skin wrinkles, slides laterally, and separates from the dermis (Nikolsky sign). *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:633.)*

695.4 Toxic Epidermal Necrolysis

Joel C. Joyce

EPIDEMIOLOGY AND ETIOLOGY

The pathogenesis of toxic epidermal necrolysis (TEN) is not proven but may involve a hypersensitivity phenomenon that results in damage primarily to the basal cell layer of the epidermis. Epidermal damage appears to result from keratinocyte apoptosis. This condition, typically attributed as a drug rash, is triggered by many of the same factors that are thought to be responsible for SJS (see Chapter 695.3), principally drugs such as the sulfonamides, β-lactam antibiotics, anticonvulsants, and allopurinol. TEN is defined by (1) widespread blister formation and morbilliform or confluent erythema, associated with skin tenderness; (2) absence of target lesions; (3) sudden onset and generalization within 24-48 hours; and (4) histologic findings of full-thickness epidermal necrosis and a minimal-to-absent dermal infiltrate. Skin involvement should be 30% or greater in contrast to SJS (10% or less) or SJS-TEN overlap (10–30%). These criteria categorize TEN as a separate entity from EM.

CLINICAL MANIFESTATIONS

The prodrome consists of fever, malaise, localized skin tenderness, and diffuse erythema. Inflammation of the eyelids, conjunctivae, mouth, and genitals may precede skin lesions. Flaccid bullae may develop, although this is not a prominent feature. Characteristically, full-thickness epidermis is lost in large sheets (Fig. 695.5). The **Nikolsky sign** (denudation of the skin with gentle tangential pressure) is present, but only in the areas of erythema (see Fig. 695.5). Healing takes place over 14 or more days. Scarring, particularly of the eyes, may result in corneal opacity. The course may be relentlessly progressive, complicated by severe dehydration, electrolyte imbalance, shock, and secondary localized infection and septicemia. Loss of nails and hair may also occur. Long-term morbidity includes alterations in skin pigmentation, eye problems (lack of tears, conjunctival scarring, loss of lashes), and strictures of mucosal surfaces.

Differential Diagnosis

The differential diagnosis includes staphylococcal scalded skin syndrome, in which the blister cleavage plane is intraepidermal; graft-versus-host disease; chemical burns; drug eruptions; toxic shock syndrome; and **pemphigus**. The use of skin histopathology to differentiate SJS-TEN from other similar **blistering disorders** can be difficult, but early full-thickness epidermal necrosis tends to portend a worse clinical prognosis.

Drug hypersensitivity syndrome (sometimes called DRESS or DIHS; see Chapter 686), is a multisystem reaction that appears approximately several weeks to 3 months after the start of therapy with the offending agent. The skin eruption is variable but can be a red-pink morbilliform eruption often associated with facial swelling; lymphadenopathy; fever; hepatic, renal, and pulmonary disease; eosinophilia; atypical lymphocytosis; and leukocytosis.

TREATMENT

Appreciation of the specific etiologic factor is crucial in the treatment of TEN. Because most cases are drug-induced, cessation of the offending agent as soon as possible is critical. Management is similar to that for severe burns and may be best accomplished in a burn unit (see Chapter 89). It may include strict reverse isolation, meticulous fluid and electrolyte therapy, use of an air-fluid bed, and daily cultures. Systemic antibiotic therapy is indicated when secondary infection is evident or suspected. Skin care consists of cleansing with isotonic saline or Burrow solution. Biologic or colloid gel (Hydrogel) dressings alleviate pain and reduce fluid loss. Opiates are often required for pain relief. Mouth and eye care, as for EM major and SJS, may be necessary. Similar considerations as in the treatment of SJS (see Chapter 695.3) with systemic agents may be considered, although controversies remain over relative efficacy and best treatment regimens.

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695.5 Mechanobullous Disorders

Joel C. Joyce

EPIDERMOLYSIS BULLOSA

Diseases categorized under the general term epidermolysis bullosa (EB) are a heterogeneous group of congenital, genetic **blistering disorders**. They differ in severity and prognosis, clinical and histologic features, and inheritance patterns but are all characterized by induction of blisters by trauma and exacerbation of blistering in warm weather. The disorders can be categorized under three major headings with multiple subgroupings: **epidermolysis bullosa simplex** (EBS), **junctional epidermolysis bullosa** (JEB), and **dystrophic epidermolysis bullosa** (DEB) (Tables 695.3-695.8). **Kindler syndrome**, which includes poikiloderma and photosensitivity, as well as easy blistering, is also considered a separate form of EB. **Epidermolysis bullosa acquisita** is an autoimmune disorder producing antibodies to the α chain of type VII collagen. It is rare in children. It is often acquired secondary to other autoimmune diseases or malignancy but has rare congenital forms. Affected mothers may pass the autoantibody to the fetus, resulting in similar but transient lesions in the newborn.

EPIDERMOLYSIS BULLOSA SIMPLEX

EBS is a nonscarring, autosomal dominant or recessive disorder. The defect in *most common* types of EBS is in keratin 5 or 14, which makes up intermediate filaments of the basal keratinocytes (see Table 695.6). The intraepidermal bullae result from cytolysis of the basal cells. There are multiple other rare variants with defects that also result in intraepidermal blistering (see Table 695.3).

Table 695.3 Epidermolysis Bullosa Simplex (EBS) Clinical Subtypes

MOST COMMON EBS CLINICAL SUBTYPES	TARGETED PROTEIN(S)
AUTOSOMAL DOMINANT EBS	
Localized	Keratin 5, keratin 14
Intermediate	Keratin 5, keratin 14
Severe	Keratin 5, keratin 14
With mottled pigmentation	Keratin 5*
Migratory circinate erythema	Keratin 5
Intermediate	Plectin
Intermediate with cardiomyopathy	**Kelch-like member 24**
AUTOSOMAL RECESSIVE EBS	
Intermediate or severe	Keratin 14, keratin 5
Intermediate	Plectin
Localized or intermediate with BP230 deficiency	Bullous pemphigoid antigen 230 (BP230) (syn. BPAG1e)
Localized or intermediate with exophilin-5 deficiency	Exophilin-5 (syn. Slac2-b)
Intermediate with muscular dystrophy	**Plectin**
Severe with pyloric atresia	**Plectin**
Localized with nephropathy	**CD151 (CD151 antigen) (syn. tetraspanin 24)**

*Typical recurrent mutation in keratin 5, but cases with other keratin 5, keratin 14 or exophilin-5 mutations have been reported; syndromic EBS subtypes in **bold**.

From Has C, Bauer JW, Bodemer C, et al: Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020;183:614-617; Table 3, p. 617.)

Localized EBS (formerly Weber-Cockayne disease) predominantly affects the hands and feet and often manifests when a child begins to walk; onset may be delayed until puberty or early adulthood, when heavy shoes are worn or the feet are subjected to increased trauma. Bullae are usually restricted to the hands and feet (Fig. 695.6); rarely, they occur elsewhere, such as the dorsal aspect of the arms and the shins. The disorder ranges from mildly incapacitating to crippling at times, with severe exacerbations. Blisters should be drained by puncturing, but the blister top should be left intact to protect the underlying skin. Erosions may be covered with a semipermeable dressing. Diligent wound care and protection of areas subject to pressure are beneficial. Observation for infection is important and should be treated promptly.

In **intermediate EBS (formerly Koebner type)**, blisters are usually present at birth or during the neonatal period. Sites of predilection are the hands, feet, elbows, knees, legs, and scalp. Intraoral lesions are minimal, nails rarely become dystrophic and usually regrow even when they are shed, and dentition is normal. Bullae heal with minimal to no scar or milia formation. Secondary infection is the primary complication. The propensity to blister decreases with age, and the long-term prognosis is good. Treatment is similar to that noted earlier.

Severe EBS (formerly EBS Dowling-Meara or EBS herpetiformis) is characterized by grouped blisters resembling those of herpes simplex (Fig. 695.7). During infancy, blistering may be severe and extensive, may involve mucous membranes, and may result in shedding of nails, formation of milia, and mild pigmentary changes, without scarring. After the first few months of life, warm temperatures do not appear to exacerbate blistering. Hyperkeratosis and hyperhidrosis of the palms and soles may develop, but generally, the condition improves with age. Maintenance of nutritional status and treatment of infections is important, particularly in infancy. Day-to-day management may involve wound care techniques as described.

JUNCTIONAL EPIDERMOLYSIS BULLOSA

Severe JEB (formerly Herlitz syndrome) is an autosomal recessive condition that is life threatening (see Tables 695.5 and 695.6). Blisters appear at birth or develop during the neonatal period, particularly on the perioral area, scalp, legs, diaper area, and thorax. Nails eventually become dystrophic and then often permanently lost. Mucous membrane involvement may be severe, and ulceration of the respiratory, gastrointestinal, and genitourinary epithelium has been documented in many affected children, although less frequently than in severe recessive DEB. Healing is delayed, and vegetating granulomas may persist for a long time. Large, moist, erosive plaques (Fig. 695.8) may provide a portal of entry for bacteria, and septicemia is a frequent cause of death. Mild atrophy may be seen in areas of recurrent blistering. Defective dentition with early loss of teeth as a result of rampant caries is characteristic. Growth retardation and recalcitrant anemia are almost invariable. In addition to infection, cachexia and circulatory failure are common causes of death. Most patients die within the first years of life.

Intermediate JEB (formerly non-Herlitz syndrome) is a heterogeneous group of disorders. Blistering may be severe in the neonatal period, making differentiation from severe JEB difficult. All conditions associated with severe JEB may be seen but are usually milder. **Localized JEB** and **JEB with pyloric atresia** are similar disorders.

In all types of JEB, a subepidermal blister is found on light microscopic examination, and electron microscopy demonstrates a cleavage plane in the lamina lucida, between the plasma membranes of the basal cells and the basal lamina. Absence or a great reduction of hemidesmosomes is seen on electron micrographs in severe JEB and some cases of intermediate JEB. The defect in severe JEB is in laminin 332 (pathogenic gene variants in *LAMA3, LAMB3,* or *LAMC2*), a glycoprotein associated with anchoring filaments beneath the hemidesmosomes. In intermediate JEB, defects have also been described in other hemidesmosomal components, such as type XVII collagen (BP180) (gene variants of *COL17A1*). In JEB with pyloric atresia, the defect is in the $\alpha_6\beta_4$ integrin (gene variants of *ITGA6* or *ITGB4*).

Treatment for JEB is supportive. The diet should provide adequate calories and *supplemental iron*. Infections should be treated promptly. Transfusions of packed red blood cells may be required if the patient shows no response to iron and erythropoietin therapy. Strict adherence to wound care regimens is essential. Wound care regimens include highly specialized nonadherent bandages designed specifically for children with chronic skin fragility. Tissue-engineered skin grafts (artificial skin derived from human keratinocytes and fibroblasts) may be beneficial. Birch bark extract topical gel containing betulin is approved by the European Union and promotes wound healing and controls inflammation.

Table 695.4 Characteristics of Major Forms of Epidermolysis Bullosa Simplex

TYPE	CLINICAL MANIFESTATIONS
Localized EBS (formerly Weber-Cockayne)	Easy blistering on palms and soles May be focal keratoderma of palms and soles in adults 25% show oral mucosal erosions Rarely show reticulated pigmentation, especially on arms and trunk and punctate keratoderma (EBS with mottled pigmentation)
Intermediate EBS (formerly Koebner)	Generalized blistering Variable mucosal involvement Focal keratoderma of palms and soles Nail involvement in 20% Improves with advancing age
Severe EBS (formerly Dowling-Meara or EB herpetiformis)	Most severe in neonate, infant; improves beyond childhood Large, generalized blisters; later, smaller (herpetiform) blisters Mucosal blistering, including esophageal Nails thickened, shed but regrow May have natal teeth
EBS with mottled pigmentation	Reticulated hyperpigmentation, especially on arms and trunk Punctate keratoses and keratoderma

EBS, Epidermolysis bullosa simplex.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 13.2, p. 319.

Table 695.6 Characteristics of Major Forms of Junctional Epidermolysis Bullosa

TYPE	CLINICAL MANIFESTATIONS
JEB, severe (formerly Herlitz)	50% of patients die by 2 yr old Blisters heal with atrophic scarring but no milia Periungual and fingerpad blistering, erythema Blistering of oral and esophageal mucosae Laryngeal and airway involvement with early hoarseness Later, perioral granulation tissue with sparing of lips Anonychia Dental enamel hypoplasia, excessive caries Growth retardation Anemia
JEB, intermediate (formerly non-Herlitz)	Less severe, but similar manifestations to Herlitz type, including dental, nail, and laryngeal involvement Granulation tissue is rare Perinasal cicatrization Less mucosal involvement Alopecia Anemia but not as severe as JEB, generalized severe
JEB, localized	Localized blisters without residual scarring or granulation tissue Minimal mucosal involvement Dental and nail abnormalities as in JEB, generalized severe
JEB, with pyloric atresia	Usually lethal in neonatal period Generalized blistering, leading to atrophic scarring May be born with large areas of cutis aplasia No granulation tissue Nail dystrophy or anonychia Pyloric atresia, genitourinary malformations Rudimentary ears Dental enamel hypoplasia (survivors) Variable anemia, growth retardation, mucosal blistering

JEB, Junctional epidermolysis bullosa.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 13.4, p. 321.

Table 695.5 Junctional Epidermolysis Bullosa (JEB) Clinical Subtypes

MOST COMMON JEB CLINICAL SUBTYPES	TARGETED PROTEIN(S)
Severe	Laminin 332*
Intermediate	Laminin 332
Intermediate	Type XVII collagen
With pyloric atresia	**Integrin α6β4**
Localized	Laminin 332, type XVII collagen, integrin α6β4, integrin α3 subunit
Inversa	Laminin 332
Late onset	Type XVII collagen
LOC syndrome	Laminin α3A
With interstitial lung disease and nephrotic syndrome	**Integrin α3 subunit**

*JEB severe is rarely caused by pathogenic variants affecting the type XVII collagen gene; syndromic JEB subtypes in **bold**.
LOC, laryngo–onycho–cutaneous.
From Has C, Bauer JW, Bodemer C, et al: Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020;183:614-617; Table 4, p. 617.)

Table 695.7 Dystrophic Epidermolysis Bullosa (DEB) Clinical Subtypes

DEB SUBTYPES	TARGETED PROTEIN
AUTOSOMAL DOMINANT DEB (DDEB)	
Intermediate	Type VII collagen
Localized	
Pruriginosa	
Self-improving	
AUTOSOMAL RECESSIVE DEB (RDEB)	
Severe	Type VII collagen
Intermediate	
Inversa	
Localized	
Pruriginosa	
Self-improving	
DOMINANT AND RECESSIVE (COMPOUND HETEROZYGOSITY)	
DEB, severe	Type VII collagen

bold, most common subtypes.
From Has C, Bauer JW, Bodemer C, et al: Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020;183:614-617; Table 5, p. 617.)

Table 695.8 Characteristics of Major Forms of Dystrophic Epidermolysis Bullosa

TYPE	CLINICAL MANIFESTATIONS
Dominant dystrophic	Onset at birth to early infancy Blistering predominates on dorsum of hands, elbows, knees, and lower legs Milia associated with scarring Some patients develop scarlike lesions, especially on the trunk 80% have nail dystrophy
Recessive dystrophic, severe generalized	Present at birth Widespread blistering, scarring, milia Deformities: pseudosyndactyly, joint contractures Severe involvement of mucous membranes, nails; alopecia Growth retardation, poor nutrition Anemia Mottled, carious teeth Osteoporosis, delayed puberty, cardiomyopathy, glomerulonephritis, renal amyloidosis, IgA nephropathy Predisposition to squamous cell carcinoma in heavily scarred areas
Recessive dystrophic, generalized intermediate	Generalized blisters from birth with milia, scarring Less anemia, growth retardation, mucosal but more esophageal issues with advancing age

IgA, Immunoglobulin A.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022: Table 13.6, p. 323.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

All forms of DEB result from pathogenic variants in collagen VII, a major component of anchoring fibrils that tether the basement membrane and overlying epidermis to its dermal foundation (see Tables 695.7 and 695.8). The blister is subepidermal in all types of DEB. The type and location of the pathogenic gene variant within *COL7A1* dictate the severity of the phenotype.

Dominant DEB is the most common type. The spectrum of dominant DEB is varied. Blisters may be manifest at birth and are often limited and characteristically form over acral bony prominences.

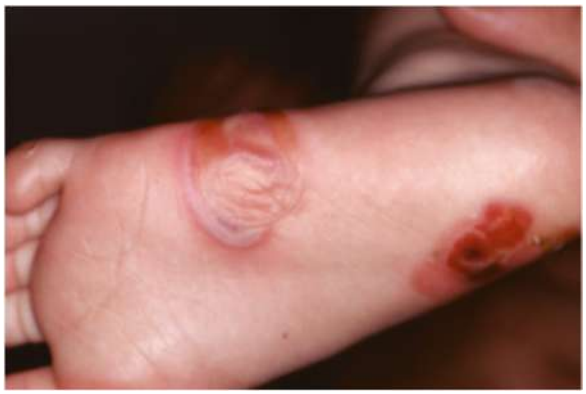

Fig. 695.6 Bullae of the feet in localized epidermolysis bullosa simplex.

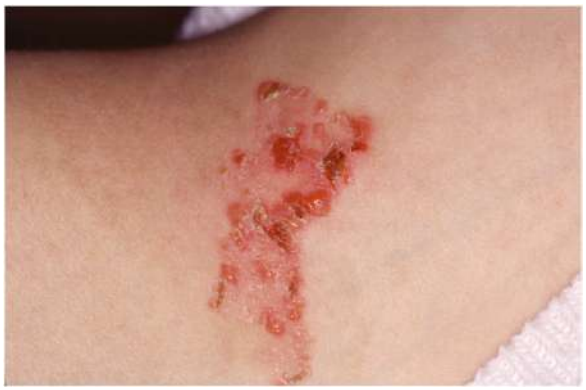

Fig. 695.7 Grouped vesicle on an erythematous base in severe epidermolysis bullosa simplex.

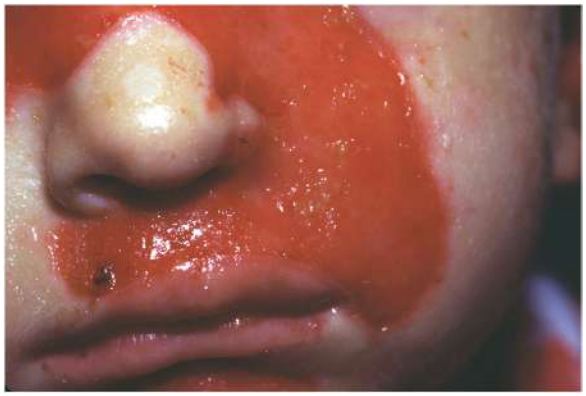

Fig. 695.8 Nonhealing granulation tissue in junctional epidermolysis bullosa.

The lesions heal promptly, with the formation of soft, wrinkled scars; milia; and alterations in pigmentation (Fig. 695.9). Abnormal nails and nail loss are common. In many cases, the blistering process is mild, causing little restriction of activity and not impairing growth and development. Mucous membrane involvement tends to be minimal.

Recessive DEB, severe generalized (formerly recessive DEB–Hallopeau-Siemens syndrome) is the most incapacitating form of EB, although the clinical spectrum is wide. Some patients have blisters, scarring, and milia formation primarily on the hands, feet, elbows, and knees (Fig. 695.10). Others have extensive erosions and blister formation at birth that seriously impede their care and feeding. Mucous membrane lesions are common and may cause severe nutritional

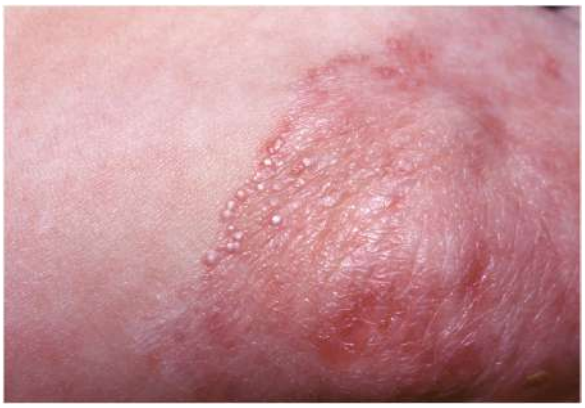

Fig. 695.9 Scarring with milia formation over the knee in dominant dystrophic epidermolysis bullosa.

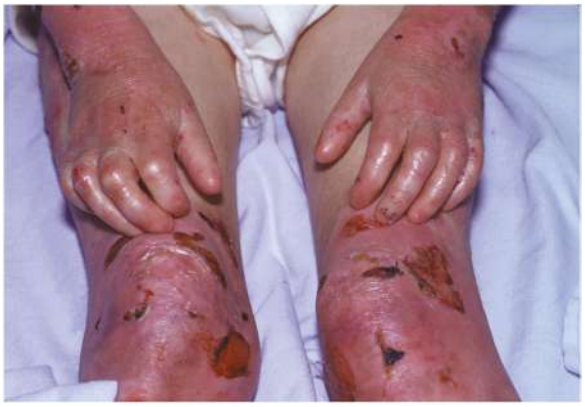

Fig. 695.10 Severe scarring of the hands and knees in recessive dystrophic epidermolysis bullosa.

deprivation, even in older children, whose growth may be restricted. During childhood, esophageal erosions and strictures, scarring of the buccal mucosa, flexion contractures of joints secondary to scarring of the integument, development of cutaneous squamous cell carcinomas, and the development of digital fusion may significantly limit the quality of life (Fig. 695.11). Squamous cell carcinomas and infection are major causes of morbidity and mortality.

Although the skin becomes less sensitive to trauma with aging in patients with recessive DEB, the progressive and permanent deformities complicate management, and the overall prognosis is poor. *Foods that traumatize the buccal or esophageal mucosa should be avoided.* If esophageal scarring develops, a semiliquid diet and esophageal dilatations may be required. Stricture excision or colonic interposition may be needed to relieve esophageal obstruction. In infants, severe oropharyngeal involvement may necessitate the use of special feeding devices such as a gastrostomy tube. Iron therapy for anemia, intermittent antibiotic therapy for secondary infections, and periodic surgery for release of digits may reduce morbidity. Wound care dressings, including nonstick dressings made from silicone, are a mainstay of treatment and the daily maintenance of the skin barrier to reduce new skin trauma and promote healing. Compounds for treating itch, reducing inflammation, and fighting infection, particularly with antimicrobial peptides, aid in promoting more effective wound healing when dressings are used, therefore reducing morbidity.

Beyond wound care and care of comorbid conditions in EB, a number of new technologies offer a wider array of practical and hypothetical treatment options for EB patients. Tissue-engineered skin grafts containing keratinocytes and fibroblasts are of some benefit. Skin grafts that have undergone gene editing may show promise. Pluripotent stem cells, taken from areas of revertant mosaicism of a patient's own skin, provide personalized options

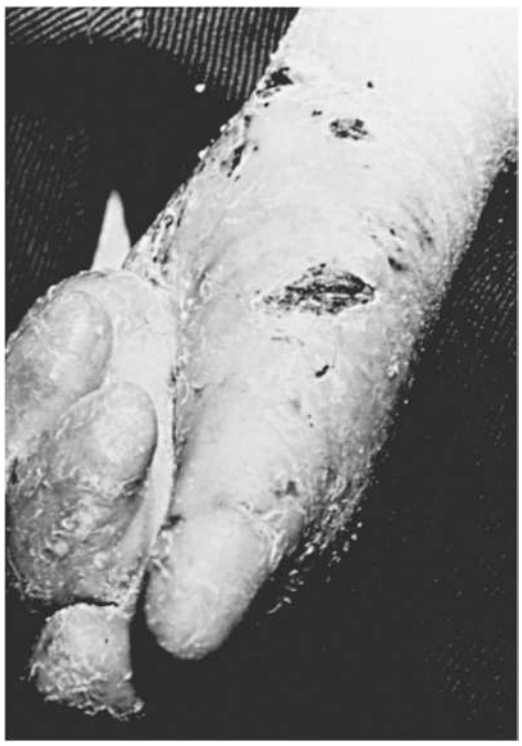

Fig. 695.11 Mitten-hand deformity of recessive dystrophic epidermolysis bullosa.

for treatments for affected patients. Redosable gene therapy with a herpes simplex virus type 1 vector carrying the *COL7A1* gene is FDA approved for patients ≥6 months of age. The therapy is applied directly to wounds and produces normal collagen type VII alpha chains. Allogeneic bone marrow transplantation has been shown to be beneficial in some cases but warrants further study.

KINDLER SYNDROME

Kindler syndrome, often considered a distant subtype of EB, contains features of both EB, such as congenital blistering, and congenital poikilodermas, such as Rothmund-Thomson syndrome and Bloom syndrome (see Chapter 697), which include photosensitivity, congenital poikiloderma, and progressive cutaneous atrophy. Blisters tend to appear on acral sites in infancy or early childhood and are provoked by trauma. Photosensitivity can appear as increased susceptibility to sunburn. Both blistering and photosensitivity can improve greatly with advancing age, but poikilodermatous changes can be progressive. Sclerodermoid-like changes and nail abnormalities of the hands and feet, as well as dental abnormalities, have been reported.

Kindler syndrome is an autosomal recessive disorder caused by pathogenic gene variants in *KIND1* (also known as *FERMT1*), which encodes kindlin-1, a protein thought to regulate interactions between the extracellular matrix and actin filaments. Blister formation has been shown to occur within the epidermis, within the basement membrane zone, and below the basement membrane. Because Kindler syndrome is often confused with EB, at least initially, it can be confirmed by electron microscopy, immunostaining for anti–kindlin-1 antibodies within the skin, or genetic analysis of the *KIND1* gene.

Treatment is similar to that for EB, with efforts to reduce trauma to the skin, meticulous wound care, and treatment of skin infections. In addition, sun avoidance measures are beneficial because they can slow the rate of the development of poikiloderma.

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695.6 Pemphigus

Joel C. Joyce

PEMPHIGUS VULGARIS

Etiology/Pathogenesis

Pemphigus vulgaris (PV) is a rare autoimmune blistering disorder caused by circulating antibodies to desmoglein III that results in suprabasal cleaving with consequent blister formation. Desmoglein III is a 30-kDa glycoprotein that is complexed with plakoglobin, a plaque protein of desmosomes. The desmogleins are a subfamily of the cadherin family of cell adhesion molecules.

Clinical Manifestations

PV usually first appears as painful oral ulcers, which may be the only evidence of the disease for weeks or months. Subsequently, large, flaccid bullae emerge on nonerythematous skin, most commonly on the face, trunk, pressure points, groin, and axillae. The **Nikolsky sign** is present. The lesions rupture and enlarge peripherally, producing painful, raw, denuded areas that have little tendency to heal. When healing occurs, it is without scarring, but hyperpigmentation is common. Malodorous, verrucous, and granulomatous lesions may develop at sites of ruptured bullae, particularly in the skinfolds; as this pattern becomes more pronounced, the condition may be more properly referred to as **pemphigus vegetans**. Because the course may rapidly lead to debility, malnutrition, and death, prompt diagnosis is essential. **Neonatal PV** develops in utero as a result of placental transfer of maternal antidesmoglein antibodies from women who have active PV, although it may occur when the mother is in remission. High antepartum maternal titers of PV antibodies and increased maternal disease activity correlate with a poor fetal outcome, including demise.

Pathology

Biopsy of a fresh small blister reveals a suprabasal (intraepidermal) blister containing loose, acantholytic epidermal cells that have lost their intercellular bridges and thus their contact with one another. Immunofluorescence staining with an IgG antibody produces a characteristic pattern ("chicken wire") on direct immunofluorescence preparations of both involved and uninvolved skin of essentially all patients. Serum IgG antibody titers to desmoglein correlate with the clinical course in many patients; thus serial determinations may have predictive value.

Differential Diagnosis

PV must be differentiated from EM, bullous pemphigoid (BP), SJS, and TEN.

Treatment

The disease is best treated initially with systemic methylprednisolone 1-2 mg/kg/day. Azathioprine, cyclophosphamide, mycophenolate mofetil, and methotrexate therapy all have been useful in maintenance regimens. IVIG given in cycles may be beneficial to patients whose disease does not respond to steroids. Rituximab with IVIG replacement has been very effective in the management of severe PV. Excellent control of the disease may be obtained, but relapse is common. It has been successfully used in children.

PEMPHIGUS FOLIACEUS

Etiology/Pathogenesis

Pemphigus foliaceus is caused by circulating antibodies to a 50-kDa portion of the 160-kDa desmosomal glycoprotein desmoglein I, which result in subcorneal cleavage leading to superficial erosions. This extremely rare disorder is characterized by subcorneal blistering; the site of cleavage is high in the epidermis rather than suprabasal as in PV.

Clinical Manifestations

The superficial blisters rupture quickly, leaving erosions surrounded by erythema that heal with crusting and scaling (Fig. 695.12). The

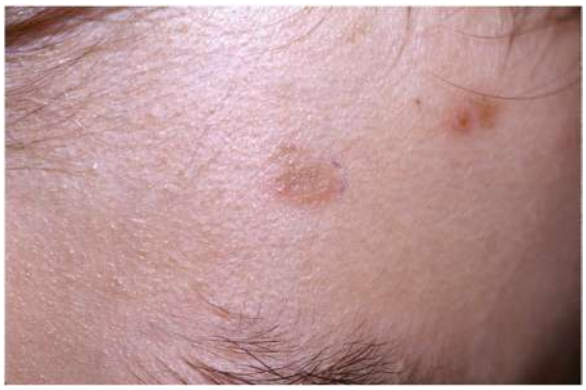

Fig. 695.12 Superficial erosions in pemphigus foliaceus.

Nikolsky sign is present. Focal lesions are usually localized to the scalp, face, neck, and upper trunk. Mucous membrane lesions are minimal or absent. Pruritus, pain, and a burning sensation are frequent complaints. The clinical course varies but is generally more benign than that of PV. **Fogo selvagem (endemic pemphigus foliaceus)**, which is endemic in certain areas of Brazil, is identical clinically, histopathologically, and immunologically to pemphigus foliaceus. Anti–desmoglein-1 antibodies in individuals with fogo selvagem cross react with sand fly (*Lutzomyia* sp.) salivary proteins, suggesting an environmental trigger for this autoimmune disease.

Pathology

An intraepidermal acantholytic bulla high in the epidermis is diagnostic. It is imperative to select an early lesion for biopsy. Immunofluorescent staining with an IgG antibody reveals a characteristic intercellular staining pattern similar to that of PV but higher in the epidermis.

Differential Diagnosis

When generalized, pemphigus foliaceus may resemble an exfoliative dermatitis or any of the chronic blistering disorders; localized erythematous plaques simulate seborrheic dermatitis, psoriasis, impetigo, eczema, and systemic lupus erythematosus.

For localized disease, super-potent topical corticosteroids used twice a day may be all that is needed for control until remission. For more generalized disease, long-term remission is usual after suppression of the disease by systemic methylprednisolone (1 mg/kg/day) therapy. Dapsone (25-100 mg/day) also may be used, with appropriate laboratory monitoring.

BULLOUS PEMPHIGOID

Etiology/Pathogenesis

BP is caused by circulating antigens to either the 180-kDa or 230-kDa BP antigen that result in a subepidermal blister. The 230-kDa protein (BP230) is part of the hemidesmosome, whereas the 180-kDa protein (BP180, now known as type XVII collagen) localizes to both the hemidesmosome and the upper lamina lucida and is a transmembrane collagenous protein.

Clinical Manifestations

The blisters of BP typically arise in crops on a normal, erythematous, eczematous, or urticarial base. Bullae appear predominantly on the flexural aspects of the extremities, in the axillae, and on the groin and central abdomen. Infants have involvement of the palms, soles, and face more frequently than older children do. Individual lesions vary greatly in size, are tense, and are filled with serous fluid that may become hemorrhagic or turbid. Oral lesions occur less frequently and are less severe than in PV. Pruritus, a burning sensation, and subcutaneous edema may accompany the eruption, but constitutional symptoms are not prominent.

Pathology

Biopsy material should be taken from an early bulla arising on an erythematous base. A subepidermal bulla and a dermal

inflammatory infiltrate, predominantly of eosinophils, can be identified histopathologically. In sections of a blister or perilesional skin, a band of Ig (usually IgG) and C3 can be demonstrated in the basement membrane zone by direct immunofluorescence. Indirect immunofluorescence studies of serum have positive results in ~70% of cases for IgG antibodies to the basement membrane zone; however, the titers do not correlate well with the clinical course.

Diagnosis and Differential Diagnoses

BP rarely occurs in children but must be considered in the differential diagnosis of any chronic blistering disorder. The differential diagnosis includes bullous EM, PV, linear IgA dermatosis, bullous drug eruption, dermatitis herpetiformis (DH), herpes simplex infection, and bullous impetigo, which can be differentiated by histologic examination, immunofluorescence studies, and cultures. The large, tense bullae of BP can generally be distinguished from the smaller, flaccid bullae of PV.

Treatment

Localized BP can be successfully suppressed with super-potent topical corticosteroids (clobetasol propionate) twice a day. Generalized disease usually requires systemic methylprednisolone (1 mg/kg/day) therapy. Doxycycline has some benefits but is not as effective as prednisone. Rarely are other immunosuppressive treatments necessary, such as azathioprine or mycophenolate mofetil. Refractory cases have been treated with rituximab, but the condition usually remits within a year in most children.

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695.7 Dermatitis Herpetiformis

Joel C. Joyce

ETIOLOGY/PATHOGENESIS

In dermatitis herpetiformis (DH), IgA antibodies are directed at epidermal transglutaminase (transglutaminase 3). **Gluten-sensitive enteropathy (celiac disease)** is found in all patients with DH, although the majority are asymptomatic or have minimal gastrointestinal symptoms (see Chapter 384). The severity of the skin disease and the responsiveness to gluten restriction do not correlate with the severity of the intestinal inflammation. An antibody to smooth muscle endomysium is found in 70–90% of patients with DH. Ninety percent of patients with the disease express HLA-DQ2. HLA-DQ2–negative patients with DH usually express HLA-DQ8.

CLINICAL MANIFESTATIONS

DH is characterized by symmetric, grouped, small, tense, erythematous, stinging, intensely pruritic papules and vesicles. The eruption is pleomorphic, including erythematous, urticarial, papular, vesicular, and bullous lesions. Sites of predilection are the knees, elbows, shoulders, buttocks, forehead, and scalp; mucous membranes are usually spared. Hemorrhagic lesions may develop on the palms and soles. When pruritus is severe, excoriations may be the only visible sign (Fig. 695.13).

PATHOLOGY

Subepidermal blisters composed predominantly of neutrophils are found in dermal papillae. The presence of granular IgA on direct immunofluorescence in the dermal papillary tips is diagnostic.

DIFFERENTIAL DIAGNOSIS

DH may mimic other chronic blistering disorders and may also resemble scabies, papular urticaria, insect bites, contact dermatitis, and papular eczema.

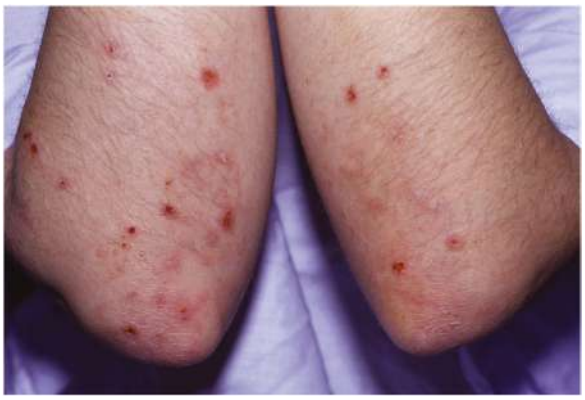

Fig. 695.13 Multiple excoriations around the elbows in dermatitis herpetiformis.

TREATMENT

Patients with DH show response within weeks to months to a gluten-free diet. Oral administration of dapsone (0.5-2.0 mg/kg/day daily or divided twice daily) provides immediate relief from the intense pruritus but must be used with caution because of possible serious side effects (methemoglobinemia, hemolysis, and drug hypersensitivity syndrome [sulfone syndrome]). Dapsone alone may not relieve the intestinal inflammation of celiac disease. Local antipruritic measures may also be useful. Jejunal biopsy is indicated to diagnose gluten-sensitive enteropathy because cutaneous manifestations may precede malabsorption. The disease is chronic, and either a gluten-free diet or dapsone must be continued indefinitely to prevent relapse.

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695.8 Linear Immunoglobulin A (IgA) Dermatosis (Chronic Bullous Dermatosis of Childhood)

Joel C. Joyce

ETIOLOGY/PATHOGENESIS

Linear IgA dermatosis is a heterogeneous autoimmune disorder with antibodies targeting multiple antigens. It has been reported to be the most common autoimmune blistering disorder in children. It is caused by circulating IgA antibodies, most commonly to LABD97 and LAD-1, which are degradation proteins of BP180 (type XVII collagen). Linear IgA dermatosis may also be seen as a drug eruption. Most cases of drug-induced linear IgA dermatosis are related to vancomycin, although anticonvulsants, ampicillin, cyclosporine, and captopril are implicated.

CLINICAL MANIFESTATIONS

This rare dermatosis is most common in the first decade of life, with a peak incidence during the preschool years. The eruption consists of many large, symmetrically located, tense bullae filled with clear or hemorrhagic fluid. The bullae are often clustered together and develop on a normal or erythematous urticarial base. Areas of predilection are the genitals and buttocks (Fig. 695.14), the perioral region, and the scalp. Sausage-shaped bullae may be arranged in an annular or rosette-like fashion around a central crust (Fig. 695.15). Erythematous plaques with gyrate margins bordered by intact bullae may develop over larger areas. Pruritus may be absent or very intense, and systemic signs or symptoms are absent.

PATHOLOGY

The subepidermal bullae are infiltrated with a mixture of inflammatory cells. Neutrophilic abscesses may be noted in the dermal papillary tips,

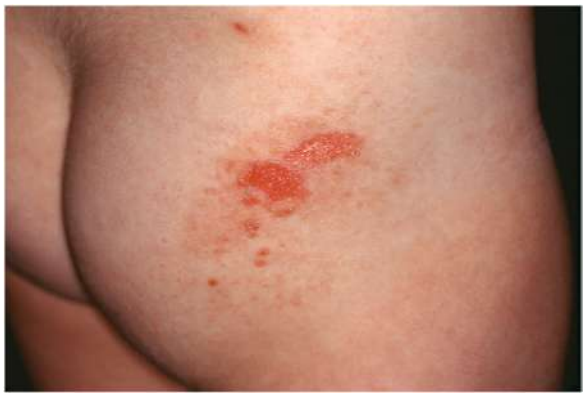

Fig. 695.14 Erosion on an erythematous base after loss of blister roof in linear IgA dermatosis.

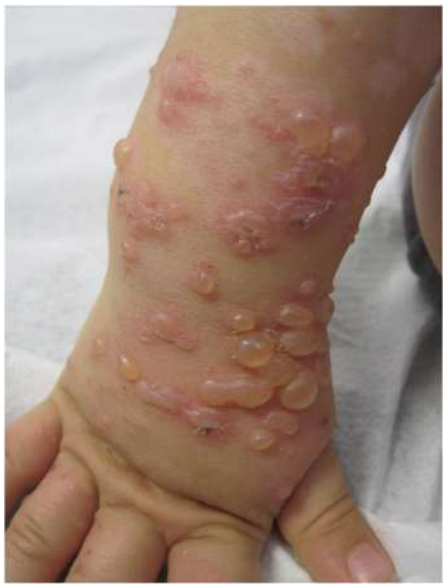

Fig. 695.15 Linear IgA bullous dermatitis. *(Modified from Gouveia AI, Teixeira A, Freitas JP, et al. Linear immunoglobulin A bullous dermatosis. J Pediatr. 2016;170:338, Fig. 1A.)*

indistinguishable from those of DH. The infiltrate may also be largely eosinophilic, resembling that in BP. Therefore direct immunofluorescence studies are required for a definitive diagnosis of linear IgA dermatosis; perilesional skin demonstrates linear deposition of IgA and sometimes IgG and C3 at the dermal-epidermal junction. Immunoelectron microscopy has localized the immunoreactants to the sublamina densa, although a combined sublamina densa and lamina lucida pattern has also been seen.

DIFFERENTIAL DIAGNOSIS

The eruption can be distinguished by histopathologic and immunofluorescence studies from PV, BP, DH, scabies, and EM. Gram stain and culture preclude the diagnosis of bullous impetigo.

TREATMENT

Many cases of linear IgA dermatosis respond favorably to oral dapsone (see treatment of DH) or sulfapyridine. Other antibiotics, including erythromycin and dicloxacillin, have been used, but the response is often transient. Children who show no response to dapsone may benefit from oral therapy with methylprednisolone (1 mg/kg/day) or a combination of these drugs. The usual course is 2-4 years, although some children have persistent or recurrent disease; there are typically no long-term sequelae. IgA nephropathy is a rare complication.

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Chapter 696

Eczematous Disorders

Julie M. Dhossche and Yvonne E. Chiu

Eczematous disorders are a broad group of cutaneous eruptions characterized by erythema, edema, and pruritus. Acute eczematous lesions demonstrate erythema, weeping, oozing, and the formation of microvesicles within the epidermis. Chronic lesions are generally thickened, dry, and scaly, with coarse skin markings (lichenification) and altered pigmentation. Many types of eczema occur in children; the most common is **atopic dermatitis** (see Chapter 186), although seborrheic dermatitis, allergic and irritant contact dermatitis, nummular eczema, and acute palmoplantar eczema (dyshidrosis) are also relatively common in childhood.

Once the diagnosis of eczema has been established, it is important to further classify the eruption more specifically for proper management. Pertinent historical data often provide the clue. In some instances, the subsequent course and character of the eruption permit classification. Histologic changes are relatively nonspecific, but all types of eczematous dermatitis are characterized by intraepidermal edema known as *spongiosis*.

696.1 Contact Dermatitis

Julie M. Dhossche and Yvonne E. Chiu

The form of eczema known as contact dermatitis can be subdivided into irritant dermatitis, in which nonspecific injury to the skin causes immediate inflammation, and allergic contact dermatitis, resulting from a delayed hypersensitivity reaction. Irritant dermatitis is more frequent in children, particularly during the early years of life. Allergic reactions increase in frequency upon maturation of the immune system.

IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis can result from prolonged or repetitive contact with physical, chemical, or mechanical irritants, including saliva, urine, feces, fragrance, detergents, dyes, henna, plants, caterpillars, abrasive materials, and chafing.

Irritant contact dermatitis may be difficult to distinguish from atopic dermatitis or allergic contact dermatitis. A detailed history and consideration of the sites of involvement, the age of the child, and contactants usually provide clues to the etiologic agent. The propensity for development of irritant dermatitis varies considerably among children; some may respond to minimal injury, making it difficult to identify the offending agent through history. Children with atopic dermatitis are more prone to irritant contact dermatitis as an exacerbating factor. Irritant contact dermatitis usually clears after removal of the stimulus and temporary treatment with a topical corticosteroid preparation (see Chapter 687). Education of patients and parents about the causes of contact dermatitis is crucial to successful therapy.

Dry skin dermatitis results from repetitive wet-to-dry behaviors such as lip licking (Fig. 696.1), thumb sucking, frequent handwashing, or excessive sweating. Involved skin is erythematous and fissured, localized to the area of exposure. Treatment of dry skin dermatitis begins with eliminating the offending wet-to-dry behavior. A thick moisturizer (cream or ointment based) applied twice daily decreases transepidermal water loss and replenishes skin lipids to improve hydration. A topical steroid is usually necessary to treat the inflammation.

Juvenile plantar dermatosis occurs mainly in prepubertal children with hyperhidrosis who wear occlusive synthetic footwear. Weight-bearing surfaces of the foot may be pruritic or painful and develop a fissured or glazed appearance (Fig. 696.2). Immediate application of a thick emollient when socks and shoes are removed or immediately after swimming usually minimizes juvenile plantar dermatosis. Severe inflammatory cases may require short-term (1-2 weeks) application of a medium- to high-potency topical steroid.

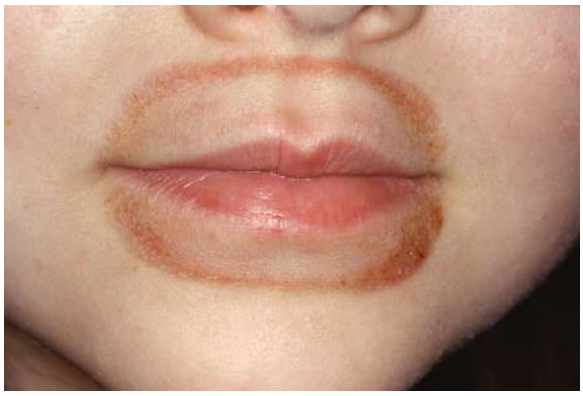

Fig. 696.1 Perioral irritant contact dermatitis from lip licking.

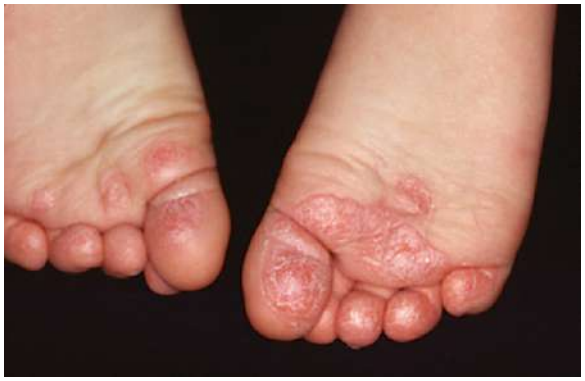

Fig. 696.2 Red, scaly juvenile plantar dermatosis.

DIAPER DERMATITIS

Diaper dermatitis refers to any rash in the diaper region; the most common of these is irritant diaper dermatitis. Elevated pH in the diaper area and synergistic activity of urinary and fecal enzymes lead to inflammation, which disrupts the normal skin barrier and increases susceptibility to other irritants and organisms. Additional factors are occlusion, friction, and use of diaper wipes and topical preparations. Loose or frequent stooling predisposes an infant to diaper dermatitis. Diaper dermatitis presents with erythema and scaling in a patchy or confluent pattern and, in severe cases, may have papulovesicular or bullous lesions, fissures, and/or erosions (Fig. 696.3). The genitocrural folds are often spared because concave areas are relatively protected. Chronic hypertrophic, flat-topped papules and infiltrative nodules may occur. **Candidal infection** typically represents a secondary process. It is characterized by "beefy" red-pink, tender skin that has numerous 1- to 2-mm pustules and satellite papules and involves both concave and convex areas. Discomfort may be marked because of intense inflammation. Allergic contact dermatitis, seborrheic dermatitis, psoriasis, candidiasis, atopic dermatitis, child abuse, and rare disorders such as Langerhans cell histiocytosis, nutritional deficiencies, and acrodermatitis enteropathica should be considered when the eruption is persistent or is recalcitrant to simple therapeutic measures (Table 696.1).

Diaper dermatitis often responds to simple measures; some infants are predisposed to diaper dermatitis, and management may be difficult. The damaging effects of overhydration of the skin and prolonged contact with feces and urine can be obviated by frequent changing of the diapers and periods of "rest" free of diaper use. Cleansing of affected skin is best accomplished with a soft cloth and lukewarm water, patted dry. Overwashing should be avoided because it leads to chapping and may worsen the dermatitis. Disposable diapers containing a superabsorbent material may help to maintain a relatively dry environment. First-line therapy for diaper dermatitis is application of a protective barrier agent (ointment or paste)

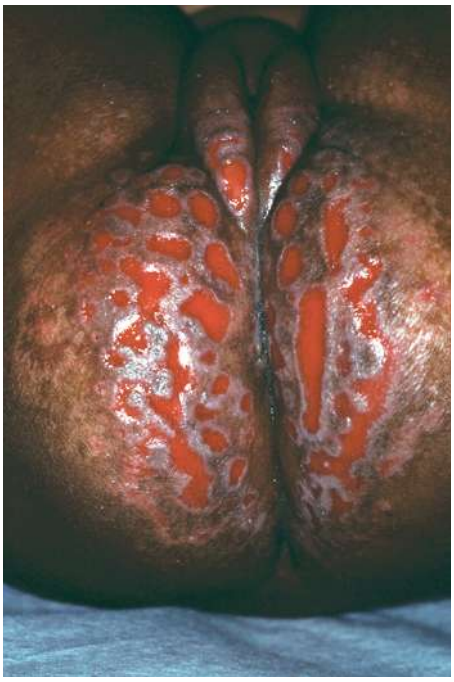

Fig. 696.3 Severe, erosive diaper dermatitis.

containing petroleum or zinc oxide at every diaper change. Topical sucralfate is an effective barrier with some antibacterial activity and is useful for recalcitrant cases. Low-potency nonhalogenated topical corticosteroids, such as 2.5% hydrocortisone, may be used for short periods (3-5 days). Treatment with a topical anticandidal agent is indicated for secondary candidal infection. Topical preparations containing triamcinolone-nystatin and betamethasone dipropionate-clotrimazole are generally inappropriate for diaper dermatitis in infants because of the higher potency of the corticosteroid component. If using multiple topical agents, the protective barrier should be applied last. When diaper dermatitis does not respond to typical prevention and treatment strategies, non–diaper-associated causes must be considered.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis is a delayed hypersensitivity cutaneous reaction to environmental allergens and should be considered in any child with recalcitrant eczema. It has been estimated to affect 16.4% of all children in the United States, though children are likely underdiagnosed, especially those with concomitant atopic dermatitis. Children of all ages may develop allergic contact dermatitis, though it is more common in older children. Allergic contact dermatitis is a T-cell–mediated hypersensitivity reaction that is provoked by application of an antigen to the skin surface. The antigen penetrates the skin, where it is conjugated with a cutaneous protein, and the hapten-protein complex is transported to the regional lymph nodes by antigen-presenting Langerhans cells. A primary immunologic response occurs locally in the nodes and becomes generalized, presumably because of dissemination of sensitized T cells. Sensitization requires several days and, when followed by a fresh antigenic challenge, manifests as allergic contact dermatitis. Generalized distribution may also occur if enough antigen finds its way into the circulation, such as by consumption. Once sensitization has occurred, each new antigenic challenge may provoke an inflammatory reaction within 8-12 hours; sensitization to a particular antigen usually persists for many years.

Acute allergic contact dermatitis is an erythematous, intensely pruritic, eczematous dermatitis. Acute cases may be edematous and vesiculobullous. The chronic condition has the features of long-standing eczema: lichenification, scaling, fissuring, and pigmentary change. Distinguishing allergic contact dermatitis from other eczematous disorders can be challenging, especially with irritant contact dermatitis, which can be clinically identical. The distribution of the eruption often provides a clue to the diagnosis. Airborne sensitizers usually affect exposed areas, such as the face and arms. Jewelry, topical agents, shoes, clothing, henna tattoo dyes, plants,

Table 696.1 Diaper Dermatitis

DISEASE	CLINICAL MANIFESTATION	OTHER FEATURES	TREATMENT
Friction	Inner surface of thighs, genitalia, buttocks, abdomen	Course waxes and wanes Aggravated by talc	Responds well to diaper changes Avoidance of diapers
Irritant	Mild erythema with shiny surface and occasional papules Confined to convex surfaces Spares intertriginous areas	Exacerbated by heat, moisture, and sweat retention	Gentle cleansing Regular diaper changes Barrier creams (zinc oxide, Vaseline) Low-potency topical steroids can help
Allergic contact	Typically confined to convex surfaces Skin involved is in direct contact with offending agent *Mild cases:* diffuse erythema, papules, vesicles, scaling *Severe cases:* papules, plaques, psoriasiform lesions, ulcerations, infiltrative nodules	Often related to topical antibiotics (neomycin, bacitracin) Certain emulsifiers in topical products Preservatives in wet wipes can be an offender	Remove offending agent Judicious use of low-potency topical steroids Barrier creams/ointments
Seborrheic dermatitis	Salmon-colored patches Often have yellow, greasy scale Fissures, erosions, maceration, and weeping can be seen	Axillae, ear creases, and neck are often involved "Cradle cap" on scalp Hypopigmentation often seen in patients with darker skin tones	Low-potency topical steroids If coexistent infection—antifungal or antibacterial agents
Candidiasis	Usually involves intertriginous areas and convex surfaces Bright-red papules and plaques Satellite lesions on abdomen and thighs	Oral thrush may be present Often occurs after treatment with systemic antibiotics or local topical steroid use	Topical anticandidal agent, including nystatin
Intertrigo	Well-demarcated, macerated plaques with weeping Gluteal cleft and fleshy folds of thighs	May be associated with miliaria	Avoiding excessive heat Cool clothing
Psoriasis	Bright red, scaly, well-demarcated plaques Can persist for months Less responsive to topical treatment	Red, sometimes scaly Can be present on extremities or trunk Nail changes seen Family history	Low-potency topical steroids Moisturizers
Staphylococcal infection	Many thin-walled pustules with pink-red base Collarette of scale after rupturing		Antistaphylococcal therapy
Acrodermatitis enteropathica (zinc deficiency)	Early lesions are vesicular and pustular Become confluent, pink, dry, scaly, crusty plaques	Perioral skin typically also involved Irritability or listlessness Failure to thrive, alopecia, diarrhea	Secondary to zinc deficiency or inborn error of zinc transporter Treat with zinc replacement
Langerhans cell histiocytosis	May mimic candidiasis or seborrheic dermatitis Persistent, does not improve with standard treatments Clusters of infiltrative, crusted, hemorrhagic papules Ulceration can be seen	Involvement of groin, axillae, periauricular skin, hairline, and scalp Anemia, thrombocytopenia, hepatosplenomegaly, and osseous lesions	Chemotherapy

From Humphrey S. Congenital cutaneous lesions and infantile rashes. In: Kliegman RM, Toth H, Bordini BJ, Basel D, eds. *Nelson Pediatric Symptom-Based Diagnosis,* 2nd ed. Philadelphia: Elsevier; 2023: Table 60.2, p. 1144.

and even toilet seats cause dermatitis at points of contact. Careful evaluation of environmental exposures, cultural customs, daily activity, animal exposures, ear piercing, tattooing, and personal product usage in the patient and all caregivers is essential. Other potential diagnoses to consider include herpes simplex virus, impetigo, cellulitis, and dermatophytoses.

Rhus dermatitis (poison ivy, poison sumac, poison oak), a response to the plant allergen urushiol, is the most common allergic contact dermatitis. It is often vesiculobullous and may be distinguished by linear streaks of vesicles where the plant leaves have brushed against the skin (Fig. 696.4). Fluid from ruptured cutaneous vesicles does not spread the eruption; antigen retained on skin, clothing, or under fingernails initiates new plaques of dermatitis if not removed by washing with soap and water. Antigen may also be carried by animals on their fur. "Black spot" poison ivy dermatitis is a rare variant that results from oxidation of concentrated urushiol left on the skin and manifests as small discrete black lacquer–like glossy papules with surrounding erythema and edema. Sensitization to one plant produces cross reactions with the others. Spontaneous resolution occurs in 1-3 weeks, with the most common complication being secondary bacterial infection with normal skin flora. Exposure avoidance and thorough washing after exposure are the mainstays for prevention. Barrier creams or organoclay compounds such as bentoquatam may be effective if applied before expected exposure.

Nickel dermatitis develops from contact with jewelry, metal closures on clothing, or even cell phones. Metal closures on pants frequently cause periumbilical dermatitis (Fig. 696.5). Some children are exquisitely sensitive to nickel, with even the trace amounts found in gold jewelry provoking eruptions. The most frequently involved sites from jewelry are the earlobes from nickel-containing earrings. Early ear piercing increases risk of sensitization, and it is recommended to delay piercing until after 10 years of age. Patch testing for nickel sensitivity is unreliable in infants and toddlers and should only be performed if there is high clinical suspicion.

Shoe dermatitis typically affects the dorsum or soles of the feet and toes, sparing the interdigital spaces; it is usually symmetric. Other forms of allergic contact dermatitis, in contrast to irritant dermatitis, rarely involve the palms and soles. Common allergens are the antioxidants and accelerators in shoe rubber, adhesives, and the chromium salts in tanned leather or shoe dyes. Excessive sweating often leaches these substances from their source.

Apparel contains a number of sensitizers, including dyes, dye fixative, fabric finishes, fibers, resins, and cleaning solutions. Dye may be poorly

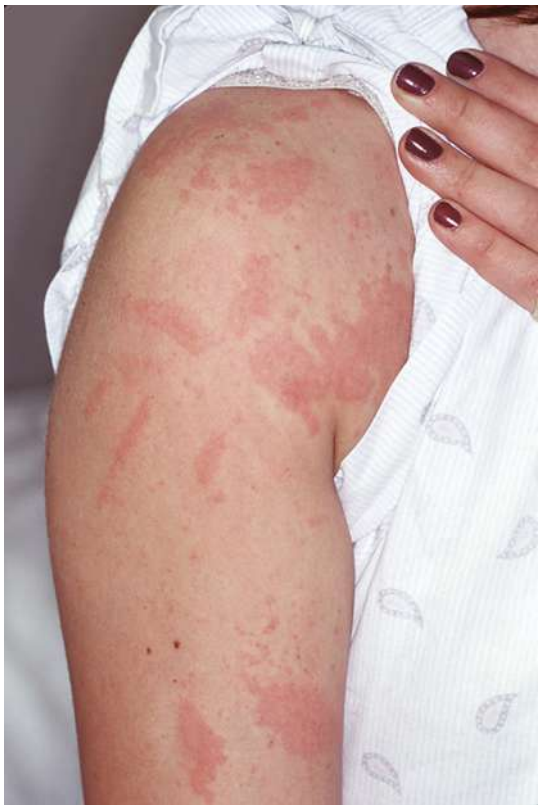

Fig. 696.4 Linear lesions in poison ivy.

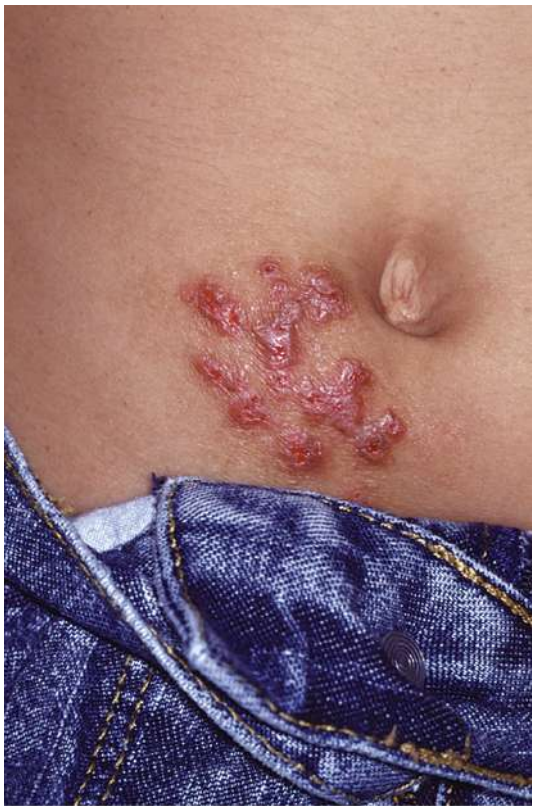

Fig. 696.5 Chronic periumbilical nickel dermatitis.

fixed to clothing and so may be leached out with sweating, as can partially cured formaldehyde resins. The elastic in garments is a frequent cause of clothing dermatitis, and contact allergy to the ink "tag" of tagless baby clothing has been reported. Exposure to other items with fabric, such as infant car seats, may induce reactions similar to clothing.

Topical medications and cosmetics may be unsuspected as allergens, particularly if a medication is being used for a preexisting dermatitis. The most common offenders are neomycin, topical antihistamines, topical anesthetics, fragrances, topical corticosteroids, oxybenzone and octocrylene in chemical sunscreens, preservatives, dye in temporary tattoos, and ethylenediamine, a stabilizer present in many medications. All types of cosmetics can cause facial dermatitis; involvement of the eyelids is characteristic for nail polish sensitivity. Another pediatric allergen has been methylisothiazolinone (MI), a chemical preservative found in rinse-off products including liquid soaps and shampoos, as well as paints and glues, which may be used in making homemade "slime" and lead to hand dermatitis.

Neomycin sulfate is present in many nonprescription topical antibiotic preparations, and thus children are frequently exposed at an early age. It is one of the most common causes of allergic contact dermatitis, and use of combination products of neomycin with other antibiotics, antifungals, or corticosteroids may induce co-reactivity with these chemically unrelated substances.

As mentioned previously, diagnosis of allergic contact dermatitis is usually based on history; however, patch testing may be helpful, especially in older children. Identification and avoidance of the offending agent is the mainstay of managing allergic contact dermatitis. First-line treatment for acute eruption is a mid-potency topical corticosteroid ointment for 2-3 weeks and symptom management with nonsensitizing and fragrance-free emollients/moisturizers, wet dressings, and sedating antihistamines to allow for sleep. Systemic corticosteroids are used when >10% of skin is involved (0.5-1.0 mg/kg prednisone to a maximum of 60 mg/day for 7-10 days, followed by a 7-10 day taper). More chronic allergic contact dermatitis is treated with low- to mid-potency topical corticosteroids. Desensitization therapy is rarely indicated. Topical calcineurin inhibitors, such as tacrolimus, may be a potential steroid-sparing alternative agent in select patients.

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696.2 Nummular Eczema

Julie M. Dhossche and Yvonne E. Chiu

Nummular eczema is characterized by coin-shaped, severely pruritic, eczematous plaques, commonly involving the extensor surfaces of the extremities (Fig. 696.6), buttocks, and shoulders with facial sparing. The plaques are relatively discrete, boggy, vesicular, slightly scaly, and exudative; when chronic, they often become thickened and lichenified and may develop central clearing. Nummular eczema may be an atypical morphology in someone with underlying atopic dermatitis or may be an independent disorder. Flares are generally sporadic but may be precipitated by xerosis, irritants, allergens, or occult staphylococcal infection. Most frequently, these lesions are mistaken for tinea corporis, but plaques of nummular eczema are distinguished by the lack of a raised, sharply circumscribed border, the lack of fungal organisms on a potassium hydroxide (KOH) preparation, and frequent weeping or bleeding when scraped. First-line treatment is with emollients, wet dressings, and potent topical corticosteroids. Steroid-impregnated tapes may simultaneously treat and provide barrier protection to these circumscribed eczematous plaques. An oral antihistamine may be helpful, particularly a sedating antihistamine at night. Antibiotics are indicated for secondary infection. Methotrexate and dupilumab have been described as systemic treatments.

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696.3 Pityriasis Alba

Julie M. Dhossche and Yvonne E. Chiu

Pityriasis alba occurs mainly in children and causes lesions that are hypopigmented, ill-defined, round or oval patches (Fig. 696.7). They may be mildly erythematous and finely scaly. Lesions occur on the face, neck, upper trunk, and proximal portions of the arms and are most pronounced on darker skin tones or after tanning of surrounding skin. Itching

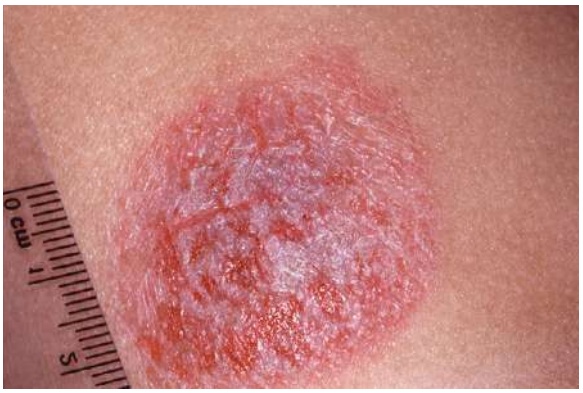

Fig. 696.6 Discrete, boggy plaque of nummular dermatitis.

is minimal or absent. The cause is unknown, but the eruption appears to be exacerbated by dryness and is often regarded as a mild form of atopic dermatitis. Pityriasis alba is frequently misdiagnosed as vitiligo, tinea versicolor, or tinea corporis. The lesions wax and wane but eventually disappear, and normal pigmentation often takes months to return. Application of a lubricant or emollient may ameliorate the condition, and avoidance of sun exposure and daily sunscreen use can help reduce the appearance of existing lesions by allowing for natural lightening of adjacent unaffected skin. If pruritus is troublesome or if the lesions are active with erythema and fine scale, a low-potency topical steroid or calcineurin inhibitor may be used.

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696.4 Lichen Simplex Chronicus

Julie M. Dhossche and Yvonne E. Chiu

Lichen simplex chronicus is a secondary skin disorder resulting from excessive scratching or rubbing. It is characterized by a chronic pruritic, eczematous, circumscribed plaque that is usually lichenified and hyperpigmented (Fig. 696.8). All affected areas must be accessible to scratching, with the most common sites being the posterior neck, genitalia, wrists, ankles, and dorsal feet. Although the initiating event may be a transient lesion such as an insect bite, trauma from rubbing and scratching accounts for persistence of the plaque. Lichen simplex chronicus may also be seen in other chronic eczematous dermatoses such as atopic dermatitis, typically when poorly controlled. Pruritus must be controlled to permit healing; thus a covering to prevent scratching may be necessary. A high-potency topical corticosteroid under occlusion is often helpful and hastens resolution. Second-line therapy includes adding 6% salicylic acid gel to the topical corticosteroid preparation.

696.5 Acute Palmoplantar Eczema

Julie M. Dhossche and Yvonne E. Chiu

A recurrent, sometimes seasonal, blistering disorder of the hands and feet, acute palmoplantar eczema (also known as dyshidrotic eczema or pompholyx) occurs in all age-groups but is uncommon in infancy. The pathogenesis is unknown, although possible predisposing factors include a history of atopy, exposure to contact allergens (especially metals) or irritants, or IV immunoglobulin therapy. The disease is characterized by recurrent crops of small, deep-seated, "tapioca-like" vesicles, which are intensely pruritic and may coalesce into tense bullae (Fig. 696.9). Sites of predilection are the palms, soles, and lateral aspects of the fingers and toes. Primary lesions are noninflammatory and are filled with clear fluid, which, unlike sweat, has a physiologic pH and contains protein. Maceration and secondary infection are frequent because of scratching. The chronic phase is characterized by thickened, fissured plaques that may cause considerable discomfort and dystrophic nails. Although acute

Fig. 696.7 Patchy hypopigmented lesions with diffuse borders characteristic of pityriasis alba.

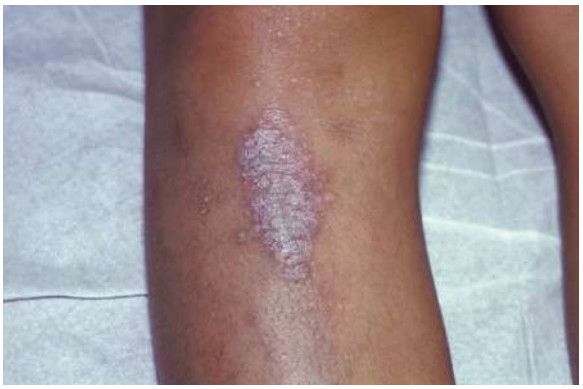

Fig. 696.8 Thickened plaque of lichen simplex chronicus.

palmoplantar eczema is frequently seen in patients with hyperhidrosis, histologic examination reveals an eczematous reaction around sweat ducts, without any structural or functional abnormalities of the sweat ducts themselves. The diagnosis is made clinically. The disorder may be confused with allergic contact dermatitis, which usually affects the dorsal rather than the volar surfaces, and with dermatophytosis, which can be distinguished by a KOH preparation of the roof of a vesicle and by appropriate cultures.

Acute palmoplantar eczema responds to wet dressings, liberal emollient use, and potent topical corticosteroid ointment applied twice daily for 2-4 weeks. Weeping skin benefits from twice-daily soaking in an astringent solution, such as aluminum subacetate. Second-line treatment includes phototherapy and systemic immunomodulators. Severe disease may require oral corticosteroids with a 2-week taper. Secondary bacterial infection should be treated systemically with an appropriate antibiotic. Patients should be told to expect recurrence and should protect their hands and feet from the damaging effects of excessive sweating, chemicals, harsh soaps, and adverse weather. Unfortunately, it is impossible to prevent recurrence or to predict its frequency.

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696.6 Seborrheic Dermatitis

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY

Seborrheic dermatitis is a chronic inflammatory disease most common in infancy and adolescence that parallels the distribution, size, and activity of the sebaceous glands. The cause is unknown, as is the role of the sebaceous glands in the disease. *Malassezia furfur* is implicated as a causative agent,

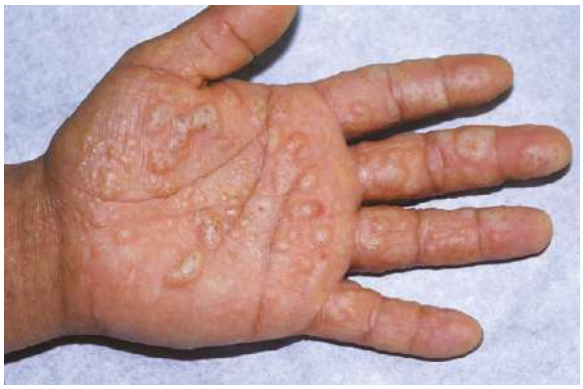

Fig. 696.9 Vesicular palmar lesions of acute palmoplantar eczema with large bullae.

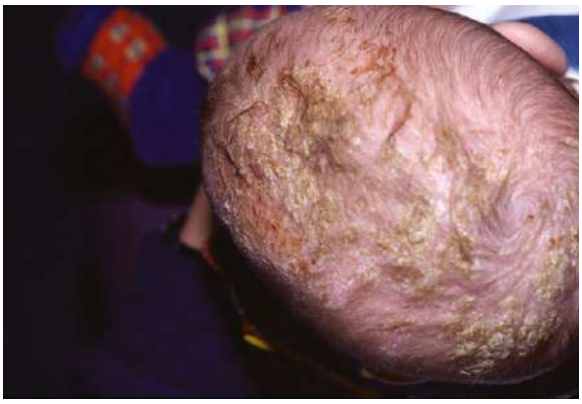

Fig. 696.10 Cradle cap in an infant.

although it remains unclear whether dermatitis results from the action of the fungus, its by-products, or an exaggerated response of the host. In adolescence, seborrheic dermatitis typically occurs after puberty, indicating a possible role for sex hormones.

It is also unknown whether infantile seborrheic dermatitis and adolescent seborrheic dermatitis are the same or different entities. There is no evidence that children with infantile seborrheic dermatitis will experience seborrheic dermatitis as adolescents.

CLINICAL MANIFESTATIONS

The disorder may begin in the first month of life and typically self-resolves by 1 year. Diffuse or focal scaling and crusting of the scalp, sometimes called *cradle cap* (Fig. 696.10), may be the initial and, at times the only, manifestation. A greasy, scaly, erythematous papular dermatitis, which is usually nonpruritic in infants, may involve the face, neck, retroauricular areas, axillae, umbilicus, and diaper area. The dermatitis may be patchy and focal or may spread to involve almost the entire body (Fig. 696.11). Postinflammatory pigmentary changes are common, particularly in infants with darker skin. When the scaling becomes pronounced, the condition may resemble psoriasis and, at times, can be distinguished only with difficulty. The possibility of coexistent atopic dermatitis must be considered when there is an acute weeping dermatitis with pruritus, and the two are often clinically inseparable at an early age. An intractable seborrhea-like dermatitis with chronic diarrhea and failure to thrive may reflect systemic dysfunction of the immune system. A chronic treatment-resistant seborrhea-like pattern may also result from cutaneous histiocytic infiltrates in infants with Langerhans cell histiocytosis. Seborrheic dermatitis is a common cutaneous manifestation of AIDS in young adults and is characterized by thick, greasy scales on the scalp and large hyperkeratotic erythematous plaques on the face, chest, and genitals.

During adolescence, seborrheic dermatitis is more localized and may be confined to the scalp, chest, and intertriginous areas. Also noted may be marginal blepharitis and involvement of the external auditory canal. Scalp changes vary from diffuse, brawny scaling to focal areas of thick, oily, yellow crusts with underlying erythema. Loss of hair is uncommon, and pruritus may be absent to marked. When the dermatitis is severe, erythema and scaling occur at the frontal hairline, the medial aspects of the eyebrows, and in the nasolabial and retroauricular folds. Red, scaly plaques may appear in the axillae, inguinal region, gluteal cleft, and umbilicus. On the extremities, seborrheic plaques may be more eczematous and less erythematous and demarcated. Unlike infantile seborrheic dermatitis, adolescent seborrheic dermatitis generally does not self-resolve and has a chronic relapsing course.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of seborrheic dermatitis includes psoriasis, atopic dermatitis, dermatophytosis, Langerhans cell histiocytosis, and candidiasis. Secondary bacterial infections and superimposed candidiasis are common.

TREATMENT

Initial management for infantile seborrheic dermatitis is generally conservative given the self-limited nature of this condition.

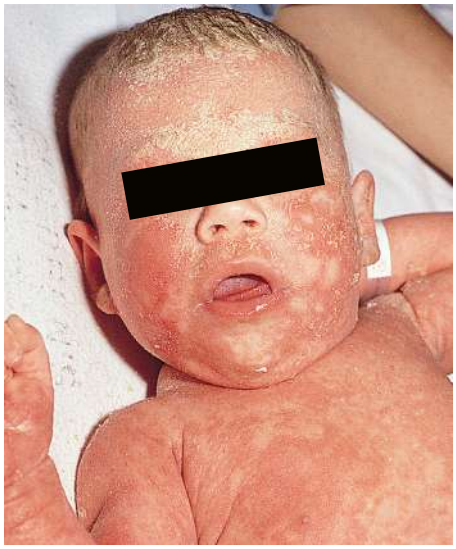

Fig. 696.11 Seborrheic dermatitis may occasionally be more widespread. *(From Tom WL, Eichenfield LF. Eczematous disorders. In: Eichenfield LF, Frieden IJ, eds. Neonatal and Infant Dermatology, 3rd ed. Philadelphia: Elsevier; 2015: Fig. 15.11, p. 225.)*

Emollients, baby oil, gentle shampooing with nonmedicated baby shampoo, and gentle use of a soft brush to remove scales are usually effective measures. Persistent lesions may be treated with low-potency topical corticosteroids if inflamed (applied once daily for 1 week) and a topical antifungal (e.g., ketoconazole 2% cream twice daily). Antifungal shampoos such as ketoconazole 2% shampoo should be used cautiously because they are not tear-free.

First-line therapy for children and adolescents with scalp seborrheic dermatitis is antifungal shampoo used several times weekly to daily (selenium sulfide, ketoconazole, ciclopirox, zinc pyrithione, salicylic acid, or tar). Mid-potency topical corticosteroids such as fluocinolone 0.01% oil or triamcinolone 0.1% lotion may also be used for inflamed lesions, applied once daily for 2-4 weeks. Nonscalp lesions are treated with topical corticosteroid cream (low-potency for facial lesions, mid-potency elsewhere), as well as topical antifungals such as ketoconazole 2% cream or ketoconazole 2% shampoo used as a body or face wash. Second-line therapy for seborrheic dermatitis includes topical calcineurin inhibitors and keratolytic agents such as urea. Severe adult cases improve with oral antifungal agents; however, pediatric studies are lacking. Once acute disease is controlled, antifungal shampoo used on a twice-weekly basis is effective maintenance to reduce the risk of relapse.

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Chapter 697

Photosensitivity

Julie M. Dhossche and Yvonne E. Chiu

Photosensitivity denotes an abnormal cutaneous reaction to UV radiation, either in sunlight or artificial light. The UV light spectrum contains UVA (320-400 nm wavelength), UVB (290-320 nm wavelength), and UVC (100-290 nm wavelength) subtypes. Transmitted radiation <300 nm is largely absorbed in the epidermis, whereas >300 nm is mostly transmitted to the dermis after variable epidermal melanin absorption. Children vary in susceptibility to UV radiation, depending on their skin type (i.e., its amount of pigment; Table 697.1).

ACUTE SUNBURN REACTION

The most common photosensitive reaction seen in children is acute sunburn, which is caused mainly by UVB radiation. Sunlight contains many times more UVA than UVB radiation, but UVA must be encountered in much larger quantities than UVB radiation to produce sunburn. Immediate pigment darkening is caused by UVA radiation–induced photo-oxidative darkening of existing melanin and its transfer from melanocytes to keratinocytes. This effect generally lasts for a few hours and is not photoprotective. UVB-induced effects appear 6-12 hours after initial exposure and reach a peak in 24 hours. Effects include redness, tenderness, edema, and blistering (Fig. 697.1). Severe sunburn induces systemic symptoms of fever, nausea, and headache. Reactive oxidation species generated by UVB induce keratinocyte membrane damage and are involved in the pathogenesis of sunburn. A portion of the vasodilation seen in UVB-induced erythema is mediated by prostaglandins E_2, E_3, and F_{2A}. Other inflammatory cytokines induced by UVB include interleukins 1, 6, and 8 and tumor necrosis factor-α. Acute sunburn is a self-limited condition that resolves within 1 week with desquamation and without scarring. Delayed melanogenesis as a result of UVB radiation begins in 2-3 days and lasts several days to a few weeks. Manufacture of new melanin in melanocytes, transfer of melanin from melanocytes to keratinocytes, increase in size and arborization of melanocytes, and activation of quiescent melanocytes produce delayed melanogenesis and pigment darkening (tanning). This effect reduces skin sensitivity to future UV-induced erythema. The amount of protection afforded depends on the skin type of the patient. Additional effects and possible complications of sun exposure include increased thickness of the stratum corneum, recurrence or exacerbation of herpes simplex labialis, lupus erythematosus, and many other conditions (Table 697.2).

Acute sunburn should be managed conservatively with cool compresses, aloe vera products, and calamine lotion. Oral analgesics such as ibuprofen and acetaminophen may decrease pain. Topical corticosteroids are only helpful in the acute phase and generally should not be used to treat sunburn once peak erythema has been reached (~24 hours). Topical anesthetics are relatively ineffective and potentially hazardous because of their propensity to cause contact dermatitis. A bland emollient, such as plain petrolatum, is effective in the desquamative phase.

Table 697.1 Sun-Reactive Skin Types

FITZPATRICK SKIN TYPE	SUNBURN, TANNING HISTORY
I	Always burns easily, no tanning
II	Usually burns, minimal tanning
III	Sometimes burns, gradual light brown tan
IV	Minimal to no burning, always tans
V	Rarely burns, tans profusely dark brown
VI	Never burns, pigmented black

The long-term sequelae of chronic and intense sun exposure are not often seen in children, but most individuals receive >50% of their lifetime UV dose by age 20 years; therefore pediatricians have a pivotal role in educating patients and their parents about the harmful effects, potential malignancy risks, and irreversible skin damage that result from prolonged exposure to the sun and tanning lights. Premature aging, senile elastosis, actinic keratoses, squamous and basal cell carcinomas, and melanomas all occur with greater frequency in sun-damaged skin. In particular, blistering sunburns in childhood and adolescence significantly increase the risk for development of malignant melanoma.

Sun protection is best achieved by sun avoidance, which includes minimizing time in the midday sun (10 AM to 4 PM), staying in the shade, and wearing protective clothing including wide-brimmed hats. Protection is enhanced by a wide variety of sunscreen agents. Physical sunscreens (zinc oxide, titanium dioxide) that block UV light are preferred, whereas chemical sunscreens (para-aminobenzoic acid [PABA], PABA esters, salicylates, benzophenones, avobenzone, cinnamates, and ecamsule) absorb damaging radiation. Some of these products may be systemically absorbed and achieve levels higher than permitted by the FDA. Most chemical sunscreens are effective for only UVB wavelengths but benzophenones and avobenzone provide protection in both the UVA and UVB ranges; ecamsule is a UVA sunscreen. Stabilizers such as octocrylene and diethyl 2,6-naphthalate increase the time of function of the chemical sunscreens. "Broad-spectrum" sunscreens are combination products that absorb both UVA and UVB, and families should be advised to use products labeled as "broad spectrum" with a sun protective factor (SPF) of at least 30, reapply liberally at least every 2 hours while outdoors, and reapply after swimming. Infants younger than 6 months of age should not be exposed to direct sunlight but may have SPF 15 physical sunscreens applied to small areas of skin if sunlight avoidance is not possible. SPF is defined as the minimal dose of sunlight required to produce cutaneous erythema after application of a sunscreen, divided by the dose required with no use of sunscreen. SPF applies only to UVB protection; there is no associated rating for UVA protection in the United States aside from the "broad spectrum" designation.

PHOTOSENSITIVE REACTIONS

Photosensitizers in combination with a particular wavelength of light (typically UVA) cause dermatitis that can be classified as phototoxic or photoallergic reactions. Contact with the photosensitizer may occur externally on the skin, internally by enteral or parenteral administration, or through host synthesis of photosensitizers in response to an administered drug.

Photoallergic reactions occur in only a small percentage of persons exposed to photosensitizers and light and require a time interval for sensitization to take place. Thereafter, dermatitis appears within 24 hours of reexposure to the photosensitizer and light. Typically, patients present with an eczematous eruption in sun-exposed areas with sparing behind the ear, under the chin, and under clothing. Photoallergic dermatitis is a T-cell–mediated delayed hypersensitivity reaction in which the drug, acting as a hapten, may combine with a skin protein to form the antigenic substance. Table 697.2 lists some of the important classes of drugs and chemicals responsible for photosensitivity reactions. The most common photoallergens are chemicals present in sunscreens.

Phototoxic reactions occur in all individuals who accumulate adequate amounts of a photosensitizing drug or chemical within the skin. UV radiation excites the agent to a state capable of causing cell or tissue damage through reactive oxygen species formation. Prior sensitization is not required. Dermatitis develops within hours after exposure to radiation in the range of 285-450 nm. The eruption is confined to light-exposed areas and often resembles exaggerated sunburn, but it

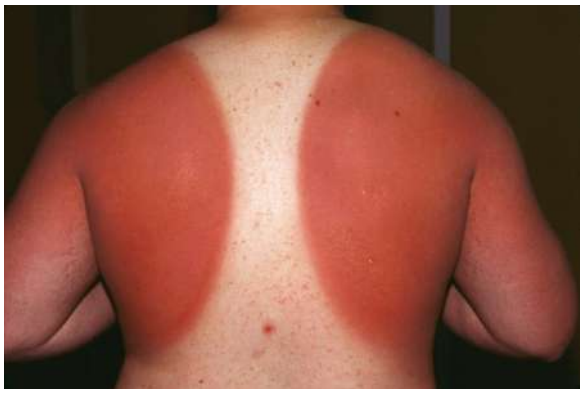

Fig. 697.1 Sunburn. Well-demarcated, severe erythema.

may be urticarial or bullous. It results in postinflammatory hyperpigmentation. All the drugs that cause photoallergic reactions may also cause a phototoxic dermatitis if given in sufficiently high doses. Several additional drugs and contactants cause phototoxic reactions (see Table 697.2). Postinflammatory hyperpigmentation develops rapidly and can be the presenting sign. Contact with furocoumarin-containing plants causes a nonallergic disorder called **phytophotodermatitis** (Figs. 697.2 and 697.3). The most common phytophotodermatitis seen in children is caused by lime juice, which presents as hyperpigmentation in streaky patterns on sun-exposed skin consistent with dripping juice or handprints (see Table 697.2).

Diagnosis of photosensitive reactions caused by drugs or chemicals relies on a high index of suspicion, an appreciation of the distribution pattern of the eruption, and a history of application or ingestion of a known photosensitizing agent. Phototesting and photopatch testing are also helpful when available. First-line treatment for both photoallergy and phototoxicity consists of discontinuation of the offending agent and good sun protection practices, including avoidance of sun exposure. Photoallergic reactions are treated similarly to contact dermatitis, with a topical corticosteroid to alleviate pruritus when necessary. Severe reactions may necessitate a 2- to 3-week course of systemic corticosteroid therapy. Phototoxic reactions are treated similarly to sunburn, with comfort measures such as cool compresses, emollients, and oral analgesics.

PORPHYRIAS

See Chapter 112.

Porphyrias are acquired or inborn disorders due to genetic variants of specific enzymes in the heme biosynthetic pathway. Some have childhood photosensitivity as a consistent feature. The pathogenesis of photosensitivity in porphyria relates to deposition of excess porphyrins in the skin; UV radiation excites these molecules, causing cell and tissue damage via generation of reactive oxygen species. Signs and symptoms may be negligible during the winter, when sun exposure is minimal.

Congenital erythropoietic porphyria (Günther disease) is a rare autosomal recessive disorder affecting the enzyme uroporphyrinogen III synthase. It may cause hydrops fetalis, but more typically manifests in the first few months of life as hemolytic anemia and exquisite sensitivity to light, which may induce repeated severe bullous eruptions that result in mutilating scars (Fig. 697.4). Hyperpigmentation, hyperkeratosis, vesiculation, and fragility of skin, as well as various nail changes, develop in light-exposed areas. Light therapy for an affected neonate presenting with jaundice may inadvertently induce skin manifestations. Hirsutism in areas of mild involvement, scarring alopecia in severely affected areas, pink to red urine, brown teeth (erythrodontia), splenomegaly, and corneal ulceration are additional characteristic manifestations. Laboratory findings include uroporphyrin I and coproporphyrin I in urine, plasma, and erythrocytes and coproporphyrin I in feces. Teeth and urine from affected patients fluoresce reddish pink under a Wood lamp as a result of the presence of porphyrins. **Hepatoerythropoietic porphyria**, a separate entity, has skin findings that closely resemble those seen in congenital erythropoietic porphyria; this extremely rare disorder presents in early childhood and is discussed in greater depth in Chapter 112.

Table 697.2 Cutaneous Reactions to Sunlight

Sunburn
Photoallergic Drug Eruptions
• Systemic drugs include tetracyclines, psoralens, chlorothiazides, sulfonamides, barbiturates, griseofulvin, thiazides, quinidine, phenothiazines
• Topical agents include coal tar derivatives, psoralens, halogenated salicylanilides (soaps), perfume oils (e.g., oil of bergamot), sunscreens (e.g., PABA, cinnamates, benzophenones)
Phototoxic Drug Eruptions
• Systemic agents include nalidixic acid, furosemide, nonsteroidal antiinflammatory agents (naproxen, piroxicam), and high doses of agents causing photoallergic eruptions
• Topical agents include 5-fluorouracial, furocoumarins and high doses of agents causing photoallergic eruptions
Phytophotodermatosis
• Furocoumarin-containing plants: fig tree leaves and sap, limes, celery, fennel, carrots, parsley, dill, parsnips
Genetic Disorders with Photosensitivity
• Xeroderma pigmentosum
• Bloom syndrome
• Cockayne syndrome
• Rothmund-Thomson syndrome
• Trichothiodystrophy
• Smith-Lemli-Opitz syndrome
• Kindler syndrome
Inborn Errors of Metabolism
• Porphyrias
• Hartnup disease and pellagra
Infectious Diseases Associated with Photosensitivity
• Recurrent herpes simplex infection
• Viral exanthems (accentuated photodistribution; e.g., varicella)
Skin Diseases Exacerbated or Precipitated by Light
• Lichen planus
• Darier disease
• Lupus erythematosus, including neonatal
• Dermatomyositis
• Psoriasis
• Erythema multiforme
• Atopic dermatitis
• Hailey-Hailey disease
Deficient Protection Because of a Lack of Pigment
• Vitiligo
• Oculocutaneous albinism
• Phenylketonuria
• Chédiak-Higashi syndrome
• Hermansky-Pudlak syndrome
• Waardenburg syndrome
• Piebaldism

PABA, para-aminobenzoic acid.

Erythropoietic protoporphyria may be autosomal dominant, autosomal recessive, or X-linked and most commonly involves the enzyme ferrochelatase (FECH), the final enzyme in the heme synthetic pathway. Symptoms develop in early childhood and manifest as intense pain, tingling, or pruritus within 30 minutes of sun exposure, followed by erythema, edema, urticaria, or mild systemic symptoms; these acute manifestations resolve completely within days. The absence of blistering distinguishes erythropoietic protoporphyria from the other cutaneous porphyrias. Nail changes consist of opacification of the nail plate, onycholysis, pain, and tenderness. Recurrent sun exposure produces a subtle chronic eczematous dermatitis with thickened, lichenified skin, especially over the finger joints (Fig. 697.5A), as well as mild facial scarring (see Fig. 697.5B). Pigmentation, hypertrichosis, skin fragility, and mutilation are not seen. Gallstones develop frequently; however, severe liver disease occurs in <5% of patients. Protoporphyrin is detected in plasma, erythrocytes, and feces. **X-linked protoporphyria**

is a similar disorder to erythropoietic protoporphyria but is due to a pathogenic genetic variant in 5-aminolevulinic acid synthetase (the first and rate-controlling enzyme of heme synthesis) and therefore does not have iron overload or associated anemia.

The wavelengths of light mainly responsible for eliciting cutaneous reactions in porphyria are in the region of 400 nm (UVA light). Window glass, including that in automobiles, transmits wavelengths >320 nm and is not protective, and fluorescent indoor lights may be pathogenic. Patients must avoid direct sunlight, wear protective clothing, and use a sunscreen agent that effectively blocks UVA light. Oral beta-carotene also provides some photoprotective benefit. Afamelanotide, an alpha-melanocyte–stimulating hormone (α-MSH) analog, is approved by the FDA for treatment of erythropoietic protoporphyria to increase pain-free light exposure. This drug serves to increase skin pigmentation by increasing melanin production by melanocytes, resulting in increased UV tolerance.

Cutaneous porphyria symptoms are typically constant throughout life, and secondary bacterial infections commonly complicate the disease course. Cutaneous porphyrias do not appear to increase the risk for skin malignancies. Additional diagnostic and treatment recommendations for the porphyrias are outlined in Chapter 112.

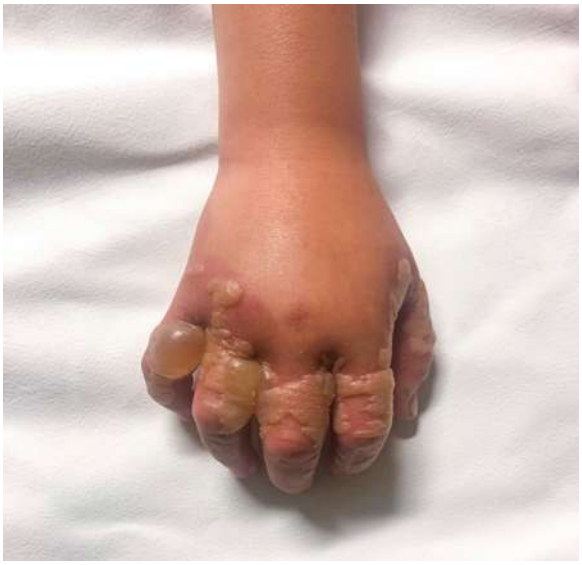

Fig. 697.2 Phytophotodermatitis (fig tree leaves). *(From Papazoglou A, Mantadakis E. Fig tree leaves phytophotodermatitis. J Pediatr. 2021;239:244–245, Fig.1A.)*

Pseudoporphyria is a porphyria-like reaction characterized by erythema, blistering, and scarring on sun-exposed skin seen occasionally in patients with juvenile idiopathic arthritis taking nonsteroidal anti-inflammatory agents.

COLLOID MILIUM

Colloid milium is a rare, asymptomatic disorder that occurs on the face (nose, upper lip, and upper cheeks) and may extend to the dorsum of the hands and the neck as a profuse eruption of tiny, ivory to yellow, firm, grouped papules. Lesions appear before puberty on otherwise normal skin, unlike the adult variant that develops on sun-damaged skin. Onset may follow an acute sunburn or long-term sun exposure. Most cases reach maximal severity within 3 years and remain unchanged thereafter, although the condition may remit spontaneously after puberty. Treatment is usually not necessary.

HYDROA VACCINIFORME

Hydroa vacciniforme is a vesiculobullous disorder with unclear etiology, although chronic or latent Epstein-Barr virus infections or lymphoproliferative disorders have been implicated. It begins in early childhood and may remit at puberty, with peak incidence in the spring and summer. Erythematous, pruritic macules develop symmetrically within hours of sun exposure over the ears, nose, lips, cheeks, and dorsal surfaces of the hands and forearms. Lesions progress to stinging tender papules and hemorrhagic vesicles and bullae, resembling chickenpox. They become umbilicated, ulcerated, and crusted, eventually healing with pitted scars and telangiectasias. Associated features are rare but include fever, malaise, hypersensitivity to mosquito bites, conjunctivitis, and other ocular symptoms. This eruption should be distinguished

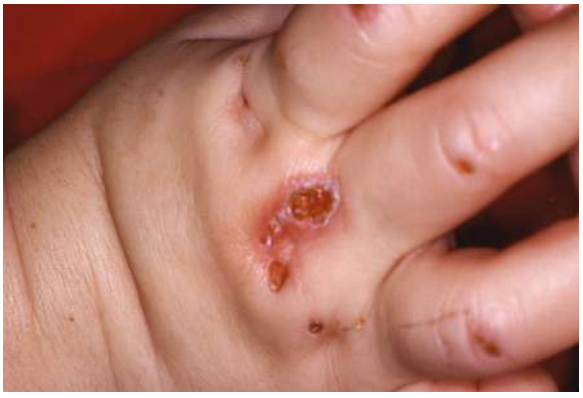

Fig. 697.4 Crusted ulcerations in an infant with congenital erythropoietic porphyria.

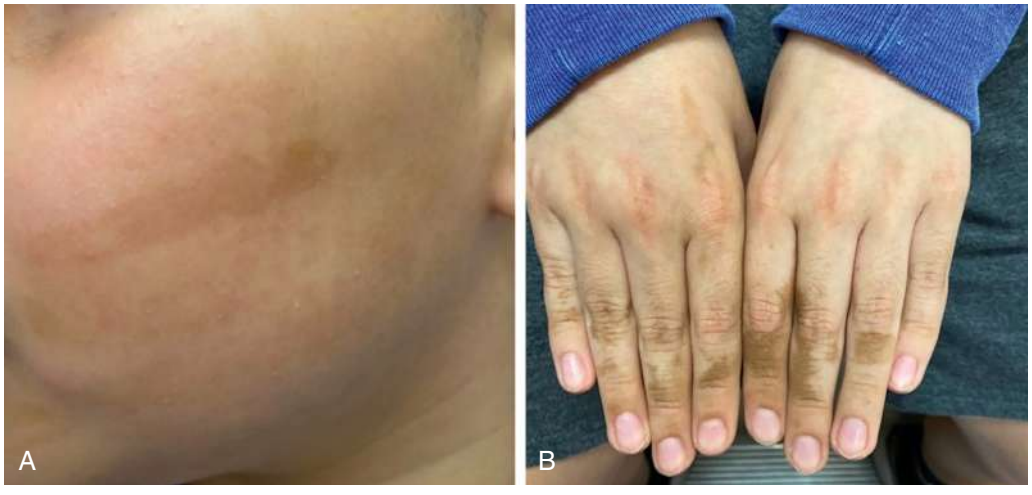

Fig. 697.3 Phytophotodermatitis (lime). **A,** Linear hyperpigmentation on the left cheek. **B,** A linear streak of hyperpigmentation on the right dorsal hand along with irregular hyperpigmentation of the bilateral dorsal fingers. *(From Dreher K, Evans MS. Linear hyperpigmentation in chronic phytophotodermatitis from limes. J Pediatr. 2021;239:245–246.)*

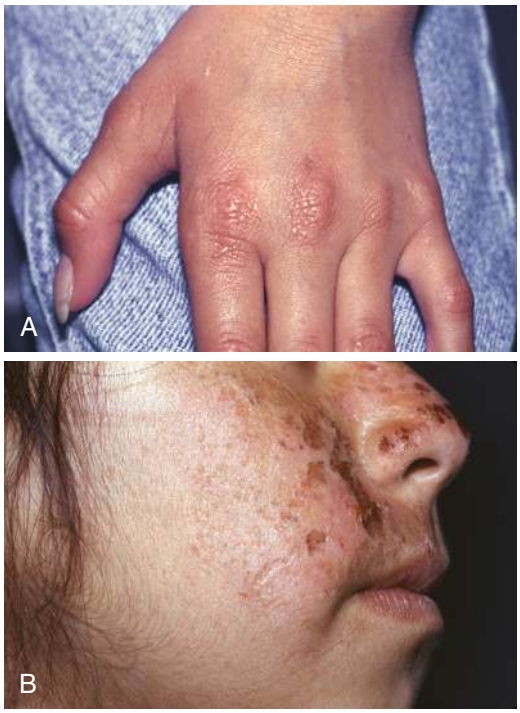

Fig. 697.5 Erythropoietic protoporphyria. **A**, Erythematous thickening over the metacarpal phalangeal joints. **B**, Linear crusts and scarring.

from erythropoietic protoporphyria, which rarely shows vesicles. Typical lesions have been reproduced with repeated doses of UVA or UVB light. First-line treatment includes sun avoidance, broad-spectrum sunscreens, and other sun-protective habits. Other potential therapies include mid-potency topical corticosteroids for inflamed lesions, low-dose courses of narrow-band UVB (NB-UVB) therapy, beta-carotene, hydroxychloroquine, or antiviral agents such as acyclovir.

SOLAR URTICARIA

Solar urticaria is a rare disorder induced by UV or visible irradiation. The disorder is mediated by immunoglobulin E antibodies to either an abnormal photoallergen present only in affected patients (type I) or a normal photoallergen ordinarily present in skin (type II), leading to mast cell degranulation and histamine release. Classic urticarial lesions consisting of erythematous pruritic wheals develop on sun-exposed skin (Fig. 697.6) within 5-10 minutes of sun exposure and fade within 24 hours. Severe reactions involving large areas of skin may lead to systemic symptoms or anaphylaxis. Diagnosis is achieved by history alone or with phototesting. First-line treatment is an oral H_1 antihistamine, plus sun avoidance and protection. Second-line therapy possibilities include oral or topical corticosteroids, photodesensitization using NB-UVB, omalizumab, or intravenous immunoglobulin.

POLYMORPHOUS LIGHT ERUPTION

Polymorphous light eruption (PMLE) is a common photosensitivity reaction that develops most commonly in females. The first eruption typically appears in the spring after the first episode of prolonged sun exposure of the season. Onset of the eruption is delayed by hours to days after sun exposure and lasts for days to sometimes weeks. PMLE usually resolves with increased sun exposure throughout the spring and summer. Areas of involvement tend to be symmetric and are characteristic for a given patient, including some, but not all, of the exposed or lightly covered skin on the face, neck, upper chest, and distal extremities. Lesions have various morphologies but most commonly are pruritic, 2- to 5-mm, grouped, erythematous papules or papulovesicles or >5-cm edematous plaques; lesions are nonscarring. A PMLE variant known as **juvenile spring eruption** characteristically occurs

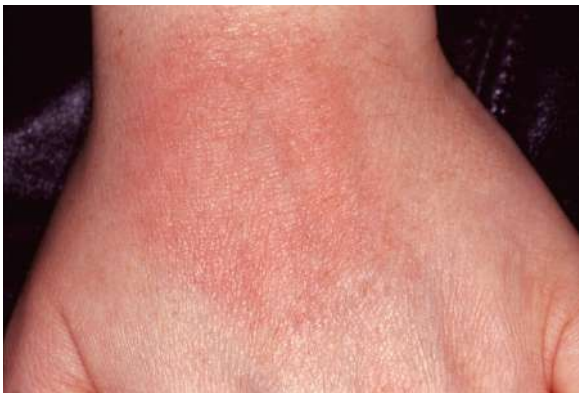

Fig. 697.6 Urticaria after 5 min of exposure to artificial ultraviolet A radiation.

on affected boys' ears each spring, and **pinpoint papular PMLE** is a variant characterized by pinpoint-sized lesions occurring in darker-skinned individuals. Most PMLE cases involve sensitivity to UVA radiation, although some are UVB induced. PMLE most likely results from a delayed-type hypersensitivity reaction to a photo-induced antigen within the skin, with individuals having a genetic predisposition. Provocative phototesting, as well as skin biopsy (showing epidermal spongiosis and superficial and deep lymphocytic infiltrate), aid in diagnosis. Treatment is aimed at prevention with sun avoidance, protective clothing, and broad-spectrum sunscreens. Topical corticosteroids (low-potency for facial lesions, high-potency for lesions elsewhere) can be used for mild eruptions. Second-line approaches include prophylactic NB-UVB phototherapy or hydroxychloroquine in early spring and short-course systemic glucocorticoids for severe flares.

ACTINIC PRURIGO

Actinic prurigo, often classified as a variant of PMLE, is a chronic familial photodermatitis inherited as an autosomal dominant trait seen most commonly in Native Americans of North and South America. Human leukocyte antigen (HLA) DRB1*0407 (60–70%) and HLA DRB1*0401 (20%) are strongly associated with actinic prurigo. Most patients are female and are sensitive to UVA radiation. The first episode generally occurs in early childhood, several hours to 2 days after intense sun exposure. The papulonodular lesions are intensely pruritic, erythematous, and crusted. Areas of predilection include the face (Fig. 697.7), lower lip, distal extremities, and, in severe cases, buttocks. Facial lesions may heal with minute pitted or linear scarring. Lesions often become chronic, without periods of total clearing, merging into eczematous plaques that become lichenified and occasionally secondarily infected. Associated features that distinguish this disorder from other photoeruptions and atopic dermatitis include cheilitis, conjunctivitis, and traumatic alopecia of the outer half of the eyebrows. Actinic prurigo is a chronic condition that generally persists into adult life, although it may improve spontaneously in the late teenage years. Sun avoidance, protective clothing, and broad-spectrum sunscreens may be helpful in preventing the eruption. Mid- to high-potency topical corticosteroids and antihistamines palliate the pruritus and inflammation. Severe acute eruptions may require oral glucocorticoids. Treatment with NB-UVB beginning in springtime has shown improved tolerance of sunlight during summer months; however, it may induce symptoms in some patients. Thalidomide 50-100 mg/day is very effective, but its use is limited by toxicity, especially severe birth defects when taken by pregnant females. Dupilumab is described in case reports to be helpful.

COCKAYNE SYNDROME

Cockayne syndrome is a rare autosomal recessive disorder. Onset occurs at 1 year of age and is characterized by facial erythema in a butterfly distribution after sun exposure. Later characteristics include loss of adipose tissue and development of thin, atrophic, hyperpigmented

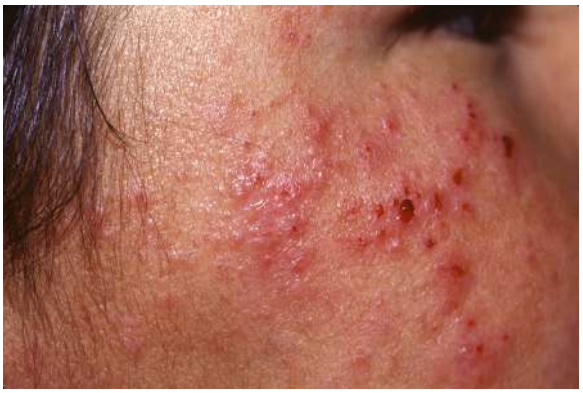

Fig. 697.7 Erythematous, excoriated papules in actinic prurigo.

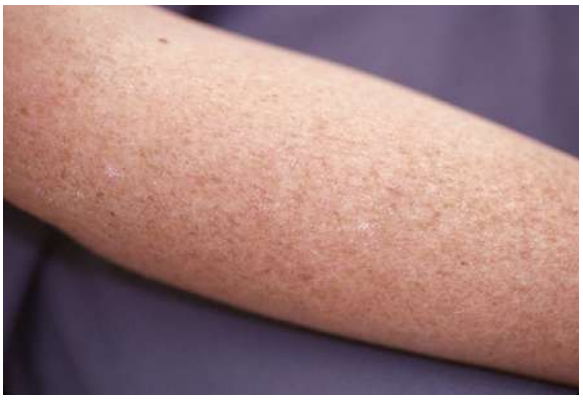

Fig. 697.8 Dyspigmentation and actinic keratoses in child with xeroderma pigmentosum.

skin, particularly over the face. Associated features include stunted growth; dwarfism; microcephaly; progressive neurologic dysfunction (caused by leukodystrophy); mental retardation; progressive dementia; distinct facies (aged look, pinched nose, sunken eyes, large protuberant ears); long limbs; disproportionately large hands and feet; cool and cyanotic extremities; carious teeth; unsteady gait with tremor; limitation of joint mobility; progressive deafness; cataracts; retinal degeneration; optic atrophy; decreased sweating and tearing; and premature graying of the hair. Complications include diabetes and hepatic or renal impairment. Diffuse extensive demyelination of the peripheral and central nervous systems ensues, and patients generally die of atheromatous vascular disease or infections (especially pneumonia) before the third decade. There are two types of Cockayne syndrome. **Type I (*CSA* gene)** is less severe than **type II (*CSB* gene)**. Patients may have xeroderma pigmentosum–Cockayne syndrome overlap, which is phenotypically more like Cockayne syndrome and is due to genetic variants in *XPB, XPD,* or *XPG* genes. Photosensitivity in Cockayne syndrome is a result of deficient nucleotide excision repair of UV-induced damage, specifically within actively transcribing regions of DNA (transcription-coupled DNA repair). The etiology of neurologic and other associated features remains unclear; however, evidence points toward a mitochondriopathy. The syndrome is distinguished from progeria (see Chapter 111) by the presence of photosensitivity and ocular abnormalities and from xeroderma pigmentosum by the fact that patients with Cockayne syndrome do not develop sun-induced pigmentation or increased risk of skin cancers. Diagnosis is accomplished by genetic testing and performing various tests on cultured fibroblasts. The mainstay of treatment for the photosensitivity of Cockayne syndrome is strict sunlight avoidance and protective measures.

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum is a rare autosomal recessive disorder that results from a defect in nucleotide excision repair. Eight genetic groups have been recognized on the basis of each group's separate defect in ability to repair (xeroderma pigmentosum A through G) or replicate (xeroderma pigmentosum V [variant]) damaged DNA. The wavelength of light that induces the DNA damage ranges from 280 to 340 nm. Skin changes are first noted during infancy or early childhood in sun-exposed areas, though lesions may occur at other sites, including the scalp. The skin lesions consist of erythema, scaling, bullae, crusting, ephelides (freckles), telangiectasia, keratoses (Fig. 697.8), basal and squamous cell carcinomas, and malignant melanomas. Interestingly, although most patients experience exaggerated acute sunburn reactions after minimal UV exposure, up to half of affected patients do not and instead develop progressive freckling. This difference in presentation depends on genetic subtype. Ocular manifestations include photophobia, lacrimation, blepharitis, symblepharon, keratitis, corneal opacities, tumors of the lids, and possible eventual blindness. Neurologic abnormalities such as cognitive deterioration and sensorineural deafness develop in approximately 20% of patients.

This disease is a serious mutilating disorder, and the life span of an affected patient is often brief. Affected families should have genetic counseling. Xeroderma pigmentosum is detectable in cells cultured from amniotic fluid or DNA analysis of chorionic villous samples. Cultured skin fibroblast tests and genetic testing after birth also confirm diagnosis. Affected children should be totally protected from sun exposure; protective clothing, sunglasses, and opaque broad-spectrum sunscreens should be used even for mildly affected children. Light from unshielded fluorescent bulbs and sunlight passing through glass windows (including vehicle windows) are also harmful; thus applied window films are recommended. Early detection and removal of malignancies is mandatory, and oral isotretinoin may be used to prevent nonmelanoma skin cancers. Average age of death of these patients is 32 years. There is crossover between several subtypes of xeroderma pigmentosum and both Cockayne syndrome and trichothiodystrophy.

ROTHMUND-THOMSON SYNDROME

Rothmund-Thomson syndrome is also known as **poikiloderma congenitale** because of the striking skin changes (Fig. 697.9). It is inherited as an autosomal recessive trait. Pathogenic genetic variants in the *RECQL4* gene, which encodes a DNA helicase involved in repair and replication of DNA and telomeres, are found in approximately 65% of patients. The other genetic variants causing Rothmund-Thomson syndrome are unknown. Skin changes are noted as early as 3 months of age and begin on the face. Plaques of erythema and edema appear in a butterfly distribution and on the forehead, ears, neck, dorsal portions of the hands, extensor surfaces of the arms, and buttocks. These are replaced gradually by **poikiloderma** (reticulated, atrophic, hyperpigmented, and hypopigmented telangiectatic patches or plaques). Palmoplantar hyperkeratosis develops in one third of patients. Light sensitivity is present in many cases, and exposure to the sun may provoke formation of bullae. Areas of involvement, however, are not strictly photodistributed. Short stature; small hands and feet; sparse eyebrows, eyelashes, and pubic and axillary hair and sparse, fine, prematurely gray scalp hair or alopecia; dystrophic nails; various tooth and skeletal abnormalities; and hypogonadism are common. One of the more distinguishing features is an increased incidence of juvenile subcapsular bilateral cataracts. Most patients have normal mental development. Keratoses and later squamous cell carcinomas may develop on exposed skin. The most worrisome association is osteosarcoma, which occurs in 30% of those patients with Rothmund-Thomson syndrome and *RECQL4* pathogenic genetic variants. Genetic testing aids in diagnosis. Management of dermatologic findings begins with sun avoidance and protection behaviors, and telangiectatic lesions have been shown to respond to pulsed dye laser therapy. In the absence of malignancy, life expectancy is normal.

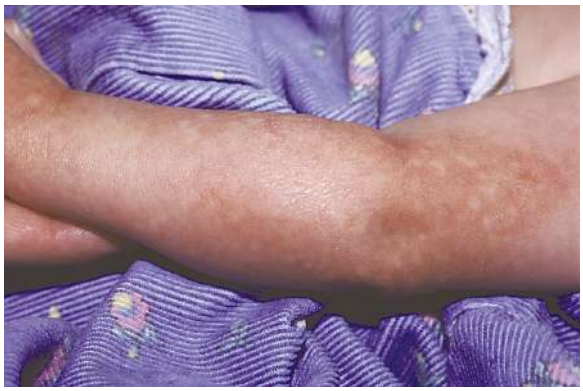

Fig. 697.9 Poikiloderma on the arm of an infant with Rothmund-Thomson syndrome.

BLOOM SYNDROME

Bloom syndrome is inherited in an autosomal recessive manner, most commonly in the Ashkenazi Jewish population. It is caused by pathogenic genetic variants in the *BLM/RECQL3* gene encoding a DNA helicase. Patients are sensitive to UV radiation, with increased rates of chromosomal breaks and sister chromatid exchanges. Erythema and telangiectasia develop during infancy in a butterfly distribution on the face after exposure to sunlight. A bullous eruption on the lips and telangiectatic erythema on the cheeks, hands, and forearms may develop. Café-au-lait spots and hypopigmented macules may be present. Intrauterine growth deficiency developing into short stature, referred to as "proportionate dwarfism," and a distinctive facies consisting of a prominent nose and ears and a small, narrow face are generally found. Intellect is average to low average. Immunodeficiency is seen in all patients, manifesting as recurrent ear and pulmonary infections. Gastrointestinal malabsorption, gastroesophageal reflux, and hypogonadism are common. Affected children have an unusual tendency to develop both solid tumors (especially of the skin) and lymphoreticular malignancies, which often result in death during childhood or early adulthood. Sister chromatid exchange analysis is generally performed to confirm diagnosis. The only effective measures to reduce skin disease are sun protection and avoidance.

HARTNUP DISEASE

See Chapter 105.5.

Hartnup disease is a rare inborn error of metabolism with autosomal recessive inheritance. Neutral amino acids, including tryptophan, are not transported across the brush border epithelium of the intestine and kidneys due to a pathogenic variant in the *SLC6A19* gene encoding the transporter. This results in deficiency of nicotinamide synthesis and causes a photo-induced **pellagra-like syndrome**. The urine contains increased amounts of monoamine monocarboxylic amino acids, distinguishing Hartnup disease from dietary pellagra. Cutaneous signs, which precede neurologic manifestations, initially develop during the early months of life. An eczematous, occasionally vesiculobullous, eruption occurs on the face and extremities in a glove-and-stocking photodistribution. Hyperpigmentation and hyperkeratosis may supervene and are intensified by further exposure to sunlight. Episodic flares may be precipitated by febrile illness, sun exposure, emotional stress, and poor nutrition. In most cases, mental development is normal, but some patients display emotional instability and episodic cerebellar ataxia. Neurologic symptoms are fully reversible. Administration of nicotinamide and protection from sunlight result in improvement of both cutaneous and neurologic manifestations.

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Chapter 698
Diseases of the Epidermis

698.1 Psoriasis

Julie M. Dhossche and Yvonne E. Chiu

Psoriasis affects 2–4% of the U.S. population, and pediatric psoriasis accounts for approximately one third of all cases.

ETIOLOGY/PATHOGENESIS

Psoriasis is an inflammatory autoimmune-related disease characterized by inflammation and keratinocyte proliferation (Fig. 698.1). Within the dermis, dendritic cells are activated by self-antigens and release cytokines such as interferon-γ, tumor necrosis factor, and interleukin (IL)-12, IL-17, IL-22, and IL-23, which recruit T cells. Once activated, the T cells release cytokines that induce proliferation and abnormal differentiation of epidermal keratinocytes; in turn, more cytokines are produced to perpetuate the cycle. Psoriasis has a complex multifactorial genetic basis. Family history of psoriasis is present in ~50% of patients, typically a first-degree relative. The major psoriasis-susceptibility gene *(PSORS1)* is human leukocyte antigen (HLA)-CW*0602, encoding a class I major histocompatibility complex protein involved in recognition of self-antigens. Numerous other psoriasis susceptibility genes have been identified.

Factors contributing to disease onset/flares in some patients include bacterial and viral infections, trauma, physical or emotional stress, tobacco use/secondhand exposure, and certain medications.

CLINICAL MANIFESTATIONS

This common chronic skin disorder is first evident within the first 2 decades of life for approximately 30% of affected individuals. **Plaque psoriasis**, the most common (>80%) subtype, is characterized by erythematous papules that coalesce to form plaques with sharply demarcated, irregular borders (Fig. 698.2A-D). If they are unaltered by treatment, a thick silvery or yellow-white scale (resembling mica) develops (see Fig. 698.2A). Removal of the scale may result in pinpoint bleeding **(Auspitz sign)**. The **Koebner phenomenon**, in which new lesions appear at sites of trauma, is a valuable diagnostic feature. Lesions may occur anywhere, but preferred sites are the scalp, knees, elbows, umbilicus, superior intergluteal fold, genitalia, and ear canal. Nail involvement, a valuable diagnostic sign, is characterized by pitting of the nail plate, detachment of the plate (onycholysis), yellowish-brown subungual discoloration, and accumulation of subungual debris (see Fig. 698.2G, H, and M). Plaques are generally asymptomatic; however, pruritus is more common in children than in adults.

Guttate psoriasis, a variant that occurs predominantly in children, is characterized by an acute eruption of many oval or round papules smaller than 1.5 cm that are morphologically identical to the larger plaques of psoriasis (see Fig. 698.2N-Q). Sites of predilection are the trunk, face, and proximal portions of the limbs. The onset usually follows a few weeks after a **streptococcal** infection such as pharyngitis; thus throat culture and serologic titers should be obtained. Guttate psoriasis has also been observed after perianal streptococcal infection, viral infections, sunburn, and withdrawal of systemic corticosteroid therapy or tumor necrosis factor (TNF)-α inhibitors. Clinical course ranges from spontaneous resolution to chronic disease.

Pustular psoriasis is a multisystem autoinflammatory disease characterized by recurrent episodes with the sudden onset of fever, malaise, extracutaneous organ involvement, and a diffuse erythematous-pustular exanthema. It may be associated with plaque psoriasis in some patients; unregulated cytokine production as a result of pathogenic genetic variants in the *IL36RN, AP1S3,* and *CARD14* genes are implicated in a subset of patients.

Psoriasis is rare in infants but may be severe and recalcitrant and may pose a diagnostic problem. Psoriatic diaper rash is a common

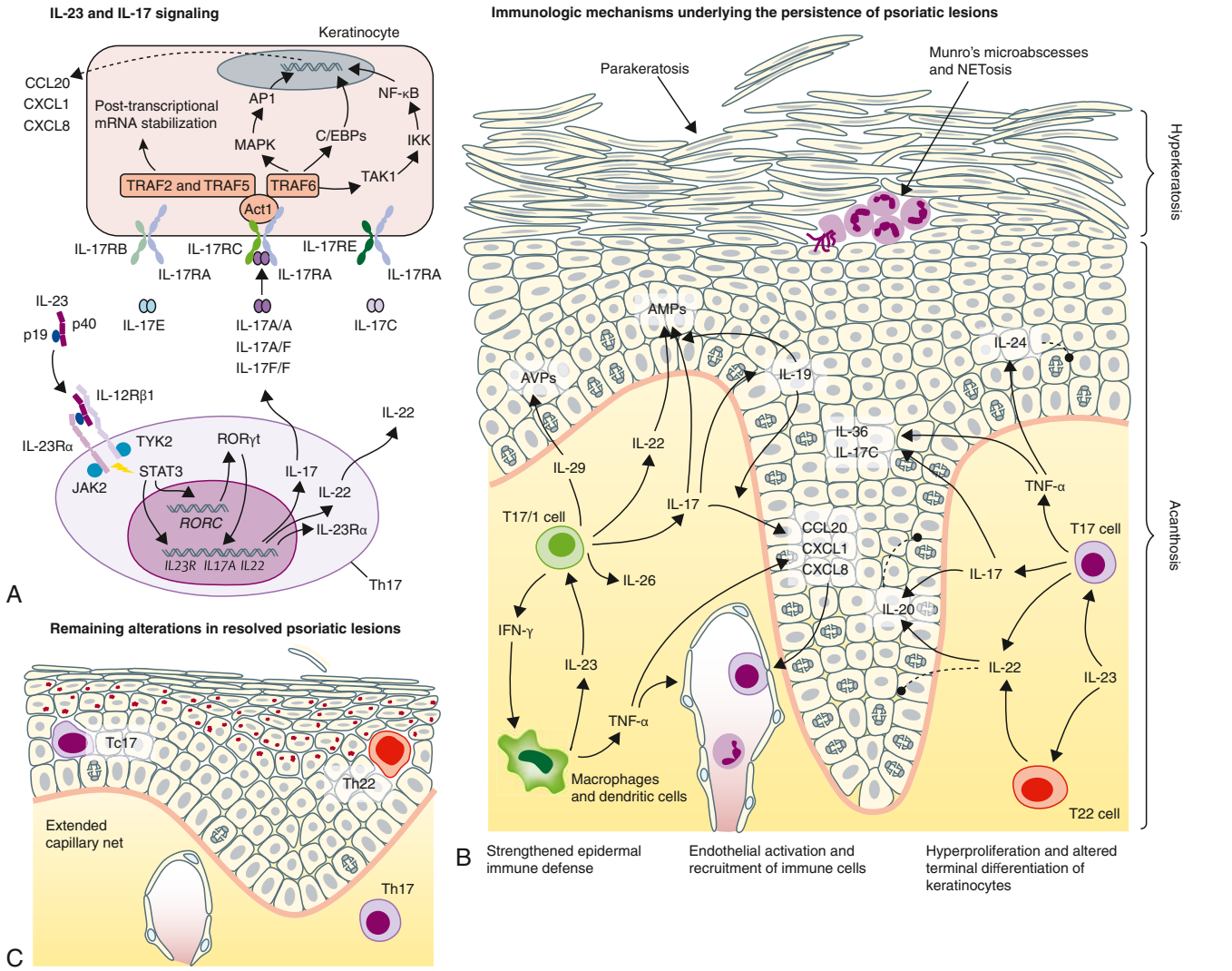

Fig. 698.1 Immune pathogenesis of psoriasis. The IL-23 and IL-17 pathway in psoriasis with elements of their signaling. **A**, IL-23 acts on Th17 cells via the transmembrane receptor complex composed of IL-12Rβ1 and IL-23Rα and intracellular JAK–STAT signaling and induces the expression of IL-17A, IL-17F, and IL-22, which act on epithelial cells through distinct receptor and signaling pathways. **B**, In psoriatic skin IL-23 is essential for the stabilization of the phenotype of IL-17–producing lymphocytes, activates these cells, and enhances their cytokine production and pathogenicity. IL-17 mostly acts synergistically with other cytokines, leading to massive activation of immunologic pathways and cytokines such as IL-22, IL-20, and IL-24, promoting the epidermal changes. **C**, After successful antipsoriatic treatment, potentially pathogenetic T cells remain in the resolved psoriatic skin. Blood capillaries extend during psoriatic inflammation by angiogenic signals and recede slowly. AMP, antimicrobial protein; AVP, antiviral protein; C/EBP, CCAAT-enhancer-binding protein; T17, Th17 and Tc17; T1, Th1 and Tc1; T22, Th22 and Tc22; Th, T helper cell; Tc, cytotoxic T cell; NETosis, activation and release of neutrophil extracellular traps. *(From Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. Lancet. 2021;397:754–766, Fig. 2.)*

presentation in children younger than 2 years old. Other rare forms include psoriatic erythroderma (>90% body surface area involvement), linear psoriasis, palmoplantar psoriasis, and inverse psoriasis (occurring in intertriginous areas). Children may also develop juvenile psoriatic arthritis, with or without skin lesions.

Psoriasis may be triggered by mild trauma (piercing, tattoos), sun or chemical burns, medications (β blockers, NSAIDs), or HIV infection. Comorbid conditions include arthritis, Crohn disease, depression, and nonalcoholic fatty liver disease.

DIFFERENTIAL DIAGNOSIS

Psoriasis is a clinical diagnosis. The differential diagnosis of plaque-type psoriasis includes nummular dermatitis, tinea corporis, seborrheic dermatitis, postinfectious arthritis syndromes, and pityriasis rubra pilaris. Scalp lesions may be confused with seborrheic dermatitis, atopic dermatitis, or tinea capitis. Diaper area psoriasis may mimic seborrheic dermatitis, eczematous diaper dermatitis, perianal streptococcal disease, candidiasis, or allergic contact dermatitis. Guttate psoriasis can be confused with viral exanthems, secondary syphilis, pityriasis rosea, and pityriasis lichenoides chronica (PLC). Nail psoriasis must be differentiated from onychomycosis, lichen planus, and other causes of onychodystrophy.

PATHOLOGY

When the diagnosis is in doubt, histopathologic examination of an untreated lesion can be helpful. Characteristic changes of psoriasis include parakeratosis, acanthosis, elongated rete ridges, neutrophilic infiltrate in the epidermis sometimes forming microabscesses, dilated dermal blood vessels, and lymphocytic infiltrate in the dermis.

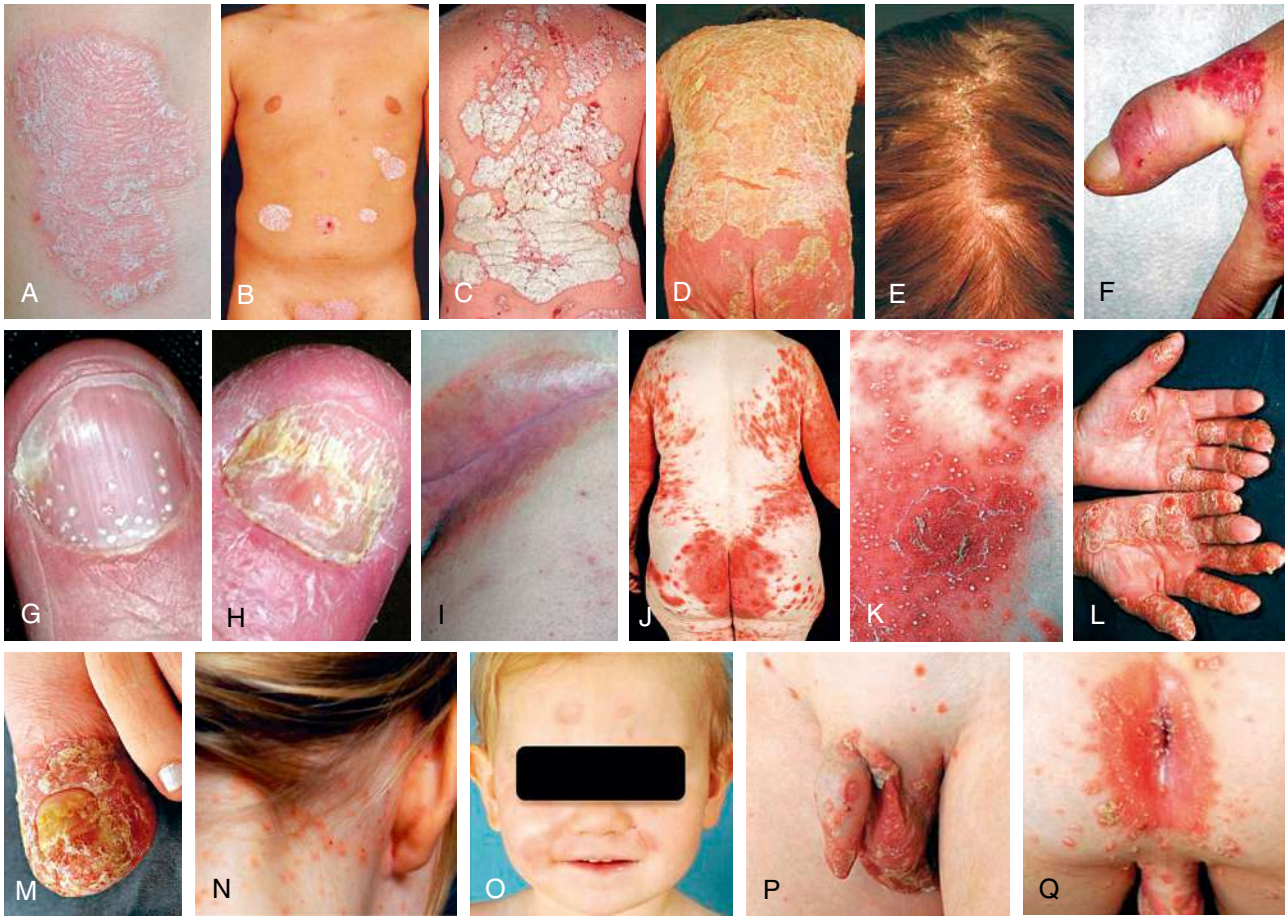

Fig. 698.2 Clinical manifestations of psoriasis. Typical erythematous plaques with silvery scales (**A**) can be scattered (**B**, psoriasis nummularis), cover larger areas of the skin (**C**, psoriasis geographica), or affect the entire body surface (**D**, erythrodermic psoriasis). Scalp involvement might be accompanied by nonscarring alopecia (**E**). Psoriatic arthritis affects up to 30% of all patients (**F**, thumb interphalangeal joint). Nail changes are frequent and range from pitting and yellow or brown discoloration (**G**) to complete dystrophy (**H**). Psoriasis inversa occurs in intertriginous areas and is usually devoid of scales (**I**). Pustular psoriasis might occur in a generalized form (**J** and **K**) or localized (**L**, palmoplantar type and **M**, acrodermatitis continua suppurativa type). In children, the onset as guttate psoriasis might follow streptococcal infection of the upper respiratory tract (**N**) and affect any site of the body (**O-Q**). *(From Boehncke WH, Schön MP. Psoriasis. Lancet. 2015;386:983–992, Fig. 1, p. 984.)*

TREATMENT

The therapeutic approach varies with the age of the child, type of psoriasis, sites of involvement, and extent of the disease. Physical and chemical trauma to the skin should be avoided as much as possible to prevent Koebner-response lesions. The treatment of psoriasis should be viewed as a four-tier process. Efficacy varies with each therapy (Table 698.1).

The first tier is topical therapy. The first-line topical agents for lesions on the body are emollients, vitamin D analogs (calcipotriene or calcitriol, although calcitriol is less irritating for children), and mid- to high-potency corticosteroids (see Chapter 687). A proprietary formulation containing both calcipotriene and betamethasone dipropionate (a high-potency topical corticosteroid) exists in ointment and solution forms. The preparation that is least potent but effective should be applied twice a day. Second-line topical options for lesions on the body include retinoids (tazarotene), tar preparations, anthralin, and keratolytics (salicylic acid or urea). Facial or intertriginous lesions may be treated with low-potency topical corticosteroids and/or topical vitamin D analogs or calcineurin inhibitors as corticosteroid-sparing agents. For scalp lesions, applications of a phenol and saline solution (e.g., Baker Cummins P&S liquid) or salicylic acid shampoo followed by a tar shampoo are effective in the removal of scales. A high-potency to superpotency corticosteroid in a foam, solution, or lotion base may be applied when the scaling is diminished. Nail lesions are difficult to treat topically; the first-line approach is a high-potency topical corticosteroid to the proximal nail fold.

The second tier of therapy is phototherapy. Narrow-band ultraviolet B (311 nm; NB-UVB) is an effective and well-tolerated alternative in pediatric patients with plaque and guttate psoriasis poorly controlled with topical treatments. Excimer (308 nm) laser UVB irradiation may be used for localized treatment-resistant plaques. Exposure to natural sunlight is often effective for less severe psoriasis.

The third tier is systemic therapy for children with moderate to severe, recalcitrant or generalized psoriasis. Methotrexate (0.2-0.7 mg/kg/wk to a maximum of 25 mg/week) is the first-line systemic agent for children; other options include oral retinoids (0.5-1.0 mg/kg/day to a maximum of 50 mg/day) and cyclosporine (modified formulation, 3-5 mg/kg/day). Oral retinoids may be cautiously combined with phototherapy, although doses may need to be decreased because of the photosensitizing effects of the medication. Oral retinoids are also considered for generalized pustular and diffuse guttate psoriasis.

Biologic response modifiers are increasingly used in place of traditional oral agents. TNF-α inhibitors such as etanercept, infliximab, and adalimumab have increasingly been used for pediatric psoriasis. Etanercept has FDA approval for those 4 years and older with psoriasis. One study reported a significant improvement in psoriatic lesions at 12 weeks with 57% versus 11% of patients receiving etanercept or placebo, respectively, achieving a 75% improvement in Psoriasis Area and Severity Index-75 (PASI-75, a metric to evaluate psoriasis severity). Ustekinumab, a human monoclonal antibody that blocks IL-12 and IL-23 and their cell-surface receptors, is approved for those 6 years and older with moderate to severe psoriasis. Biologic IL-17 inhibitors

Table 698.1 Recommendations for Pediatric Psoriasis

RECOMMENDATION	STRENGTH OF RECOMMENDATION	LEVEL OF EVIDENCE
Topical corticosteroids are recommended for the treatment of pediatric psoriasis as an off-label therapy	B	II
The use of ultra-high-potency topical corticosteroids as monotherapy is effective for short-term treatment of localized psoriasis in pediatric patients	C	II
Tacrolimus 0.1% ointment is recommended for off-label use as monotherapy for pediatric psoriasis of the face and genital region	C	II-III
Calcipotriene/calcipotriol is recommended as a treatment option for childhood plaque psoriasis	B	II
Because of the theoretical risk of increased calcium absorption and systemic effects of hypercalcemia, occlusion of calcipotriene/calcipotriol applied to large body surface areas is not recommended	B	III
Monitoring of vitamin D metabolites may be considered during calcipotriene/calcipotriol therapy when applied to a large body surface area	B	I-II
The combination of calcipotriol/betamethasone dipropionate ointment applied once daily for up to 4 weeks at a time is recommended as a safe and effective treatment for children ages 12 yr and older with mild to moderate plaque psoriasis	B	I-II
The combination of calcipotriol/betamethasone dipropionate suspension applied once daily for up to 8 wk at a time is recommended as a safe and effective treatment for children ages 12 yr and older with mild to moderate plaque psoriasis of the scalp	B	II
The use of emollients (at the same time or different time of day) with topical calcipotriene may be considered to reduce irritation and enhance the efficacy of calcipotriene	C	III
Rotational therapy with topical vitamin D analogues, topical calcineurin inhibitors, emollients, tar-based therapies, and topical corticosteroids may be considered in children as steroid-sparing regimens that may reduce potential adverse effects from overreliance on topical steroid therapy	C	II
The off-label use of topical tazarotene may be recommended as monotherapy or in combination with topical corticosteroids for the treatment of localized pediatric skin or nail psoriasis	C	III
Long-term use (12 wk or longer) of topical anthralin is recommended for the treatment of mild to moderate psoriasis. Short-contact anthralin protocols are recommended to limit adverse effects	B	II
Coal tar preparations can be used as a monotherapy or combined with other topical therapies for the treatment of pediatric psoriasis	C	II-III
The use of coal tar preparations in conjunction with phototherapy is effective for the treatment of psoriasis in children but may be limited by the theoretical long-term risk of carcinogenesis	B	II-III
NB-UVB is recommended as a treatment option for moderate to severe pediatric plaque and guttate psoriasis	B	II-III
The use of excimer laser or PUVA therapy in children with psoriasis may be efficacious and well tolerated but has limited supporting evidence	C	III
Methotrexate is recommended as an effective systemic therapy for moderate to severe plaque psoriasis and other psoriasis subtypes in children	B	II-III
Methotrexate is recommended as an effective systemic therapy for pustular psoriasis in children	B	III
Methotrexate weight-based dosing is recommended in younger children, ranging from 0.2 to 0.7 mg/kg/wk (maximum, 25 mg/wk)	B	III
Folic acid supplementation daily or six times weekly during treatment with methotrexate is recommended	B	II
Routine clinical and laboratory monitoring is recommended before and during treatment with methotrexate	B	III
Cyclosporine is recommended as an effective systemic therapy for moderate to severe plaque psoriasis in children	B	II-III
Cyclosporine is recommended as an effective systemic therapy for moderate to severe pustular psoriasis in children	B	III
Cyclosporine is recommended for short-term crisis management of severe or unstable plaque, erythrodermic, or pustular psoriasis until the patient can be transitioned to a medication appropriate for long-term use	C	III
Routine blood pressure clinical and laboratory monitoring is recommended during therapy with cyclosporine	A	III
Modified cyclosporine (for microemulsion in capsules or solution) is recommended for use and is not interchangeable with unmodified forms of cyclosporine	C	III

Continued

Table 698.1 Recommendations for Pediatric Psoriasis—cont'd

RECOMMENDATION	STRENGTH OF RECOMMENDATION	LEVEL OF EVIDENCE
Acitretin is recommended as an effective, nonimmunosuppressive systemic therapy for children with extensive guttate or moderate to severe (ideally thin plaque) psoriasis vulgaris at a dosage of 0.1-1 mg/kg/d	B	II
Acitretin is recommended as an effective systemic therapy for pustular psoriasis in children	B	II-III
Acitretin combined with NB-UVB therapy may be synergistic for plaque and pustular psoriasis in childhood and allows for a reduction in dosing of both agents	C	III
Acitretin may be combined with other systemic therapies such as methotrexate or cyclosporine, or biologics, depending on the individual clinical situation	C	III
Routine clinical and laboratory monitoring is recommended during therapy with acitretin	C	III
Fumaric acid esters may be considered as a potentially effective alternative therapy for pediatric patients with moderate to severe psoriasis who are candidates for systemic therapy	C	II-III
Clinical and laboratory monitoring is recommended during treatment with fumaric acid esters	C	III
Etanercept is recommended as an effective therapy for moderate to severe psoriasis in children 6 yr of age and older	A	I-III
Etanercept dosing is typically once weekly and is dosed subcutaneously at 0.8 mg/kg with a maximum of 50 mg weekly	A	I, III
Adalimumab is recommended for off-label use as an effective therapy in children and adolescents with moderate to severe psoriasis	B	I, III
The dose of adalimumab is 0.8 mg/kg (maximum, 40 mg) at weeks 0 and 1 and then is given every other week; adalimumab administered at a dose of 0.8 mg/kg is more efficacious than at a dose of 0.4 mg/kg	B	I
Infliximab can be recommended as monotherapy or in combination with methotrexate for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening	C	III
The starting dose of infliximab is an infusion of 5 mg/kg administered on weeks 0, 2, and 6 and then every 8 weeks	C	III
Ustekinumab is recommended as an effective therapy for adolescents 12 yr and older with moderate to severe plaque psoriasis	A	I, III
Ustekinumab can be used as an effective therapy for pediatric patients younger than 12 yr old with moderate to severe plaque psoriasis	C	III
Ustekinumab is given at weeks 0, 4, and 16 and then every 12 weeks with weight-based dosing as follows: 0.75 mg/kg if < 60 kg, 45 mg if 60 to 100 kg, and 90 mg if > 100 kg	B	I
Biologics may be safely combined with topical corticosteroids, with or without a vitamin D analogue, to augment effectiveness for the treatment of moderate to severe plaque psoriasis	C	III
The major risk for biologics in children is injection site reaction, but patients should be monitored for their increased risk of infection	B	II

Data from Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol.* 2020;82(1):161–201, Tables XX–XLVIII, pp. 173–189.

secukinumab and ixekizumab are also FDA approved for those 6 and older. The safety and efficacy data of these biologic agents show they are generally well tolerated and efficacious in the treatment of moderate to severe plaque psoriasis. The primary risk is injection site reaction. A small-molecule inhibitor of phosphodiesterase 4, apremilast, is also used for pediatric psoriasis. IL-23 inhibitors may also have a role in the treatment of severe disease and are being studied in pediatric populations.

PROGNOSIS

Prognosis is best for children with limited disease. Psoriasis is a lifelong disease characterized by remissions and exacerbations. Arthritis or various eye diseases may be extracutaneous complications. Metabolic and cardiovascular disorders also occur with increased frequency in patients with psoriasis. For example, an increasing degree of obesity and the associated metabolic syndrome (hyperglycemia, hyperlipidemia, and hypertension) correlates with psoriasis severity. Patients with psoriasis also have increased rates of stroke, myocardial infarction, and other vascular diseases later in adult life. A proposed mechanism involves the systemic proinflammatory state induced by both psoriasis and these associated conditions, although the direction of causality remains unclear. Furthermore, children suffering from psoriasis have a greater risk of taking psychotropic medications for anxiety or depression and are more likely to report impairment in quality of life due to their chronic disease.

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698.2 Pityriasis Lichenoides

Julie M. Dhossche and Yvonne E. Chiu

Pityriasis lichenoides encompasses a disease spectrum ranging from PLC to pityriasis lichenoides et varioliformis acuta (PLEVA; Mucha-Habermann disease). The designation of pityriasis

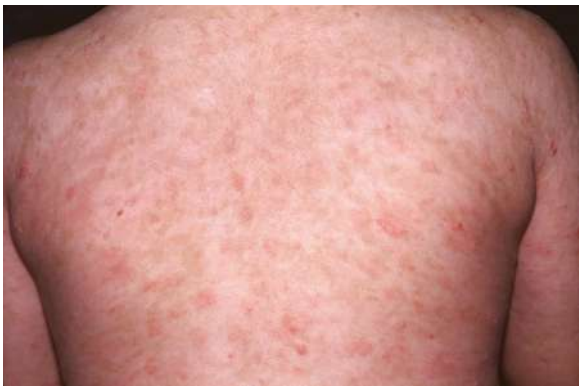

Fig. 698.3 Widespread plaques with fine scale in pityriasis lichenoides chronica.

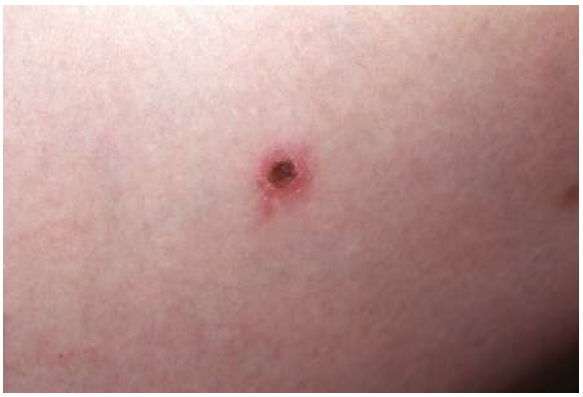

Fig. 698.4 Necrotic lesion with erythematous halo in pityriasis lichenoides et varioliformis acuta.

lichenoides as acute or chronic refers to the morphologic appearance of the lesions rather than to the duration of the disease. No correlation is found between the type of lesion at the onset of the eruption and the duration of the disease. Many patients have both acute and chronic lesions simultaneously, and transition of lesions from one form into another occurs occasionally. As a result, some authors advocate using pityriasis lichenoides as the general diagnosis rather than differentiating between PLC and PLEVA. Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare subtype of PLEVA that is more severe and potentially life-threatening.

ETIOLOGY/PATHOGENESIS

Two main theories exist for the etiology of pityriasis lichenoides. The first is that it arises in a genetically susceptible individual as a hypersensitivity reaction to an infection. The second is that it represents a monoclonal T-cell lymphocytic proliferation on the pathway to cutaneous T-cell dyscrasia.

CLINICAL MANIFESTATIONS

Pityriasis lichenoides most commonly manifests in the second and third decades of life; 30% of cases manifest before age 20 years, with peaks of incidence at 5 and 10 years of age. The overall eruption persists for months to years with a tendency to eventually remit.

PLC manifests gradually as generalized, multiple, brown-red papules to plaques that are covered by a fine grayish scale (Fig. 698.3). Lesions may be asymptomatic or may cause minimal pruritus and occasionally become vesicular, hemorrhagic, crusted, or superinfected. Individual papules become flat and brownish in 2-6 weeks, ultimately leaving hyperpigmented or hypopigmented macules and patches. Scarring is unusual. Various stages of lesions are present, most commonly on the trunk and extremities and generally spare the face, palmoplantar surfaces, scalp, and mucous membranes.

PLEVA manifests as an abrupt eruption of numerous 2- to 3-mm papules that have a vesiculopustular and then a purpuric center, are covered by a dark adherent hemorrhagic or necrotic crust, and are surrounded by an erythematous halo (Fig. 698.4). Constitutional symptoms, such as fever, malaise, headache, and arthralgias, may be present for 2-3 days after the initial outbreak. Lesions are distributed diffusely on the trunk and extremities, as in PLC. Individual lesions heal within a few weeks, sometimes leaving a varioliform scar, and successive crops of papules produce the characteristic polymorphous appearance of the eruption, with lesions in various stages of evolution.

FUMHD manifests as high fever and ulceronecrotic nodules up to a few centimeters in diameter, which are most common on the anterior trunk and flexor surfaces of the proximal upper extremities. Histopathology of lesions is consistent with PLEVA. Hemorrhagic bullae, mucosal ulcers, arthritis, cardiomyopathy, vasculitis, abdominal complaints, hematologic abnormalities (megaloblastic anemia, pancytopenia, and diffuse intravascular coagulation), and superinfection of cutaneous lesions with *Staphylococcus aureus* may also develop. These patients may have a history of previous PLEVA diagnosis. Although there is no reported standardized treatment and there have been reports of fatalities, typically the ulceronecrotic lesions heal with hypopigmented scarring in a few weeks.

PATHOLOGY

PLC histologically shows a parakeratotic, thickened corneal layer; epidermal spongiosis; a superficial perivascular infiltrate of macrophages and predominantly CD8 lymphocytes that may extend into the epidermis; and small numbers of extravasated erythrocytes in the papillary dermis.

The histopathologic changes of PLEVA and FUMHD reflect their more severe nature. Intercellular and intracellular edema in the epidermis may lead to degeneration of keratinocytes. A dense perivascular mononuclear cell infiltrate, endothelial cell swelling, and extravasation of erythrocytes into the epidermis and dermis are additional characteristic features.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pityriasis lichenoides includes guttate psoriasis, pityriasis rosea, drug eruptions, secondary syphilis, viral exanthems, lymphomatoid papulosis, and lichen planus. The chronicity of pityriasis lichenoides helps preclude pityriasis rosea, viral exanthems, and some drug eruptions. A skin biopsy can help distinguish pityriasis lichenoides from other entities in the differential diagnosis.

TREATMENT

Pityriasis lichenoides should be considered a benign condition that does not alter the health of the child. A lubricant to remove excessive scaling may be all that is necessary if the patient is asymptomatic. If treatment is required, first-line agents are oral antiinflammatory antibiotics such as erythromycin (30-50 mg/kg/day to a maximum of 4000 mg/day for 2-3 months) or doxycycline for children >8 years. Topical corticosteroids (mid-potency, applied twice daily) and topical calcineurin inhibitors may help the pruritus and inflammation but do not alter the course of the disease. Phototherapy (NB-UVB) is the second-line treatment option. Methotrexate should be reserved for severely symptomatic cases. The rare FUMHD usually requires inpatient treatment; initially, systemic corticosteroids, methotrexate, intravenous immunoglobulin, or cyclosporine may be necessary, with eventual transition to another form of treatment, as mentioned earlier, once the disease improves and stabilizes.

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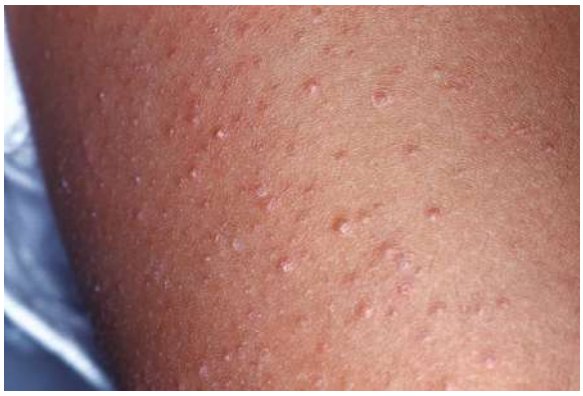

Fig. 698.5 Keratotic follicular plugs with surrounding erythema in keratosis pilaris.

698.3 Keratosis Pilaris

Julie M. Dhossche and Yvonne E. Chiu

Keratosis pilaris is a common papular eruption resulting from keratin plugging of hair follicles. It displays an autosomal dominant transmission with variable penetrance. Typical areas of involvement include the upper extensor surfaces of the arms and thighs, cheeks, and buttocks. The lesions may resemble gooseflesh; they are noninflammatory, scaly, follicular papules that do not coalesce. They are generally asymptomatic but may be pruritic. Irritation of the follicular plugs occasionally causes erythema surrounding the keratotic papules (Fig. 698.5). A subset of patients has keratosis pilaris associated with facial telangiectasia and ulerythema ophryogenes, a rare cutaneous disorder characterized by inflammatory keratotic facial papules that may result in scars, atrophy, and alopecia. Because the lesions of keratosis pilaris are associated with and accentuated by dry skin, they are often more prominent during the winter. Keratosis pilaris is more frequent in patients with atopic dermatitis and is most common during childhood and early adulthood, tending to subside in the third decade of life. Treatment of keratosis pilaris is optional. Measures to decrease pruritus include moisturization with a bland emollient. Regular applications of a 10–40% urea cream or an alpha-hydroxy acid preparation such as 12% lactic acid cream or lotion can improve the appearance of keratosis pilaris but may further contribute to pruritus and irritation. Therapy may improve the condition but does not cure it.

698.4 Lichen Spinulosus

Julie M. Dhossche and Yvonne E. Chiu

Lichen spinulosus is an uncommon disorder that occurs principally in children and more frequently in boys. The cause is unknown. The lesions consist of sharply circumscribed irregular plaques of spiny, keratotic, follicular plugs. Plaques may occur anywhere on the body and are often distributed symmetrically on the trunk, elbows, knees, and extensor surfaces of the limbs. Although sometimes erythematous or pruritic, the lesions are usually skin colored and asymptomatic.

Treatment is usually unnecessary. For patients who regard the eruption as a cosmetic defect, urea-containing lubricants (10–40%) are often effective in flattening the projections. The plaques usually disappear spontaneously after several months or years.

698.5 Pityriasis Rosea

Julie M. Dhossche and Yvonne E. Chiu

Pityriasis rosea is a common benign papulosquamous disorder typically affecting adolescents and young adults 15-30 years of age. The disease is more commonly seen in the winter and is usually self-limited.

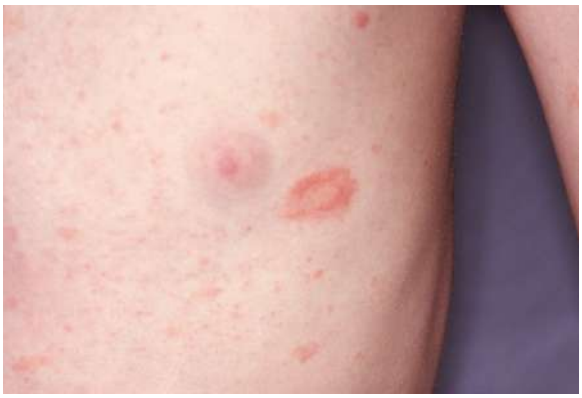

Fig. 698.6 Herald patch and surrounding pityriasis rosea.

ETIOLOGY/PATHOGENESIS

The cause of pityriasis rosea is unknown; a viral agent is suspected, with a current focus on human herpesviruses 6 and 7. Supporting evidence for an infectious etiology includes the tendency for it to occur in (familial) case clusters, presence of a prodrome and seasonal variation, and infrequent recurrences, although the rash itself does not appear to be contagious.

CLINICAL MANIFESTATIONS

This benign, common eruption occurs most frequently in children and young adults. Although a prodrome of fever, malaise, arthralgia, and pharyngitis may precede the eruption, children rarely complain of such symptoms. A **herald patch** classically precedes the generalized eruption and may occur anywhere on the body. Herald patches are generally larger than other lesions and vary from 1 to 10 cm in diameter; they are annular in configuration and have a raised border with fine, adherent scales. Approximately 5-10 days after the appearance of the herald patch, a widespread, symmetric eruption involving mainly the trunk and proximal limbs becomes evident (Fig. 698.6). In the inverse form of pityriasis rosea, the face, scalp, and distal limbs may be preferentially involved. Lesions may appear in crops for several days. Typical lesions are oval or round, <1 cm in diameter, slightly raised, and pink to brown. The developed lesion is covered by a fine scale, which gives the skin a crinkly appearance. Some lesions clear centrally and produce a collarette of scale that is attached only at the periphery. Papular, vesicular, urticarial, hemorrhagic, large annular, and mucosal lesions are unusual variants. The long axis of each lesion is usually aligned with the cutaneous cleavage lines, a feature that creates the so-called **Christmas tree pattern** on the back. Conformation to skin lines is often more discernible in the anterior and posterior axillary folds and supraclavicular areas. The lesions most commonly are asymptomatic but may be mildly to severely pruritic. Duration of the eruption varies from 2 to 12 weeks, with self-resolution. After the eruption has resolved, postinflammatory hypopigmentation or hyperpigmentation may be pronounced, particularly in dark-skinned patients. These changes disappear in subsequent weeks to months.

DIFFERENTIAL DIAGNOSIS

The herald patch may be mistaken for tinea corporis, a pitfall that can be avoided if microscopic evaluation of a potassium hydroxide preparation of scrapings of the lesion is performed. The generalized eruption resembles a number of other diseases; secondary syphilis is the most important. Drug eruptions, viral exanthems, guttate psoriasis, PLC, and nummular dermatitis can also be confused with pityriasis rosea.

TREATMENT

Therapy is unnecessary for asymptomatic patients with pityriasis rosea. If scaling is prominent, a bland emollient may suffice. Pruritus may be suppressed by a lubricating lotion containing menthol and camphor or by an oral antihistamine for sedation, particularly at night, when itching may be troublesome. Occasionally, a mid-potency topical corticosteroid preparation may be necessary to alleviate pruritus. Exposure to natural sunlight and NB-UVB phototherapy may reduce disease duration and severity. Acyclovir has been used in some cases to treat symptoms and shorten duration.

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698.6 Pityriasis Rubra Pilaris

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The cause of pityriasis rubra pilaris remains unclear. Pityriasis rubra pilaris can be subdivided into six clinical subtypes based on age of onset, characteristics, and other features. Most cases are sporadic, but familial forms are commonly seen in the fifth subtype, with gain-of-function variants in the *CARD14* gene. The sixth subtype occurs in those with HIV infection. Some studies have indicated a role for TNF-α in disease development, whereas other hypotheses for causal factors include abnormal vitamin A metabolism, trauma, infections, immunosuppression, and UV light exposure.

CLINICAL MANIFESTATIONS

This rare inflammatory dermatosis is known for its variability in clinical presentation and course of disease. It often has an insidious onset with diffuse scaling and erythema of the scalp, which is indistinguishable from the findings in seborrheic dermatitis, and with thick hyperkeratosis of the palms and soles (Fig. 698.7A). Lesions over the elbows and knees are also common (see Fig. 698.7B), and generalized erythroderma develops in some patients. The characteristic primary lesion is a firm, dome-shaped, tiny, acuminate, pink to red papule, which has a central keratotic plug pierced by a vellus hair. Masses of these papules coalesce to form large, erythematous, sharply demarcated orange-pink plaques with overlying scale, within which islands of normal skin can be distinguished. Typical papules on the dorsum of the proximal phalanges are readily palpated. Gray plaques or papules resembling lichen planus may be found in the oral cavity. Dystrophic changes in the nails may occur and mimic those of psoriasis. Lesions are commonly pruritic. In childhood, the prognosis for eventual resolution is relatively good.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes ichthyosis, seborrheic dermatitis, keratoderma of the palms and soles, and psoriasis. The "Wong" variant of dermatomyositis may present with a pityriasis rubra pilaris–like eruption.

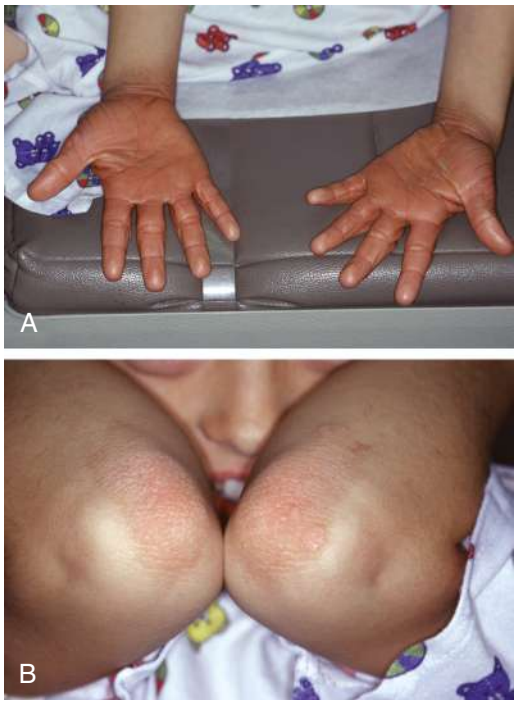

Fig. 698.7 Pityriasis rubra pilaris. A, Orange palmar hyperkeratosis. B, Elbow lesions.

HISTOLOGY

Skin biopsy revealing follicular plugging, epidermal acanthosis, perivascular infiltrate, checkerboard pattern of orthokeratosis and parakeratosis, and an intact granular layer may differentiate this condition from psoriasis and seborrheic dermatitis.

TREATMENT

The numerous therapeutic regimens recommended are difficult to evaluate because pityriasis rubra pilaris has a capricious course with exacerbations and remissions. Moisturization alone is useful in mild cases. Topical agents, such as mid- to high-potency corticosteroids, keratolytics (urea, salicylic acid), vitamin D analogs (calcipotriene), retinoids (tazarotene, tretinoin), and tar, are used in combination with systemic agents for widespread disease and as monotherapy for localized disease. When further treatment is necessary, oral retinoids (isotretinoin or acitretin 0.5-1 mg/kg/day; maximum daily dose of isotretinoin is 80 mg/day and acitretin is 50 mg/day) are used as first-line agents, whereas methotrexate is used as a second-line agent. Third-line treatment options include biologic TNF-α inhibitors, cyclosporine, azathioprine, and NB-UVB phototherapy. Ustekinumab and secukinumab have also been described as efficacious.

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698.7 Darier Disease (Keratosis Follicularis)

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

A rare genetic disorder, Darier disease is inherited as an autosomal dominant trait and is caused by pathogenic genetic variants in the *ATP2A2* gene. This gene encodes a cellular calcium pump, SERCA2, and dysfunction results in loss of adhesion between epidermal cells and abnormal keratinization.

CLINICAL MANIFESTATIONS

Onset usually occurs in late childhood and persists throughout life. Typical lesions are small, firm, skin-colored, warty papules that are not always follicular in location. The lesions eventually acquire yellow, malodorous, greasy crusts and coalesce to form large, gray-brown, vegetative plaques (Fig. 698.8). The scalp, face, neck, shoulders, chest, back, axillae, limb flexures, and groin are symmetrically involved. Papules, fissures, crusts, and ulcers may appear on the mucous membranes of the lips, tongue, buccal mucosa, pharynx, larynx, and vulva. Hyperkeratosis of the palms and soles and nail dystrophy with subungual hyperkeratosis and longitudinal red and white banding are variable features. Severe pruritus, secondary infection, offensive odor, and pain may occur. Several exacerbating triggers have been identified: sweating, UV light exposure, heat, friction, surgery, and infections; thus Darier disease has a chronic relapsing course that usually worsens in summertime.

HISTOLOGY

Histologic changes seen in Darier disease are diagnostic. Hyperkeratosis with keratin plugging, intraepidermal separation (acantholysis) with formation of suprabasal clefts, and dyskeratotic epidermal cells are characteristic features.

DIFFERENTIAL DIAGNOSIS

Darier disease is most likely to be confused with seborrheic dermatitis, acanthosis nigricans, flat warts, or Hailey-Hailey disease.

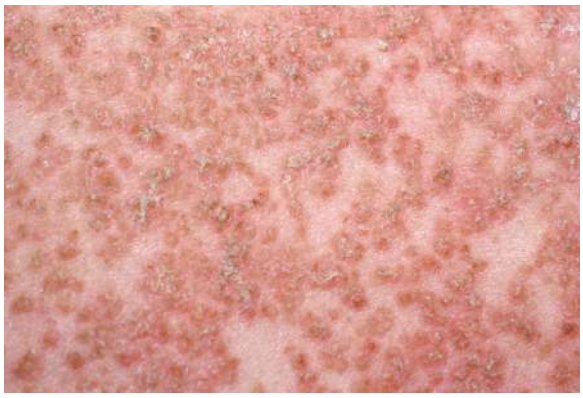

Fig. 698.8 Papules coalescing into a large plaque on the back of a patient with Darier disease.

TREATMENT

Treatment is nonspecific and begins with emollients and avoidance of triggers. First-line treatment for mild/localized disease is low- to mid-potency corticosteroids; second-line treatment are topical retinoids. Further treatment options include topical keratolytic agents (urea, lactic acid), antiseptic washes (triclosan, chlorhexidine gluconate, or bleach), or calcineurin inhibitors. More severe/generalized disease is treated with oral isotretinoin or acitretin (0.5-1.0 mg/kg/day for 3-4 months; maximum daily dose of isotretinoin is 80 mg/day and acitretin is 50 mg/day). Secondary infections are common and must be treated appropriately. Novel treatments currently being investigated include anti–IL-6 antibodies, cyclooxygenase-2 (COX2) inhibitors and miglustat (a glucosylceramide synthase inhibitor).

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698.8 Lichen Nitidus

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The etiology of lichen nitidus is unknown but has been linked to immune alteration.

CLINICAL MANIFESTATIONS

This uncommon, chronic, benign, papular eruption is characterized by minute (1-2 mm), flat-topped, shiny, firm papules of uniform size. The papules are most often skin-colored but may be pink or red. In darker-skinned individuals, they are usually hypopigmented (Fig. 698.9). Sites of predilection are the genitals, abdomen, chest, forearms, wrists, and inner aspects of the thighs. The lesions may be sparse or numerous and may form large plaques; careful examination usually discloses linear papules in a line of a scratch (Koebner phenomenon), a valuable clue to the diagnosis because it occurs in only a few diseases. Lichen nitidus occurs in all age-groups but is most prevalent in school-age children and young adults. Patients with lichen nitidus are usually asymptomatic and constitutionally well, although pruritus may be severe. The lesions may be confused with those of lichen planus, and lichen nitidus can rarely occur concurrently with lichen planus.

DIFFERENTIAL DIAGNOSIS

Widespread keratosis pilaris can also be confused with lichen nitidus, but the follicular localization of the papules and the absence of Koebner phenomenon in the former distinguish them. Verruca plana (flat warts), if small and uniform in size, may occasionally resemble lichen nitidus.

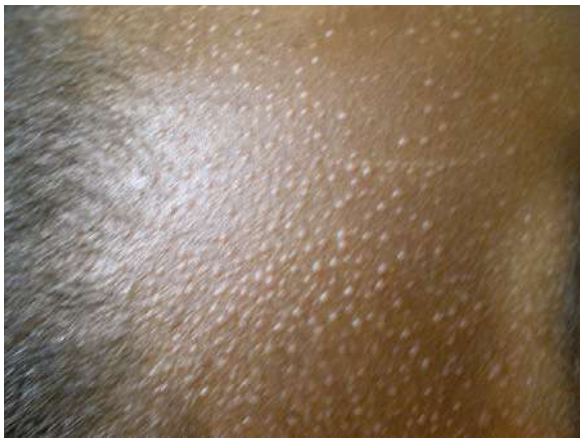

Fig. 698.9 Slightly hypopigmented, uniform papules of lichen nitidus.

HISTOLOGY

Although the diagnosis can be made clinically, a biopsy is occasionally indicated. The lichen nitidus papule consists of sharply circumscribed nests of lymphocytes and histiocytes in the upper dermis enclosed by clawlike epidermal rete ridges.

TREATMENT

The course of lichen nitidus spans months to years, but the lesions eventually involute completely. No treatment is necessary, but mid- to high-potency topical steroids may be used for pruritus.

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698.9 Lichen Striatus

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

Lichen striatus is hypothesized to be caused by a combination of a genetic predisposition present in a mosaic manner in the skin (following the lines of Blaschko) and an infectious trigger.

CLINICAL MANIFESTATIONS

A benign, self-limited eruption, lichen striatus consists of a continuous or discontinuous linear band of papules in a Blaschkoid distribution. The primary lesion is a flat-topped, hypopigmented or pink papule covered with fine scale. Aggregates of these papules form multiple bands or plaques. The papules are gradually replaced by hypopigmented macules, which may be the presenting lesion in some cases. The eruption evolves over a period of days or weeks in an otherwise healthy child, remains stationary for weeks to months, and finally remits without sequelae, usually within 2 years. Symptoms are usually absent, although some children complain of itching. Nail dystrophy may occur when the eruption involves the proximal nail fold and matrix (Fig. 698.10).

DIFFERENTIAL DIAGNOSIS

Lichen striatus is occasionally confused with other disorders. The initial plaque may resemble papular eczema or lichen nitidus until the linear configuration becomes apparent. Linear lichen planus and linear psoriasis are usually associated with typical individual lesions elsewhere on the body. Linear epidermal nevi are permanent lesions that often become more hyperkeratotic and hyperpigmented than those of lichen striatus.

TREATMENT

Treatment is not necessary and generally not very effective. A low-potency topical corticosteroid preparation or topical calcineurin

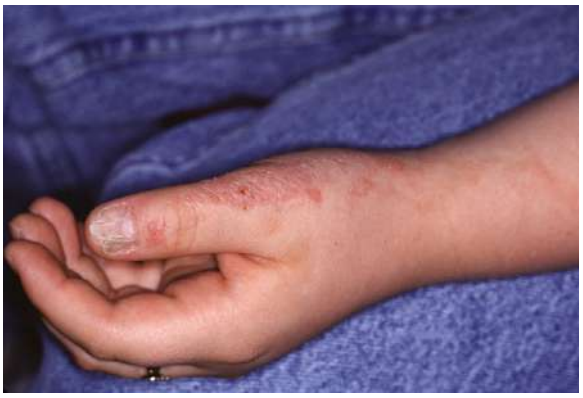

Fig. 698.10 Lichen striatus with nail dystrophy.

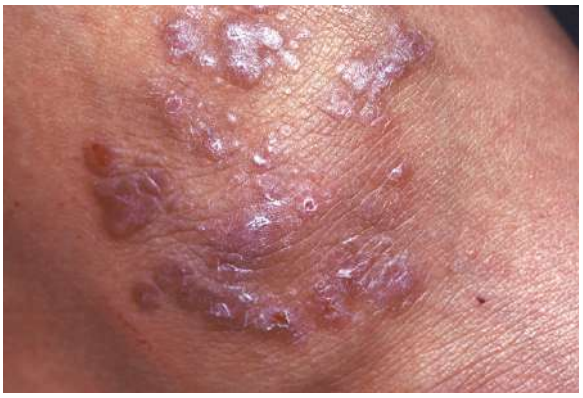

Fig. 698.11 Flat-topped, purple polygonal papules of lichen planus.

inhibitor can be used when pruritus is a problem in a patient with lichen striatus.

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698.10 Lichen Planus

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The cause of lichen planus is unknown, but an immune attack on the skin by cytotoxic T cells is postulated. A genetic predisposition may exist, and other proposed triggers include metal exposure, certain medications, liver disease, vaccinations (especially hepatitis B vaccination), and infections (especially hepatitis C virus).

CLINICAL MANIFESTATIONS

This is a rare disorder in young children and uncommon in older ones. The classic form of lichen planus is the most common subtype in children, often exhibiting an acute eruptive onset. The lesions erupt in an explosive fashion, much like a viral exanthem, and spread to involve most of the body surface. The primary lesion is a violaceous, sharply demarcated, polygonal papule with fine white lines (Wickham's striae) or scale on the surface. Papules may coalesce to form large plaques (Fig. 676.11). The papules are intensely pruritic, and additional papules are often induced by scratching (Koebner phenomenon) so that lines of them are detected. Sites of predilection are the flexor surfaces of the wrists, the forearms, the inner aspects of the thighs, and the ankles.

Hypertrophic, linear, bullous, atrophic, annular, follicular, erosive, ulcerative, and actinic forms of lichen planus may also occur in children. Characteristic lesions of mucous membranes consist of pinhead-size white papules that coalesce to form reticulated and lacy patterns on the buccal mucosa. Erosive ulcers are also common in the oral mucosa and may also involve the gastrointestinal tract. Nail involvement causes nail dystrophy. The disorder may persist for months to years, but self-resolution eventually occurs in most cases. Intense hyperpigmentation frequently persists for a long time after the resolution of lesions.

HISTOLOGY

The histopathologic findings in lichen planus are specific, consisting of hyperkeratosis, irregular acanthosis, wedge-shaped hypergranulosis, apoptotic keratinocytes in the lower epidermis and upper dermis, and basal cell degeneration with a bandlike lymphocytic infiltrate at the epidermal-dermal junction. Pigment incontinence is frequently seen. Biopsy is indicated if the diagnosis is unclear.

TREATMENT

Treatment is directed at alleviation of the intense pruritus and amelioration of the skin lesions. First-line treatment with a high-potency topical corticosteroid applied twice daily is effective for localized disease on the trunk or extremities; lesions on the face and genitals may be treated with low- to mid-potency corticosteroids. Alternatives to topical steroids include topical calcineurin inhibitors or vitamin D analogs. Thick lesions may require intralesional corticosteroid injection. Oral antihistamines (hydroxyzine) are often added for the pruritus. Short courses of systemic glucocorticoids or phototherapy (NB-UVB) are used as second-line approaches for rare cases of widespread, intractable lesions. Other medications with reported efficacy include oral retinoids (acitretin), dapsone, metronidazole, griseofulvin, and methotrexate.

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698.11 Porokeratosis

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

Porokeratoses are a group of uncommon dermatoses due to abnormal epidermal keratinization. Genetic variants in the mevalonate pathway with autosomal dominant transmission, chronic sun exposure (particularly with the disseminated superficial actinic form), and immunosuppression (particularly organ transplantation) may contribute.

CLINICAL MANIFESTATIONS

Porokeratosis is a rare, chronic, progressive disease of keratinization. The prototypical lesion is an atrophic papule or plaque with a surrounding ridge of hyperkeratosis, called *cornoid lamella.* Several forms have been delineated: solitary plaques, linear porokeratosis, hyperkeratotic lesions of the palms and soles, disseminated eruptive lesions, and superficial actinic porokeratosis. **Classic porokeratosis of Mibelli** begins in childhood and is more common in males. Sites of predilection are the limbs, face, genitals, mucous membranes, palms, and soles. The primary lesion is a small, keratotic papule that slowly enlarges peripherally so that the center becomes depressed, with the edge forming an elevated wall or collar (Fig. 698.12). The configuration of the plaque may be round, oval, or gyrate. The elevated border is split by a thin groove from which minute cornified projections protrude. The central atrophic area is yellow, gray, or tan and sclerotic, smooth, and dry, whereas the hyperkeratotic border is a darker gray, brown, or black. **Linear porokeratosis** is also more common in childhood and typically follows the lines of Blaschko. The disease is slowly progressive but relatively asymptomatic; some patients experience pruritus or pain.

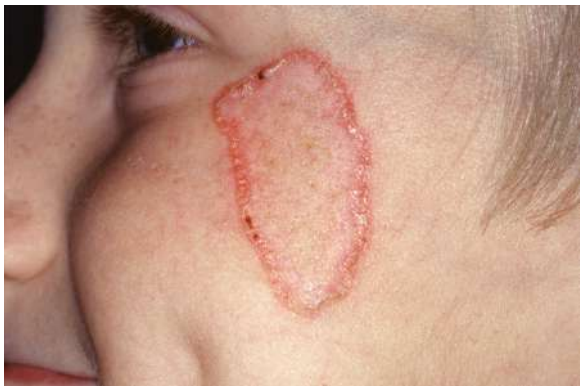

Fig. 698.12 Large plaque of porokeratosis of Mibelli with raised border and depressed center.

HISTOLOGY

A skin biopsy is usually unnecessary but will disclose the characteristic cornoid lamella (plug of stratum corneum cells with retained nuclei), which is responsible for the invariable linear ridge of the lesion. The granular layer is absent beneath the cornoid lamella.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of porokeratosis includes warts, epidermal nevi, lichen planus, granuloma annulare, tinea corporis, nummular eczema, pityriasis rosea, and elastosis perforans serpiginosa.

TREATMENT

No treatment is uniformly successful; thus therapeutic decisions depend largely on lesion size, location, symptoms, and patient preference. Most lesions are asymptomatic and do not require any intervention; however, when treatment is necessary, options include pharmacologic management (topical vitamin D analogs, topical retinoids, topical 5-fluorouracil, topical imiquimod, or oral retinoids [severe cases only]); destructive therapy (liquid nitrogen cryotherapy, electrodessication and curettage, or various lasers); and surgical removal. In general, the less invasive topical agents should be attempted first. Good UV protection should also be encouraged. Patients should be monitored for malignant transformation.

PROGNOSIS

Typically, the course of porokeratosis is slowly progressive, with an increase in size and number of individual lesions. Some cases undergo spontaneous resolution, and infrequently porokeratosis lesions may undergo malignant transformation into squamous cell carcinoma. At-risk lesions appear to be long-standing (average 33.5 years duration), large size, and location on limbs.

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698.12 Gianotti-Crosti Syndrome (Papular Acrodermatitis)

Julie M. Dhossche and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The pathogenesis of Gianotti-Crosti syndrome, also known as *papular acrodermatitis,* is unclear, but an immunologic reaction to viral infections and immunizations has been postulated. Historically, the most common associations are with Epstein-Barr virus, hepatitis B virus (primarily in countries without routine childhood vaccination programs), coxsackievirus A16, and parainfluenza virus, as well as with many childhood immunizations.

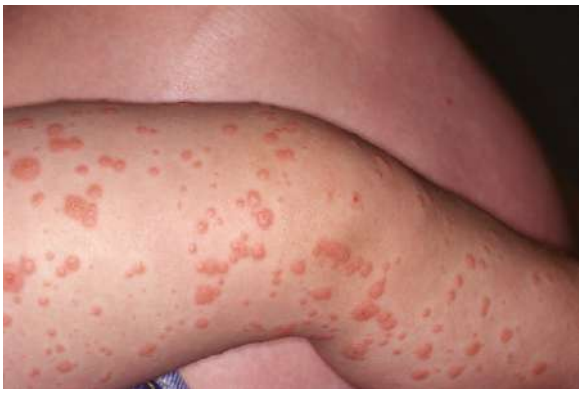

Fig. 698.13 Numerous flat-topped, red papules in Gianotti-Crosti syndrome.

CLINICAL MANIFESTATIONS

This distinctive eruption is benign and predominantly occurs in children younger than 5 years old about 1 week after a viral illness. Cases are usually sporadic, but epidemics have been recorded. Skin lesions are monomorphic, firm, dusky, or coppery red papules ranging in size from 1 to 10 mm (Fig. 698.13), although there is considerable variation in lesion appearance between patients. The papules often have the appearance of vesicles; however, when opened, no fluid is obtained. The papules sometimes become hemorrhagic. Lines of papules **(Koebner phenomenon)** may be noted on the extremities after minor local trauma. The papules occur in crops and may become profuse and coalesce into plaques, forming a symmetric eruption on the face, ears, buttocks, and limbs, including the palms and soles. The trunk is relatively spared, as are the scalp and mucous membranes. The eruption is occasionally associated with malaise and low-grade fever but few other constitutional symptoms. The underlying viral infection may cause signs and symptoms, such as lymphadenopathy and hepatomegaly in patients with hepatitis B viremia. The eruption resolves spontaneously but may take up to 2 months. Some residual pigment change may occur but is not scarring.

HISTOLOGY

Skin biopsy in Gianotti-Crosti syndrome is not specific, being characterized by a dermal perivascular mononuclear cell infiltrate, capillary endothelial swelling, and epidermal spongiosis and parakeratosis.

DIFFERENTIAL DIAGNOSIS

Gianotti-Crosti syndrome can be confused with other viral exanthems, erythema infectiosum, lichen planus, erythema multiforme, and Henoch-Schönlein purpura (IgA vasculitis).

TREATMENT

The lesions are typically asymptomatic and resolve spontaneously, thus requiring no treatment. If present, pruritus may be relieved by emollients or calamine lotion. Mid-potency topical steroids may relieve pruritus but do not alter disease course. Sedating antihistamines at bedtime are also helpful.

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698.13 Acanthosis Nigricans

Julie M. Dhossche and Yvonne E. Chiu

See also Chapter 65.

ETIOLOGY/PATHOGENESIS

The skin lesions of acanthosis nigricans may be genetic due to variants in the fibroblast growth factor receptor gene or acquired as a manifestation of insulin resistance. In familial cases, acanthosis nigricans

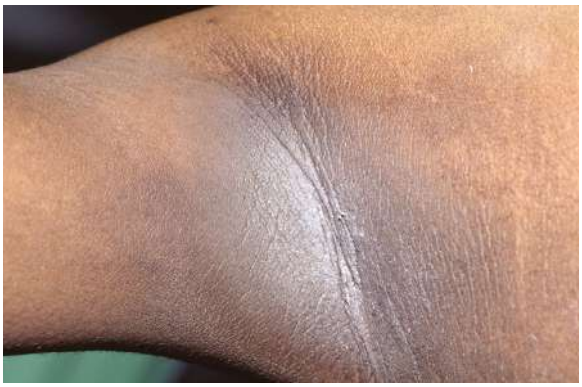

Fig. 698.14 Velvety hyperpigmentation of the axilla in acanthosis nigricans.

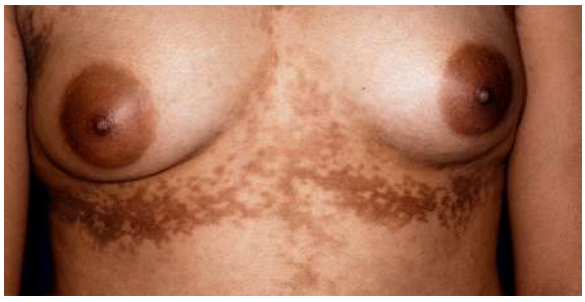

Fig. 698.15 Confluent and reticulated papillomatosis. Reticulate tan papules, patches, and plaques involving the epigastrium, inframammary areas, and sternum. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022, Fig. 23.34, p. 641.)*

is inherited as an autosomal dominant trait and develops in infancy. Insulin resistance with compensatory hyperinsulinism may lead to insulin binding to and activation of insulin-like growth factor receptors, promoting epidermal and fibroblast growth. Common causes of insulin resistance in children are obesity and diabetes mellitus, with acanthosis nigricans seen in >60% of children with a body mass index >98%. Other endocrinopathies such as pituitary hypogonadism, Cushing syndrome, polycystic ovarian syndromes, thyroid disease, and acromegaly, as well as certain drugs (insulin, oral contraceptives and other sex hormones, nicotinic acid, corticosteroids, and heroin) are also implicated as potential underlying causes. In the paraneoplastic form (rare in children), tumor-secreted growth factors induce acanthosis nigricans.

CLINICAL MANIFESTATIONS

Acanthosis nigricans is characterized by symmetric, hyperpigmented, velvety, hyperkeratotic plaques with exaggerated skin lines in intertriginous areas. The most common locations are the posterior neck and axillae (Fig. 698.14), but it is also seen in the inframammary areas, groin, inner thighs, and anogenital region. Before plaque development, patients notice a "dirty" appearance of affected skin that does not wash clean. Skin lesions remain asymptomatic unless maceration or secondary infection occurs. The clinical severity and histopathologic features of acanthosis nigricans correlate positively with the degree of hyperinsulinism and with the degree of obesity. The differential diagnosis includes **confluent and reticulated papillomatosis (CARP)**, Addison disease, pellagra, and erythrasma. CARP is an idiopathic disorder characterized by hyperpigmented papules with reticulation peripheral to the papules and is commonly distributed in the intermammary region (Fig. 698.15) and the epigastrium and upper back; less often it involves the axilla (Fig. 698.16) or neck and face.

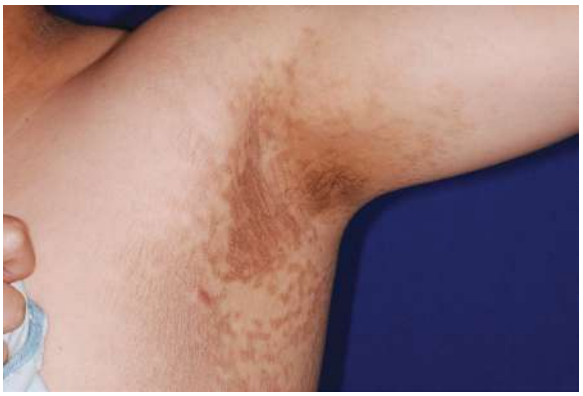

Fig. 698.16 Confluent and reticulated papillomatosis. Hyperpigmented thin plaques, which were confluent centrally and reticulated at the periphery, were present in the bilateral axillae of this 16-year-old male patient who also had classic acanthosis nigricans affecting the neck folds. These axillary changes resolved completely with oral minocycline and lactic acid–containing emollients. *(From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology, 6th ed. Philadelphia: Elsevier; 2022, Fig. 23.35, p. 641.)*

HISTOLOGY

The histologic changes are those of papillomatosis and hyperkeratosis rather than acanthosis or excessive pigment formation. A mild dermal inflammatory infiltrate may be present.

TREATMENT

Treatment is aimed at the underlying disorder. Acanthosis nigricans in the obese child is associated with risk factors for glucose homeostasis abnormalities, and counseling families on its causes and consequences may motivate them to make healthy lifestyle changes that can decrease the risk for development of cardiac disease and diabetes mellitus. In children with obesity-related acanthosis nigricans, weight loss should be the primary goal. If a drug or malignancy is suspected, removal of that agent or treatment of cancer typically results in resolution. Appearance of skin lesions responds poorly to local medical management; some patients benefit from topical keratolytic agents (40% urea cream or 12% ammonium lactate cream) and agents that inhibit keratinocyte proliferation (topical retinoids and vitamin D analogs).

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Chapter 699

Disorders of Keratinization

Kari L. Martin

DISORDERS OF CORNIFICATION

Mendelian disorders of cornification (ichthyoses) are a primary group of inherited conditions characterized clinically by patterns of scaling and histopathologically by hyperkeratosis. They are usually distinguishable by inheritance patterns, clinical features, associated defects, and histopathologic changes (Tables 699.1, 699.2, and 699.3). The two main categories of ichthyotic diseases are whether they are limited to the skin or have syndromic associations.

COLLODION BABY

Collodion baby is not a single entity, but a newborn phenotype that is most often seen in babies who eventually demonstrate lamellar ichthyosis or congenital ichthyosiform erythroderma (CIE). Less commonly, collodion babies evolve into babies with Gaucher disease or neutral lipid storage disease with ichthyosis, Loricrin keratoderma, trichothiodystrophy, Sjögren-Larsson syndrome, Conradi-Hünerman syndrome, or harlequin ichthyosis. A small subset become otherwise healthy babies without chronic skin disease (self-healing collodion baby).

Collodion babies are covered at birth by a thick, taut membrane resembling oiled parchment or collodion (Fig. 699.1), which is subsequently shed. Affected neonates have ectropion (eversion of the eyelid away from the globe), flattening of the ears and nose, and fixation of the lips in an O-shaped configuration. Hair may be absent or may perforate the abnormal covering. The membrane cracks with initial respiratory efforts and, shortly after birth, begins to desquamate in large sheets. Admission to a neonatal intensive care unit and a high-humidity environment and application of nonocclusive lubricants facilitate shedding of the membrane. Complete shedding may take several weeks, and a new membrane may occasionally form in localized areas.

Neonatal morbidity and mortality may be due to cutaneous infection, aspiration pneumonia (squamous material), hypothermia, or hypernatremic dehydration from excessive transcutaneous fluid losses as a result of increased skin permeability. The outcome is uncertain, and accurate prognosis depends on identification of the underlying ichthyosis.

NONSYNDROMIC ICHTHYOSES

Ichthyosis Vulgaris

Etiology/Pathogenesis

Autosomal dominant or recessive pathogenic variants in the filaggrin gene cause ichthyosis vulgaris. Filaggrin is a filament-aggregating protein that assembles the keratin filament cytoskeleton, causing collapse of the granular cells into a classic flattened squamous cell shape. Pathogenic variants in filaggrin lead to absence of or marked reductions in keratohyalin granules (see Table 699.2).

Clinical Manifestations

Ichthyosis vulgaris is *the most common* of the disorders of keratinization, with an incidence of 1/250 live births. Onset generally occurs in the first year of life. In most cases, it is trivial, consisting only of slight roughening of the skin surface. Scaling is most prominent on the extensor aspects of the extremities, particularly the legs (Fig. 699.2). Flexural surfaces are spared, and the abdomen, neck, and face are relatively uninvolved. Keratosis pilaris—particularly on the upper arms and thighs, accentuated markings, and hyperkeratosis on the palms and soles—and atopy are relatively common. Scaling is most pronounced during the winter months and may abate completely during warm weather. There is no accompanying disorder of hair, teeth, mucosal surfaces, or other organ systems; however, patients are at increased risk of atopy.

Treatment

Scaling may be diminished by daily applications of an emollient or a lubricant containing urea (10–40%), salicylic acid, or an alpha-hydroxy acid such as lactic acid (5–12%).

X-Linked Ichthyosis

Etiology/Pathogenesis

X-linked ichthyosis involves a deficiency of steroid sulfatase, which hydrolyzes cholesterol sulfate and other sulfated steroids to cholesterol. Cholesterol sulfate accumulates in the stratum corneum and plasma. In the epidermis this accumulation causes malformation of intercellular lipid layers, leading to barrier defects and delay of corneodesmosome degradation, resulting in corneocyte retention.

Clinical Manifestations

Skin peeling may be present at birth but typically begins at 3-6 months of life. Scaling is most pronounced on the sides of the neck, lower face, preauricular areas, anterior trunk, and the limbs, particularly the legs. The elbow (Fig. 699.3) and knee flexures are generally spared but may be mildly involved. The palms and soles may be slightly thickened but are also usually spared. The condition gradually worsens in severity and extent. Keratosis pilaris is not present, and there is no increased incidence of atopy. Deep corneal opacities that do not interfere with vision develop in late childhood or adolescence and are a useful marker for the disease because they may also be present in carrier females. Some patients have larger deletions on the X chromosome that encompass neighboring genes, generating *contiguous gene deletion syndromes*. These include Kallmann syndrome (*KAL1* gene), which consists of hypogonadotrophic hypogonadism and anosmia, X-linked chondroplasia punctata (*ARSE* gene), short stature, and ocular albinism. The rate of testicular cancer may be increased in patients with coexistent Kallmann syndrome. There is also an increased risk of attention-deficit/hyperactivity disorder and autism owing to a contiguous gene defect in neuroligin 4.

Reduced steroid sulfatase enzyme activity can be detected in fibroblasts, keratinocytes, and leukocytes and, prenatally, in amniocytes or chorionic villus cells. In affected families, an affected male can be detected by restriction enzyme analysis of cultured chorionic villus cell DNA or amniocytes or by in situ hybridization, which identifies steroid sulfatase gene deletions prenatally in chorionic villus cells. A placental steroid sulfatase deficiency in carrier mothers may result in low urinary and serum estriol values, prolonged labor, and insensitivity of the uterus to oxytocin and prostaglandins.

Treatment

Daily application of emollients and a urea-containing lubricant (10–40%) is usually effective. Glycolic or lactic acid (5–12%) in an emollient base and propylene glycol (40–60%) in water with occlusion overnight are alternative forms of therapy.

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSES

Harlequin Ichthyosis

Etiology/Pathogenesis

Harlequin ichthyosis is caused by pathogenic variants in the *ABCA12* gene. Pathogenic variants in the gene lead to defective lipid transport, and *ABCA12* activity is required for the generation of long-chain ceramides that are essential for the development of the normal skin barrier.

Clinical Manifestations

At birth, markedly thickened, ridged, and cracked skin forms horny plates over the entire body, disfiguring the facial features and constricting the digits. Severe ectropion and chemosis obscure the orbits, the nose and ears are flattened, and the lips are everted and gaping. Nails

Table 699.1 Inherited Ichthyoses – Syndromic

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRACUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
X-LINKED ICHTHYOSIS SYNDROMES							
RXLI (recessive X-linked ichthyosis) syndromic presentation		308100	XR	Large, dark scales Sparing of body folds	Prolongation of labor Cryptorchidism Corneal opacities, asymptomatic	*STS* Larger deletions with contiguous gene defects	Steroid sulfatase
IFAP syndrome (ichthyosis-follicularis-atrichia-photophobia)		398205	XR	Spiny follicular ichthyosis Nail dystrophy Alopecia	Photophobia Psychomotor delay Short stature	*MBTPS2*	Membrane-bound transcription factor peptidase, site 2
Conradi-Hünermann-Happle syndrome (CDPX2)	X-linked chondrodysplasia punctata (Conradi-Hünermann syndrome)	302960	XD	Striated ichthyosiform hyperkeratosis Follicular atrophoderma Alopecia	Cataracts Frontal bossing Short proximal limbs	*EBP*	Emopamil-binding protein
CHILD syndrome		308050	XD	Unilateral ichthyosiform erythroderma	Chondrodysplasia punctata Cataracts Limb reduction defects Asymmetric organ hypoplasia	*NSDHL*	3-β-hydroxysteroid-Δ8,Δ7-isomerase
AUTOSOMAL ICHTHYOSIS SYNDROMES WITH PROMINENT HAIR ABNORMALITIES							
NS (Netherton syndrome)		256500	AR	Erythroderma in infancy Ichthyosis linearis circumflexa Alopecia	Atopic diathesis Food allergies Structural hair defects (trichorrhexis invaginata) Growth delay	*SPINK5*	LETKI
IHS (ichthyosis hypotrichosis syndrome)		610765	AR	Adherent platelike scale Hypohidrosis Hypotrichosis	Photophobia Pingueculum	*ST14*	Serine protease 14
IHSC syndrome (ichthyosis-hypotrichosis-sclerosing cholangitis)		607626	AR	Fine thin scale Hypotrichosis with coarse thick hair	Sclerosing cholangitis Congenital paucity of bile ducts	*CLDN1*	Claudin 1
TTD (trichothiodystrophy)		601675	AR	May have collodion membrane Can vary from mild scaling to marked adherent plaques	Photosensitivity Brittle hair with "tiger tail" pattern Decreased fertility Short stature Susceptibility to infection	*ERCC2, XPD ERCC3, XPB GTF2H5, TTDA*	Xeropigmentosum group D protein Xeropigmentosum group B protein
TTD (not associated with congenital ichthyosis)		234050	AR	Delayed onset Fine scale	Nonphotosensitive Brittle hair Short stature Decreased fertility	*C7Orf11, (TTDN1)*	M-phase–specific PLK1-interacting protein, (TTD non-photosensitive 1 protein)
AUTOSOMAL ICHTHYOSIS SYNDROMES WITH FATAL DISEASE COURSE							
Gaucher syndrome, type 2		230900	AR	Collodion baby, mild scaling later	Hepatosplenomegaly retroflexion of the head, strabismus, dysphagia, choking spells, hypertonicity Death usually occurs in the first year	*GBA*	Acid β-glucosidase

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Table 699.1 Inherited Ichthyoses – Syndromic—cont'd

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRACUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
Multiple sulfatase deficiency		272200	AR	Mild scale	Mental retardation Mucopolysaccharidosis Metachromatic leukodystrophy Death within first year of life	*SUMF1*	Sulfatase-modifying factor-1
CEDNIK syndrome (cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma)		609528	AR	Coarse platelike white scale Fine, sparse hair	Sensorineural deafness Cerebral dysgenesis Neuropathy Microcephaly Neurogenic muscle atrophy Optic nerve atrophy Cachexia Lethal within first decade	*SNAP29*	Synaptosomal-associated protein, 29kDA
ARC syndrome (arthrogryposis-renal dysfunction-cholestasis)		208085	AR	Fine scale	Arthrogryposis Intrahepatic bile duct hypoplasia with cholestasis Renal tubular degeneration Metabolic acidosis Abnormal platelet function Death within first year of life	*VPS33B*	Vacuolar protein sorting–associated protein 33B
AUTOSOMAL ICHTHYOSIS SYNDROMES WITH OTHER ASSOCIATED SIGNS							
SLS (Sjögren-Larsson syndrome)		270200	AR	Fine lamellar scale	Diplegia or tetraplegia Retinal glistening white dots	*ALDH3A2*	Long-chain aldehyde dehydrogenase
RS (Refsum syndrome) (HMSN4: hereditary motor sensory neuropathy type 4)	Refsum disease	266500	AR	Late onset, fine scale	Retinitis pigmentosa Cardiac failure	*PAHX* or *PHYH* *PEX7*	Phytanoyl-CoA hydroxylase Peroxin-7
KID syndrome (keratitis-ichthyosis-deafness syndrome)	KID; includes HID syndrome	242150 602540	AD	Verrucous plaques Stippled pattern of keratoderma	Keratitis Sensorineural deafness	*GJB2 (GJB6)*	Connexin 26
Neutral lipid storage disease with ichthyosis	Chanarin-Dorfman syndrome (also termed NCIE2)	275630	AR	Fine scales with occasional background erythema	Myopathy Hepatosplenomegaly	*ABHD5*	CGI-58
IPS (ichthyosis prematurity syndrome)		608649	AR	White caseous scale, attenuated on scalp and eyebrows Follicular keratosis	Atopic manifestations	*SLC27A4*	Long-chain fatty acid transport protein 4
CHIME syndrome		280000	AR	Ichthyotic erythema Occasionally migratory plaques	Colobomas Conductive hearing loss Mental retardation	NK	NK
MEDNIK syndrome (mental retardation-enteropathy-deafness-neuropathy-ichthyosis-keratodermia)		Not on OMIM	AR	Rough, thickened skin	Congenital sensorineural deafness Psychomotor and growth retardation Chronic diarrhea	*AP1S1*	Adapter-related protein complex 1 sigma-1A subunit

AD, Autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XR, X-linked recessive.
Modified from Foley CC, Paller AS, Irvine AD. Disorders of cornification (ichthyosis). In: Eichenfield LF, Frieden IJ, eds. *Neonatal and Infant Dermatology,* 3rd ed. Philadelphia: Elsevier; 2015: Table 19.1, p. 283–284.

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Table 699.2 Inherited Ichthyoses – Nonsyndromic

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRA-CUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
COMMON ICHTHYOSES							
IV (ichthyosis vulgaris)		146700	AD (autosomal semidominant)	Fine, white scale Accentuated palmoplantar markings	Strong association with atopic manifestations	*FLG*	Filaggrin
RXLI (recessive X-linked ichthyosis) (nonsyndromic presentation)		308100	XR	Large, dark scales Sparing of body folds	Prolongation of labor Cryptorchidism Corneal opacities, asymptomatic	*STS*	Steroid sulfatase
AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS (ARCI)							
MAJOR TYPES							
HI (harlequin ichthyosis)		242500	AR	Rigid plates Severe erythema Hypohidrosis Scarring alopecia	Ectropion Eclabion Contractures Failure to thrive Short stature	*ABCA12*	ATP-binding cassette, subfamily a, member 12
LI (lamellar ichthyosis)		242300 601277 604777	AR	Large adherent plates Hypohidrosis	Ectropion Eclabium Short stature if severe	*TGM1, ABCA12, PNPLA1, LIPN*	Transglutaminase 1, ABCA12 transporter, PNPLA1, lipase N
CIE (congenital ichthyosiform erythroderma)		242100	AR	Fine white scales Background erythema Hypohidrosis Mild PPK White nails	Failure to thrive Short stature if severe Occasional neurologic deficits	*TGM1, ALOX12B, ALOXE3, ABCA12, CYP4F22, NIPAL4*	Transglutaminase 1 Arachidonate lipoxygenases, cytochrome P450 enzyme, ichthyin, ABCA12 transporter
MINOR VARIANTS							
SHCB (self-healing collodion baby)		242300	AR	Collodion baby at birth, not subsequent ichthyotic phenotype	None	*TGM1, ALOX12B, ALOXE3*	Keratinocyte transglutaminase 1
Acral SHCB (self-healing collodion baby)		242300	AR	Acral collodion membranes that heal	None	*TGM1*	Transglutaminase 1
BSI (bathing suit ichthyosis)		242300	AR	Collodion membrane at birth, extremities heal	None	*TGM1*	Transglutaminase 1
KERATINOPATHIC ICHTHYOSIS (KPI)							
MAJOR TYPES							
EI (epidermolytic ichthyosis)	BCIE/EH	113800	AD, rarely AR	Widespread skin blistering in neonates Warty hyperkeratosis	Growth failure if severe	*KRT1, KRT10*	Keratins 1 and 10
SEI (superficial EI)	Ichthyosis bullosa of Siemens	146800	AD	Mild flexural hyperkeratosis Adherent fine scale Pruritus	None	*KRT2E*	Keratin 2
MINOR VARIANTS							
AEI (annular epidermolytic ichthyosis)		607602	AD	Intermittent annular, polycyclic erythematous scaly plaques		*KRT1, KRT10*	Keratins 1 and 10
ICM (ichthyosis Curth-Macklin)	Ichthyosis hystrix	146590 146600	AD	Spiky hyperkeratosis	None	*KRT1*	Keratin 1
Epidermolytic epidermal nevi		Not in OMIM	Somatic pathogenic variants			*KRT1, KRT10*	Keratins 1 and 10

Continued

Table 699.2 Inherited Ichthyoses – Nonsyndromic—cont'd

DISORDER	PREVIOUS NAME	MIM #	INHERITANCE	CUTANEOUS FINDINGS	EXTRA-CUTANEOUS FINDINGS	GENE DEFECT(S)	PROTEIN(S)
OTHER FORMS							
LK (loricrin keratoderma)		604117	AD	Collodion baby Mild, fine, white scale Diffuse PPK	None	*LOR*	Loricrin
EKV (erythrokeratoderma variabilis)		133200	AD	Transient, migratory erythematous patches Hyperkeratosis Diffuse PPK	None	*GJB3, GJB4*	Connexins 31, 30.3
PSD (peeling skin disease)		270300	AR		None	*CDSN, TGM5*	Corneodesmin, Transglutaminase 5
CRIE (congenital reticular ichthyosiform erythroderma)		609165	AD (isolated cases)		None	*KRT10*	Keratin
KLICK (keratosis linearis-ichthyosis congenita-keratoderma)		Not in OMIM	AR	Linear keratoses in skin folds Sclerosing PPK	None	*POMP*	Proteasome maturation protein

AD, Autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.
Modified from Foley CC, Paller AS, Irvine AD. Disorders of cornification (ichthyosis). In: Eichenfield LF, Frieden IJ, eds. *Neonatal and Infant Dermatology,* 3rd ed. Philadelphia: Elsevier; 2015: Table 19.2, p. 285–286.

Table 699.3 Differential Diagnosis of Netherton Syndrome: Disorders with Ichthyosis and Alopecia (Hereditary Disorders Only)*

DISORDER	INHERITANCE	GENE	FEATURES RESEMBLING NETHERTON SYNDROME	DIFFERENTIATION FROM NETHERTON SYNDROME
SAM syndrome	AR Loss-of-function pathogenic variants	*DSG1*	CIE with PPK, no collodion membrane; failure to thrive; hypernatremia; barrier defect; dermatitis; high IgE; malabsorption; eosinophilic esophagitis; multiple food allergies; recurrent infections; hypotrichosis; hypoalbuminemia	May have microcephaly, growth hormone deficiency, developmental delay, cardiac defects; psoriasiform dermatitis with acantholysis in skin sections; absence of desmoglein
ADAM17 deficiency	AR Loss-of-function pathogenic variants	*ADAM17*	Psoriasiform erythroderma/widespread pustules; failure to thrive; malabsorption; short, broken hair; recurrent infections	Bloody diarrhea; cardiomyopathy/ cardiomyositis
EGFR deficiency	AR Loss-of-function pathogenic variants	*EGFR*	Erythema, scaling, and widespread pustules; alopecia; failure to thrive, watery diarrhea, high IgE and eosinophils, hypernatremia, hypoalbuminemia; recurrent bronchiolitis	Cardiovascular issues
Trichothiodystrophy	AR Loss-of-function pathogenic variants	*ERCC2, ERCC3, GTF2H5, C7Orf11*	CIE-like ichthyosis; short, brittle hair; "tiger tail" hair shaft defect under polarized microscopy	May have impaired intelligence, decreased fertility, short stature, and photosensitivity
IHS (also called autosomal recessive ichthyosis with hypotrichosis [ARIH] syndrome)	AR Loss-of-function pathogenic variants	*ST14* (encodes matriptase); abnormal filaggrin processing	Generalized, congenital ichthyosis with sparing of face, palms, and soles; diffuse nonscarring alopecia of scalp, eyelashes, and eyebrows from birth, but improves to sparse, unruly hair during adolescence and merely recession of the frontal hair line by adulthood	May have patchy follicular atrophoderma and hypohidrosis; photophobia from corneal abnormalities; blepharitis; dental abnormalities; hair microscopy may show pili torti or pili bifurcati
IHSC (or NISCH) syndrome	AR Loss-of-function pathogenic variants	*CLDN1* (encodes claudin 1, structural protein of tight junctions)	Congenital generalized scaling, predominantly on the limbs and abdomen and sparing skinfolds, palms, and soles; coarse, curly hair with frontotemporal cicatricial alopecia	Congenital paucity of bile ducts or sclerosing cholangitis leads to neonatal jaundice with hepatomegaly; oligodontia, and enamel dysplasia; blood smears show small eosinophils and keratinocyte vacuoles without lipid contents

*Netherton syndrome must also be distinguished from severe atopic dermatitis and immunodeficiency disorders.
AR, Autosomal recessive; CIE, congenital ichthyosiform erythroderma; Ig, immunoglobulin; IHS, ichthyosis hypotrichosis syndrome; IHSC, ichthyosis-hypotrichosis-sclerosing cholangitis; NISCH, neonatal ichthyosis sclerosing cholangitis; PPK, palmoplantar keratoderma; SAM, severe dermatitis, multiple allergies, and metabolic wasting.

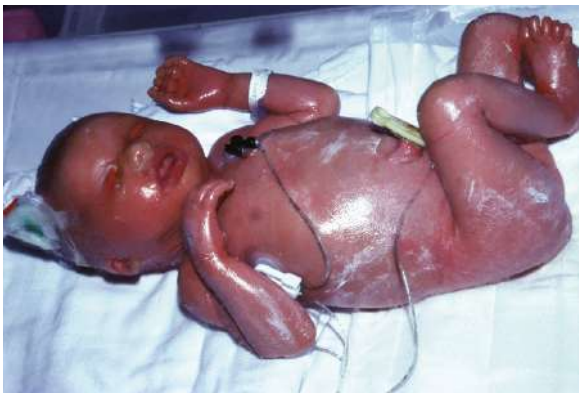

Fig. 699.1 Typical appearance of a collodion baby.

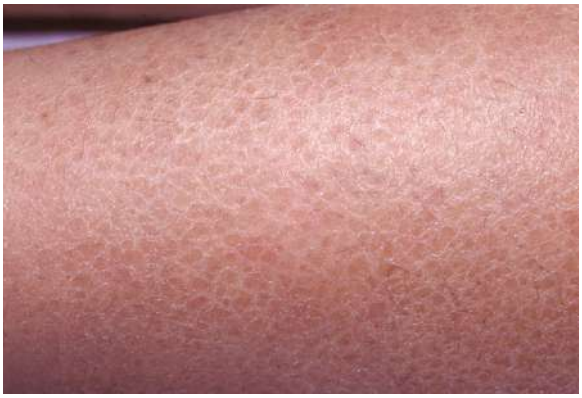

Fig. 699.2 Scale over the shin in ichthyosis vulgaris.

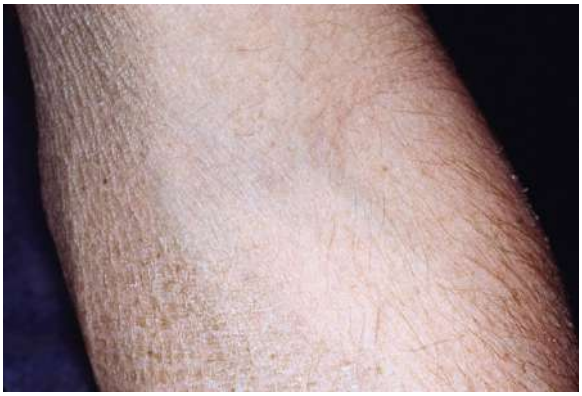

Fig. 699.3 Sparing of the antecubital fossa in X-linked ichthyosis.

and hair may be absent. Joint mobility is restricted, and the hands and feet appear fixed and ischemic. Affected neonates have respiratory difficulty, suck poorly, and are subject to severe cutaneous infection. Harlequin ichthyosis used to be uniformly fatal in the neonatal period, but with the use of oral retinoids, more patients survive (~80%) beyond infancy and have severe ichthyosis usually resembling lamellar ichthyosis or nonbullous CIE as adolescents and adults. Those with a compound heterozygous genotype have a better prognosis. Prenatal diagnosis has been accomplished by fetoscopy, fetal skin biopsy, and microscopic examination of cells from amniotic fluid.

Treatment

Initial treatment includes high fluid intake to avoid dehydration from transepidermal water loss and use of a humidified heated incubator, emulsifying ointments, careful attention to hygiene, and oral retinoids.

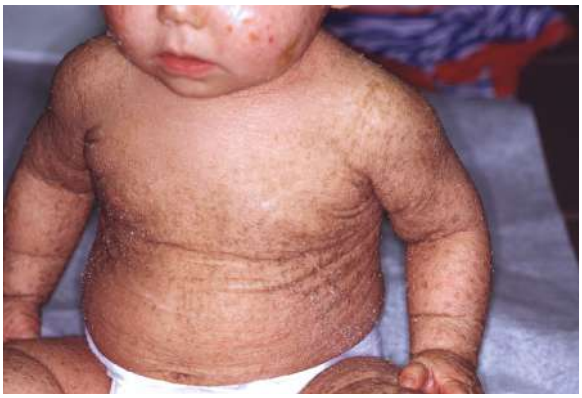

Fig. 699.4 Generalized scaling of lamellar ichthyosis.

Intubation may be required until nares are patent and parenteral nutrition required until eclabium has resolved. Consultation with ophthalmology is often required given the extensive ectropion. If constrictive bands are around the digits, debridement may be performed to prevent ischemia.

Lamellar Ichthyosis and Congenital Ichthyosiform Erythroderma (Nonbullous Congenital Ichthyosiform Erythroderma)

Lamellar ichthyosis and CIE (nonbullous congenital ichthyosiform erythroderma; non-harlequin ichthyosis autosomal recessive congenital ichthyoses [ARCI]) are the most common types of autosomal recessively inherited ichthyosis. Both forms are present at or shortly after birth. Most infants with these forms of ichthyosis present with erythroderma and scaling, but among collodion babies, most turn out to have one of these ichthyosis variants.

Etiology/Pathogenesis

Six genes have been identified that cause non-harlequin ichthyosis ARCI: *TGM* (the gene encoding transglutaminase), *ABCA12, NIPAL4* (also known as *ICHTHYIN*), *CYP4F22,* and the lipoxygenase genes *ALOX12B* and *ALOXE3*. Transglutaminase pathogenic variants lead to abnormalities in the cornified envelope, whereas defects in *ABCA12* cause abnormal lipid transport and those in *CYP4F22* produce abnormal lamellar granules. The lipoxygenases are likely to play a role in epidermal barrier formation by affecting lipid metabolism.

Clinical Manifestations

After shedding of the collodion membrane, if present, lamellar ichthyosis evolves into large, quadrilateral, dark scales that are free at the edges and adherent at the center. Scaling is often pronounced and involves the entire body surface, including flexural surfaces (Fig. 699.4). The face is often markedly involved, including ectropion and small, crumpled ears. The palms and soles are generally hyperkeratotic. The hair may be sparse and fine, but the teeth and mucosal surfaces are normal. Unlike in CIE, there is little erythema.

In CIE, erythroderma tends to be persistent, and scales, although they are generalized, are finer and whiter than in lamellar ichthyosis (Fig. 699.5). Hyperkeratosis is particularly noticeable around the knees, elbows, and ankles. Palms and soles are uniformly hyperkeratotic. Patients have sparse hair, cicatricial alopecia, and nail dystrophy. Neither form includes blistering.

Treatment

Pruritus may be severe and responds minimally to antipruritic therapy. The unattractive appearance of the child and the bad odor from bacterial colonization of macerated scales may cause severe emotional distress. A high-humidity environment in winter and air conditioning in summer reduce discomfort. Generous and frequent applications of emollients and keratolytic agents such as lactic or glycolic acid (5–12%), urea (10–40%), tazarotene (0.1% gel), and retinoic acid (0.1% cream) may lessen the scaling to some extent, although these agents

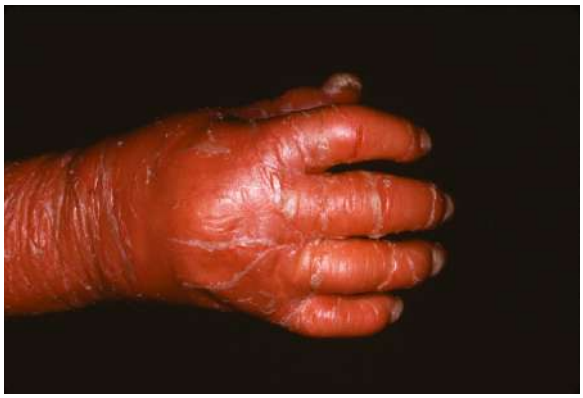

Fig. 699.5 Prominent erythema and scale in congenital ichthyosiform erythroderma.

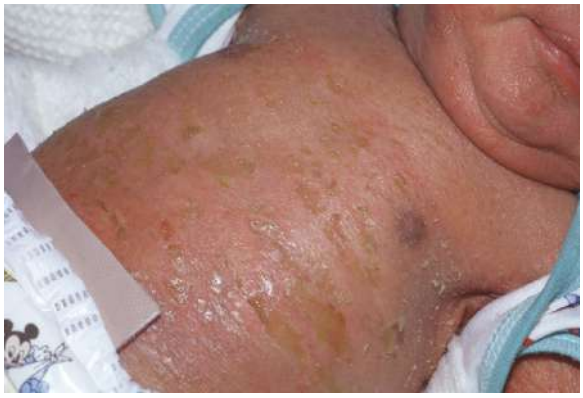

Fig. 699.6 Superficial erosions and hyperkeratosis in epidermolytic hyperkeratosis.

produce stinging if applied to fissured skin. Oral retinoids have a beneficial effect in these conditions but do not alter the underlying defect and therefore must be administered indefinitely. The long-term risks of these compounds (teratogenic effects and toxicity to bone) may limit their usefulness. Ectropion requires ophthalmologic care and, at times, plastic surgical procedures.

KERATINOPATHIC ICHTHYOSES

Epidermolytic Ichthyosis (Bullous Congenital Ichthyosiform Erythroderma; Epidermolytic Hyperkeratosis)

Etiology/Pathogenesis

Epidermolytic ichthyosis is an autosomal dominant trait that has been shown to be due to defects in either keratin 1 or keratin 10. These keratins are required to form the keratin-intermediate filaments in cells of the suprabasilar layers of the epidermis.

Clinical Manifestations

The clinical manifestations are initially characterized by the onset at birth of widespread blisters and erosions on a background of generalized erythroderma (Fig. 699.6). Recurrent blistering may be widespread in neonates and may cause diagnostic confusion with other blistering disorders. With time, the blister formation ceases, erythema decreases, and generalized hyperkeratosis develops. The scales are small, hard, and verrucous. Distinctive, parallel hyperkeratotic ridges develop over the joint flexures, including the axillary, popliteal, and antecubital fossae, and on the neck and hips. Palmoplantar keratoderma (PPK) is associated with keratin 1 defects. The hair, nails, mucosa, and sweat glands are normal. Malodorous secondary bacterial infection is common and requires appropriate antibiotic therapy.

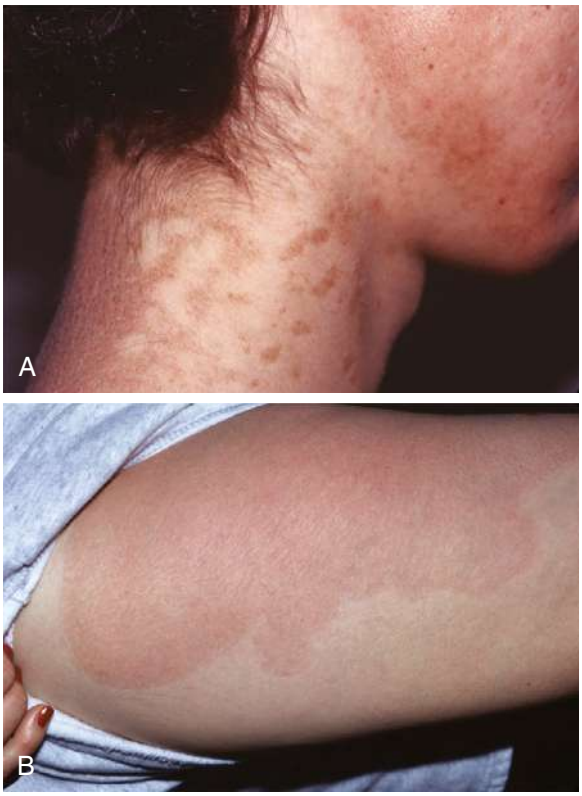

Fig. 699.7 Erythrokeratoderma variabilis. **A**, Fixed, hyperkeratotic plaques. **B**, Migratory, erythematous lesion.

Histopathology

The histopathology is diagnostic of epidermolytic ichthyosis, consisting of hyperkeratosis, degeneration of the epidermal granular layer with an increased number of keratohyalin granules, clear spaces around nuclei, and indistinct cellular boundaries of cells in the upper epidermis. On electron microscopic examination, keratin-intermediate filaments are clumped, and many desmosomes are attached to only one keratinocyte instead of connecting neighboring keratinocytes. Localized forms of the disease may resemble epidermal nevi or keratoderma of the palms and soles but share the distinctive histopathologic changes of epidermolytic ichthyosis.

Treatment

Treatment of epidermolytic ichthyosis is difficult. Morbidity is increased in the neonatal period as a result of prematurity, sepsis, and fluid and electrolyte imbalance. Bacterial colonization of macerated scales produces a distinctive bad odor that can be controlled somewhat by use of an antibacterial cleanser. Intermittent oral antibiotics are generally necessary. Keratolytic agents are often poorly tolerated. Oral retinoids may produce significant improvement. Prenatal diagnosis for affected families is possible by examination of DNA extracts from chorionic villus cells or amniocytes, provided that the specific pathogenic variant in the affected parent is known.

OTHER NONSYNDROMIC ICHTHYOSES

Erythrokeratoderma Variabilis

Etiology/Pathogenesis

An autosomal dominant disorder, erythrokeratoderma variabilis (EKV), is caused by pathogenic variants in connexins 31 and 30.3. Connexins are proteins that form gap junctions between cells that allow for transport and signaling between neighboring epidermal cells.

Clinical Manifestations

EKV usually manifests in the early months of life, progresses in childhood, and stabilizes in adolescence. It is characterized by two distinctive manifestations: sharply demarcated, hyperkeratotic plaques (Fig. 699.7A)

and transient figurate erythema (see Fig. 699.7B). The distribution is generalized but sparse; sites of predilection are the face, buttocks, axillae, and extensor surfaces of the limbs. The palms and soles may be thickened, but hair, teeth, and nails are normal.

Treatment
There are case reports that topical tazarotene gel 0.1% and oral retinoids are effective for treatment of EKV.

Symmetric Progressive Erythrokeratoderma
Etiology/Pathogenesis
Symmetric progressive erythrokeratoderma is an autosomal dominant disorder caused by pathogenic variants in the gene encoding loricrin. Loricrin is a major component of the epidermal cornified cell envelope.

Clinical Manifestations
The disorder manifests in childhood as large, fixed, geographic and symmetric, fine, scaling, hyperkeratotic, erythematous plaques primarily on the extremities, buttocks, face, ankles, and wrists. The primary feature distinguishing this disorder from EKV is the lack of variable erythema seen in the latter condition.

Treatment
Symmetric progressive erythrokeratoderma is a very rare disorder, but reports of response to topical and oral retinoids exist.

SYNDROMIC ICHTHYOSES
Sjögren-Larsson Syndrome
Etiology/Pathogenesis
The autosomal recessive inborn error of metabolism known as Sjögren-Larsson syndrome is an abnormality of fatty alcohol oxidation that results from a deficiency of fatty aldehyde dehydrogenase *(FALDH3A2)*, a component of the fatty alcohol–nicotinamide adenine dinucleotide oxidoreductase enzyme complex (see Table 699.1).

Clinical Manifestations
The clinical picture of Sjögren-Larsson syndrome consists of ichthyosis, cognitive impairment, and spasticity. The ichthyosis is generalized but is accentuated on the flexures and the lower abdomen and consists of erythroderma, fine scaling, larger platelike scales, and dark hyperkeratosis. The degree of scale varies markedly from patient to patient. Most individuals have palmoplantar hyperkeratosis. The skin changes may be identical to the other forms of ichthyosis, and diagnosis is often delayed until the onset of neurologic symptoms. Pruritus is severe, and hypohidrosis is common. Glistening dots in the foveal area are a cardinal ophthalmologic sign. About half the patients have primary retinal degeneration. Motor and speech developmental delays are usually noted before 1 year of age, and spastic diplegia or tetraplegia, epilepsy, and intellectual disability generally become evident in the first to third years of life. Some patients may walk with the aid of braces, but most are confined to wheelchairs. This deficiency can be demonstrated in cultured skin fibroblasts of affected patients and carriers and, prenatally, in cultured chorionic villus cells and amniocytes from affected fetuses. Elevation of urinary leukotriene B4 (LTB4) may provide an easier approach to diagnosis.

Treatment
Treatment is similar to the other forms of ichthyosis (humectants, emollients, topical or oral retinoids); 5-lipoxygenase inhibitors have been used to decrease pruritus.

Netherton Syndrome
Etiology/Pathogenesis
A rare autosomal recessive disorder, Netherton syndrome is caused by pathogenic variants in the *SPINK 5* gene, which encodes a serine protease inhibitor *(LEKT1)*.

Clinical Manifestations
Netherton syndrome is characterized by ichthyosis (usually ichthyosis linearis circumflexa, but occasionally the lamellar or congenital types of ichthyosiform erythroderma), trichorrhexis invaginata and other hair shaft anomalies, and atopic diathesis. The disorder manifests at birth or in the first few months of life as generalized erythema and scaling. The trunk and limbs have diffuse erythema and superimposed migratory, polycyclic, and serpiginous hyperkeratotic lesions (Fig. 699.8), some with a distinctive double-edged margin of scale. Lichenification or hyperkeratosis tends to persist in the antecubital and popliteal fossae. The face and scalp may remain erythematous and scaling. Many hair shaft deformities, most notably trichorrhexis invaginata, have been described in most patients with Netherton syndrome.

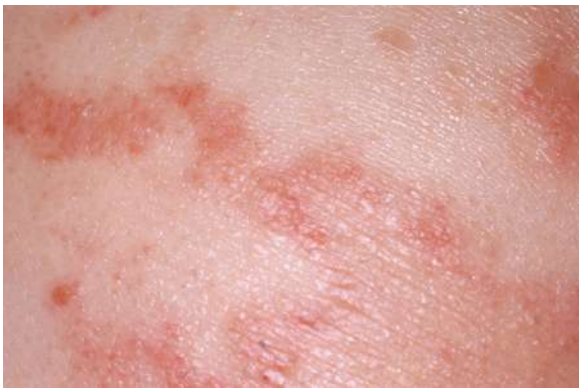

Fig. 699.8 Serpiginous, erythematous, hyperkeratotic lesions of ichthyosis linearis circumflexa.

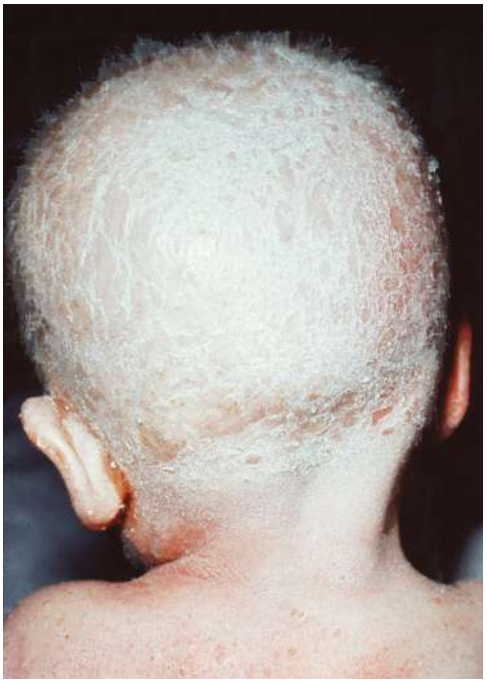

Fig. 699.9 Very short scalp hair and thick scale in Netherton syndrome.

The ichthyosis is present in the first 10 days of life and may be especially marked around the eyes, mouth, and perineal area. The erythroderma is often intensified after infection. Infants may suffer from failure to thrive, recurrent bacterial and candidal infections, elevated serum immunoglobulin IgE values, and marked hypernatremic dehydration. The most frequent allergic manifestations are urticaria, angioedema, atopic dermatitis, and asthma. Scalp hair is sparse and short and fractures easily (Fig. 699.9); eyebrows, eyelashes, and body hair are also abnormal. The characteristic hair abnormality can be identified with light microscopy; in the newborn, it may best be identified in eyebrow hair. The differential diagnosis is noted in Table 699.3.

Treatment
Owing to the inflammatory nature of the skin disease, oral antihistamines and topical steroids, as used in the treatment of atopic dermatitis, are helpful for Netherton syndrome.

Refsum Syndrome
See Chapters 106.2 and 653.5.

Etiology/Pathogenesis
There are two types of Refsum syndrome. The classic form is autosomal recessive and caused by pathogenic variants in the *PAHX* gene that result in an increase in phytanic acid. The infantile forms of Refsum syndrome are also autosomal recessive and caused by pathogenic variants in the *PEX1, PEX2,* or *PEX26* genes. These are peroxisomal abnormalities that lead to an increase in very long-chain fatty acids, di- and tri-hydroxycholestanoic acid, and pipecolic acid, as well as phytanic acid.

Clinical Manifestations
Refsum syndrome is a multisystem disorder that becomes symptomatic in the second or third decade of life. The ichthyosis may be generalized, is relatively mild, and resembles ichthyosis vulgaris. The ichthyosis may also be localized to the palms and soles. Chronic polyneuritis with progressive paralysis and ataxia, retinitis pigmentosa, anosmia, deafness, bony abnormalities, and electrocardiographic changes are the most characteristic features. The condition is diagnosed through lipid analysis of the blood or skin, which shows elevated phytanic acid values.

The infantile form begins, as suggested by the name, early in life, and in addition to the changes seen in the classic form, affected patients have hepatomegaly, abnormal bile acid profiles, developmental delay, and cognitive impairment.

Treatment
Phytanic acid is exclusively derived from dietary chlorophyll. Lifelong dietary avoidance of phytanic acid–containing products leads to clinical improvement in classic Refsum syndrome.

Chondrodysplasia Punctata
See Chapter 106.2.

Etiology/Pathogenesis
Chondrodysplasia punctata (CPD) is a clinically and genetically heterogeneous condition. X-linked dominant CPD, also known as *Conradi-Hünermann syndrome,* is the best-characterized form. There is also an X-linked recessive form caused by a pathogenic variant in the *ARSE* gene. Rhizomelic CPD type 1 is an autosomal recessive disorder caused by pathogenic variants in the *PEX7* gene, which encodes the *PTS2* receptor. CPD can also be caused by maternal vitamin K deficiency or warfarin teratogenicity.

Clinical Manifestations
These heterogeneous disorders are marked by ichthyosis and bone changes. Nearly all patients with the X-linked dominant form and approximately 25% of those with the recessive type have cutaneous lesions, ranging from severe, generalized erythema and scaling to mild hyperkeratosis. Rhizomelic CPD is associated with cataracts, hypertelorism, optic nerve atrophy, disproportionate shortening of the proximal extremities, psychomotor retardation, failure to thrive, and spasticity; most affected patients die in infancy. Patients with the X-linked dominant form have asymmetric, variable shortening of the limbs and a distinctive ichthyosiform eruption at birth. Thick, yellow, tightly adherent, keratinized plaques are distributed in a whorled pattern over the entire body. The eruption typically resolves in infancy and may be superseded by a follicular atrophoderma and patchy alopecia.

Additional features in all variants include cataracts and abnormal facies with saddle nose and frontal bossing. The pathognomonic defect, termed CPD, is stippled epiphyses in the cartilaginous skeleton. This defect, which is seen in various settings and inherited disorders, often in association with peroxisomal deficiency and disturbance of cholesterol biosynthesis, disappears by 3-4 years of age.

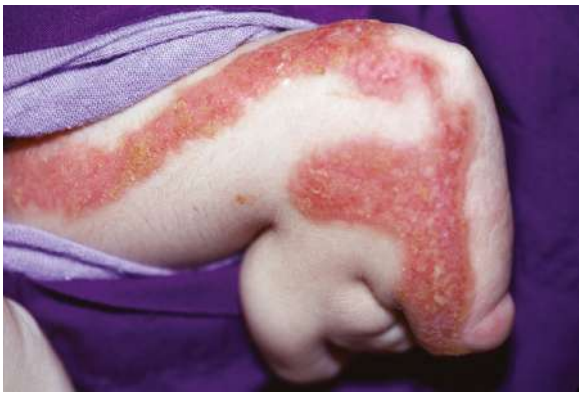

Fig. 699.10 Limb dysplasia and ichthyosiform eruption in CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome.

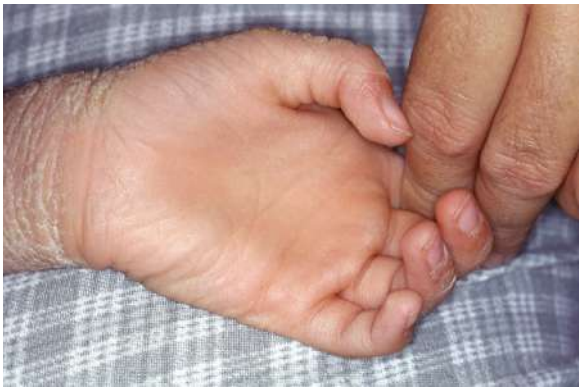

Fig. 699.11 Palmar keratoderma with epidermolytic changes seen on biopsy.

OTHER SYNDROMES WITH ICHTHYOSIS
A number of other rare syndromes with ichthyosis as a consistent feature include the following: keratitis with ichthyosis and deafness (KID syndrome, connexin 26 gene), ichthyosis with defective hair having a banded pattern under polarized light and a low sulfur content (trichothiodystrophy), multiple sulfatase deficiency, neutral lipid storage disease with ichthyosis (Chanarin-Dorfman syndrome; *CGI58* gene), and CHILD syndrome (Fig. 699.10; congenital hemidysplasia with ichthyosiform erythroderma and limb defects; *NSDHL* gene).

Palmoplantar Keratodermas
Excessive hyperkeratosis of the palms and soles may occur as a manifestation of a focal or generalized congenital hereditary skin disorder or may result from such chronic skin diseases as psoriasis, eczema, pityriasis rubra pilaris, lupus erythematosus, or postinfectious arthritis syndrome.

Diffuse Hyperkeratosis of Palms and Soles (Unna-Thost, Vorner)
Unna-Thost and Vorner type PPKs, although clinically inseparable, were thought to be separate entities. They were separated histologically by the presence (Vorner) or absence (Unna-Thost) of epidermolytic hyperkeratosis. They represent the clinical spectrum of the same disease caused by pathogenic variants in keratin (*KRT1* and *KRT9* genes). This autosomal dominant disorder manifests in the first few months of life as erythema that

gradually progresses to sharply demarcated, hyperkeratotic, scaling plaques over the palms (Fig. 699.11) and soles. The margins of the plaques often remain red; plaques may extend along the lateral aspects of the hands and feet and onto the volar wrists and the heels. Hyperhidrosis is usually present, but hair, teeth, and nails are usually normal. Striate (*DSG1*, *DSP*, *KRT1* genes) and punctate forms of palmar and plantar hyperkeratosis represent distinct entities.

Mal De Meleda (*SLURP-1* Gene)

A rare, progressive autosomal recessive condition, mal de Meleda is characterized by erythema and thick scales on the palms, fingers, soles, and flexor aspects of the wrists, knees, and elbows. Hyperhidrosis, nail thickening or koilonychia, and eczema may also occur.

Vohwinkel Palmoplantar Keratoderma (Mutilating Keratoderma)

Vohwinkel PPK is a progressive autosomal dominant disease consisting of honeycombed hyperkeratosis of palms and soles, sparing the arches; starfish-like and linear keratoses on the dorsum of the hands, fingers, feet, and knees; and ainhum-like constriction of the digits that sometimes leads to autoamputation. Varying degrees of alopecia may be seen. Two forms have been identified. Vohwinkel PPK with ichthyosis is caused by pathogenic variants in the loricrin gene, and Vohwinkel PPK with deafness by pathogenic variants in connexin 26.

Papillon-Lefèvre Syndrome (Cathepsin C Gene)

An autosomal recessive erythematous hyperkeratosis of the palms and soles, Papillon-Lefèvre syndrome sometimes extends to the dorsal hands and feet, elbows, and knees later in childhood. The PPK may be either diffuse, striate, or punctuate. This syndrome is characterized by periodontal inflammation, leading to loss of teeth by age 4-5 years if untreated.

Other Syndromes

Keratoderma of palms and soles also occurs as a feature of some forms of ichthyosis and ectodermal dysplasia. Richner-Hanhart syndrome is an autosomal recessive focal PPK with corneal ulcers, progressive mental impairment, and a deficiency of tyrosine aminotransferase, which leads to tyrosinemia. **Pachyonychia congenita** is transmitted as an autosomal dominant trait with variable expressivity. The classic type I form (Jadassohn-Lewandowski syndrome) is due to pathogenic variants in the gene for keratin 16. Major features of the syndrome are onychogryphosis; PPK; follicular hyperkeratosis, especially of the elbows and knees; and oral leukokeratosis. The nail dystrophy is the most striking feature and may be present at birth or develop early in life. The nails are thickened and tubular, projecting upward at the free edge to form a conical roof over a mass of subungual keratotic debris. Repeated paronychial inflammation may result in shedding of the nails. The feature seen most consistently among patients with this condition is keratoderma of the palms and soles. Additional associated features include hyperhidrosis of the palms and soles and bullae and erosions on the palms and soles. Some patients have shown a selective cell-mediated defect in recognition and processing of *Candida.* Surgical removal of the nails and excision of the nail matrix have been helpful in some patients.

Treatment

Treatment for PPK is the same no matter what its cause. In mild cases, emollient therapy may suffice. Keratolytic agents such as salicylic acid, lactic acid, and urea creams may be required. Oral retinoids are the treatment of choice for severe cases unresponsive to topical therapy.

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Chapter 700

Diseases of the Dermis

Jacquelyn R. Sink and Yvonne E. Chiu

KELOID

Etiology and Pathogenesis

Keloids are usually induced by trauma and commonly follow ear piercing, burns, scalds, and surgical procedures. The resulting keloid is larger than the initial area of trauma to the skin. Certain individuals are predisposed to keloid formation; a familial tendency (recessive or dominant inheritance) or the presence of foreign material in the wound may have a pathogenic role. Keloids are a rare feature of Ehlers-Danlos syndrome, Rubinstein-Taybi syndrome, and pachydermoperiostosis. Keloids result from an abnormal fibrous wound-healing response in which tissue repair and regeneration-regulation control mechanisms are lost. Collagen production is 20 times that seen in normal scars, and the type I:III collagen ratio is abnormally high. In keloids, tissue levels of tumor growth factor-β and platelet-derived growth factor are elevated; fibroblasts are more sensitive to their effects, and their degradation rate is decreased.

Clinical Manifestations

A *keloid* is a sharply demarcated, benign, dense growth of connective tissue that forms in the dermis after trauma. The lesions are firm, raised, pink to hyperpigmented, and rubbery; they may be tender or pruritic. Sites of predilection are the face, earlobes (Fig. 700.1), neck, shoulders, upper trunk, sternum, and lower legs. Unlike hypertrophic scars, keloids frequently recur after attempted removal and outgrow the original boundaries of the wound.

Histology

A keloid consists of whorled and interlaced hyalinized collagen fibers.

Differential Diagnosis

Keloids should be differentiated from *hypertrophic scars,* which remain confined to the site of injury and may involute over time.

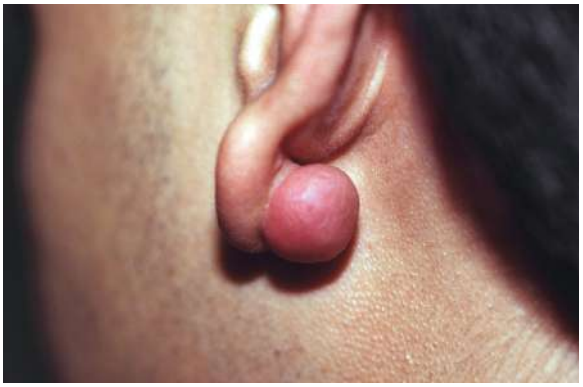

Fig. 700.1 Keloid of earlobe after piercing.

Treatment
Treatment of keloids is difficult. Young keloids may diminish in size if injected intralesionally at 4-week intervals with triamcinolone suspension (10-40 mg/mL). At times, a more concentrated suspension is required. Large or old keloids may require surgical excision followed by serial intralesional injections of corticosteroid; however, recurrence rates are high. Earlobe keloids may respond favorably to surgical excision followed by use of pressure earrings and serial intralesional steroid injections. Silicone scar sheeting may help in some patients. Other therapeutic modalities that have been used with variable success include laser therapy, radiation therapy, and intralesional injection of bleomycin, interferon, verapamil, or fluorouracil.

STRIAE CUTIS DISTENSAE (STRETCH MARKS)
Etiology and Pathogenesis
Striae formation is common in adolescence. The most frequent causes are rapid growth, pregnancy, obesity, Cushing disease, and prolonged use of systemic or topical corticosteroid therapy. They may also be seen in patients with Ehlers-Danlos syndrome. The pathogenesis is unknown, but alterations in collagen and elastic fibers are thought to play a role.

Clinical Manifestations
Striae appear as linear, depressed, pink bands of atrophic skin that eventually become silvery, opalescent, and smooth. They occur most frequently in areas subject to distention, such as the lower back (Fig. 700.2), buttocks, thighs, breasts, abdomen, and shoulders.

Differential Diagnosis
Striae distensae resemble atrophic scars.

Treatment
Striae tend to spontaneously become less conspicuous as the color fades with time, and treatment is not necessary.

CORTICOSTEROID-INDUCED ATROPHY
Etiology and Pathogenesis
Both topical and systemic corticosteroid treatment can result in cutaneous atrophy. This is particularly common when a potent or superpotent topical corticosteroid is applied under occlusion or to an intertriginous area for a prolonged period. Keratinocyte growth is decreased, but epidermal maturation is accelerated, resulting in thinning of the epidermis and stratum corneum. Fibroblast growth and function are also decreased, leading to dermal changes. The mechanism involves inhibition of synthesis of collagen type I, noncollagenous proteins, and total protein content of the skin, along with progressive reduction of dermal proteoglycans and glycosaminoglycans.

Clinical Manifestations
Affected skin is thin, fragile, smooth, and semitransparent, with telangiectasia, prominent veins, and loss of normal skin markings.

Histology
On histology, thinning of the epidermis is present. Spaces between dermal collagen and elastic fibers are small, producing a more compact yet thin dermis.

Treatment
Optimal treatment is prevention by monitoring and educating on the proper use of topical steroids to avoid side effects.

GRANULOMA ANNULARE
Etiology and Pathogenesis
The cause of granuloma annulare (GA) is unknown. A possible association with diabetes mellitus has been proposed, particularly with the generalized form of GA; however, this hypothesis is controversial and has not been confirmed in children.

Clinical Manifestations
This common dermatosis occurs predominantly in healthy children and young adults. Typical lesions begin as firm, smooth, erythematous papules. They gradually enlarge to form annular plaques with a papular border and a normal, slightly atrophic or discolored central area up to several centimeters in size. Lesions may occur anywhere on the body, but mucous membranes are notably spared. Favored sites include the dorsum of the hands (Fig. 700.3) and feet. The disseminated papular form is rare in children. Subcutaneous GA tends to develop on the scalp and limbs, particularly in the pretibial area. These lesions are firm, usually nontender, skin-colored nodules. Perforating GA is characterized by the development of grouped papules, some with a yellowish, crusted, or scaly center, and occur because of transepidermal elimination of altered collagen.

Differential Diagnosis
Annular lesions are often mistaken for tinea corporis due to the elevated, advancing border; however, GA characteristically lacks scale. Papular lesions may simulate rheumatoid nodules, particularly when grouped on the fingers and elbows.

Histology
The lesions of GA demonstrate granuloma formation on histology with a central area of necrotic collagen, mucin deposition, and a peripheral palisading infiltrate of lymphocytes, histiocytes, and foreign body giant cells. The pattern resembles that of necrobiosis lipoidica and rheumatoid nodules, but subtle histologic differences usually permit differentiation.

Treatment
The eruption persists for months to years, but spontaneous resolution without residual change is typical; approximately 50% of lesions clear within 2 years. Application of a potent or superpotent topical corticosteroid preparation or intralesional injections (5-10 mg/mL)

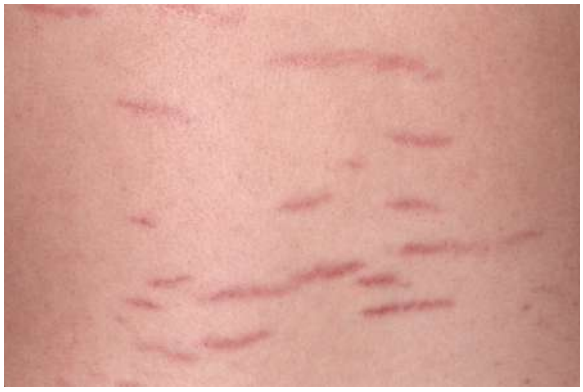

Fig. 700.2 Striae on the back of an adolescent.

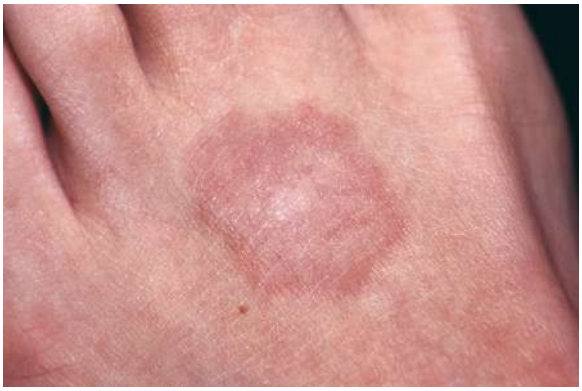

Fig. 700.3 Annular lesion with a raised papular border and depressed center, characteristic of granuloma annulare.

of corticosteroid may hasten involution, but nonintervention is also appropriate.

NECROBIOSIS LIPOIDICA

Etiology and Pathogenesis

The cause of necrobiosis lipoidica (NL) is unclear, but 50–75% of patients have diabetes mellitus, though NL occurs in less than 1% of all diabetic patients. NL has also been noted in patients with obesity, hypertension, and dyslipidemias. Its presence may signify a higher risk for diabetic complications such as nephropathy and retinopathy.

Clinical Manifestations

This disorder manifests as erythematous papules that evolve into irregularly shaped, sharply demarcated, erythematous to yellow, sclerotic plaques with central telangiectasias and a violaceous border. Scaling, crusting, and ulceration may occur. Lesions develop most commonly on the anterior tibial surfaces (Fig. 700.4). Slow extension of a given lesion over the years is usual, but long periods of quiescence or complete healing with scarring may occur.

Histology

Poorly defined areas of necrobiotic collagen are seen on microscopic evaluation, primarily low in the dermis with mucin deposition. Surrounding the necrobiotic, disordered areas of collagen is a palisading lymphohistiocytic granulomatous infiltrate. Some lesions are more characteristically granulomatous, with limited necrobiosis of collagen.

Differential Diagnosis

NL must be differentiated clinically from xanthomas, morphea, GA, erythema nodosum, and pretibial myxedema.

Treatment

The lesions of NL usually persist despite good control of the diabetes but may improve minimally after applications of high-potency topical steroids or local injection of a corticosteroid. Ulcerated areas should be managed with meticulous wound care. Pentoxifylline and antiplatelet therapy with aspirin have also been used.

LICHEN SCLEROSUS

Etiology and Pathogenesis

Lichen sclerosus (LS) is a chronic inflammatory dermatosis whose cause is largely unknown. Several studies have identified the presence of autoantibodies against the glycoprotein extracellular matrix protein 1 (ECM-1).

Clinical Manifestations

Lichen sclerosus (LS) manifests as shiny, ivory-colored, flat-topped papules, often with a violaceous halo. The surface shows prominent dilated pilosebaceous or sweat duct orifices that may contain yellow or brown follicular plugs. The papules coalesce to form irregular plaques of variable size, and hemorrhagic bullae can be seen in the margins. In the later stages, atrophy results in a depressed plaque with a wrinkled surface. This disorder occurs more commonly in girls than in boys. Sites of predilection in girls are the vulvar (Fig. 700.5), perianal, and perineal skin. Extensive involvement may produce an atrophic plaque of hourglass configuration; shrinkage of the labia and stenosis of the introitus may result. Erythema and purpura are possible. Vaginal discharge precedes vulvar lesions in approximately 20% of patients. In boys, the prepuce and glans penis are often involved, usually in association with phimosis *(balanitis xerotica obliterans)*; most boys with the disorder were not circumcised early in life. Commonly involved extragenital sites include the upper trunk, neck, axillae, flexor surfaces of wrists, and areas around the umbilicus and the eyes. Pruritus, pain, and dysuria may be severe, and constipation due to withholding may occur.

Differential Diagnosis

In children, LS is most frequently confused with focal morphea (see Chapter 201), with which it may coexist. In the genital area, it may be mistakenly attributed to sexual abuse, irritant dermatitis, or vulvovaginitis. The vitiligoid form associated with depigmentation must be differentiated from vitiligo or postinflammatory hypopigmentation.

Histology

Biopsy is rarely necessary but shows hyperkeratosis with follicular plugging, hydropic degeneration of basal cells, a bandlike dermal lymphocytic infiltrate, homogenized collagen, and thinned elastic fibers in the upper dermis.

Treatment

Vulvar LS in childhood usually improves with puberty but does not always resolve completely, and symptoms can recur throughout life. Long-term observation for the development of squamous cell carcinoma is necessary in patients with later disease onset or persistence beyond puberty. Superpotent topical corticosteroids are the treatment of choice, including for the genital area, providing relief from pruritus and producing clearing of lesions. Topical tacrolimus and pimecrolimus have also been used. It is not known how response to treatment affects long-term cancer risk.

MORPHEA

Etiology and Pathogenesis

Morphea is an autoimmune sclerosing condition of the dermis and subcutaneous tissue of unknown etiology.

Clinical Manifestations

Morphea is characterized by solitary, multiple, or linear circumscribed areas of erythema that evolve into indurated, sclerotic, atrophic plaques, with or without a lilac border (Fig. 700.6). Affected areas may resolve

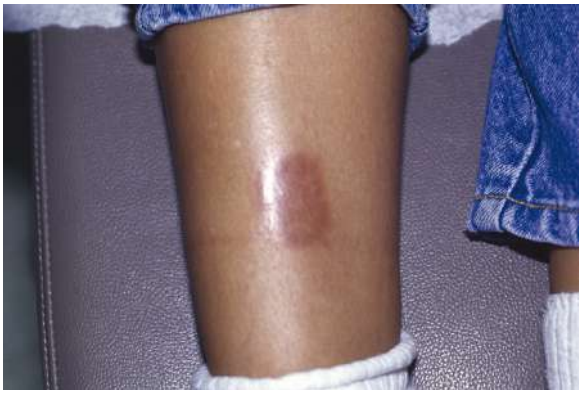

Fig. 700.4 Yellow sclerotic plaque of necrobiosis lipoidica on the shin.

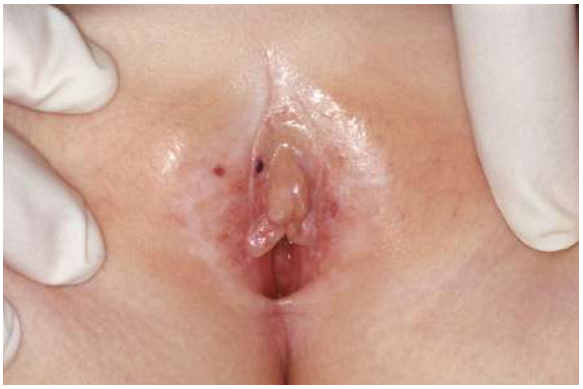

Fig. 700.5 Ivory-colored perivaginal plaque with hemorrhage.

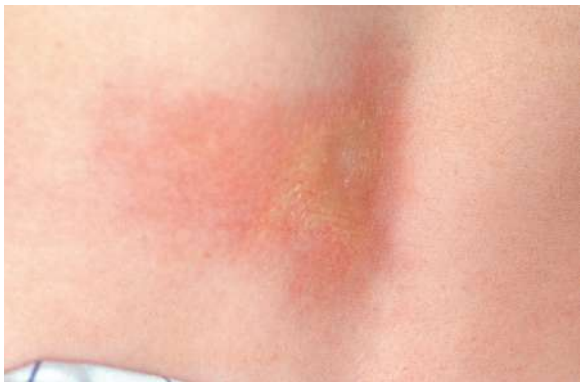

Fig. 700.6 Erythematous, hyperpigmented plaque of early morphea.

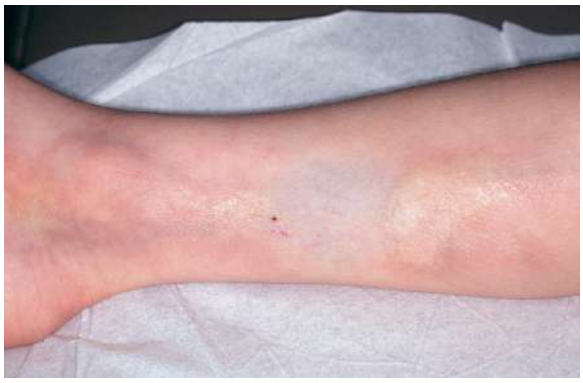

Fig. 700.7 Linear morphea with involvement over the ankle.

without sequelae or with subsequent atrophy and/or pigment change. Morphea is seen more commonly in females. Five types of morphea have been described: circumscribed, linear, generalized, mixed, and pansclerotic; the most common types in children are circumscribed and linear. Morphea can affect any area of skin. When confined to the frontal scalp, forehead, and midface in a linear band, it is referred to as **en coup de sabre**. When located on one side of the face, it is termed **progressive hemifacial atrophy**, also known as **Parry-Romberg syndrome**. These forms of morphea carry a poorer prognosis because of the associated underlying central nervous system involvement or musculoskeletal atrophy that can be cosmetically disfiguring. Linear morphea over a joint may lead to limb undergrowth or restriction of mobility (Fig. 700.7). Pansclerotic morphea is a rare, severe, disabling variant.

Differential Diagnosis

The differential diagnosis of morphea includes GA, NL, LS, and late-stage European Lyme borreliosis (acrodermatitis chronica atrophicans).

Histology

Thickening or sclerosus of the dermis with collagen degeneration is seen.

Treatment

Morphea tends to persist, with gradual outward expansion for months to years until spontaneous cessation of the inflammatory phase occurs. Topical calcipotriene, alone or in combination with high-potency to superpotency topical steroids or topical tacrolimus, has been used for less severe disease. For severe morphea, methotrexate with or without pulsed intravenous or oral glucocorticosteroids may halt progression and help shorten the disease course. Ultraviolet A-1 (UVA-1) phototherapy, mycophenolate mofetil, and other therapies are also used. Physical therapy is recommended in linear morphea involving a joint to maintain mobility. Significant postinflammatory pigment alteration may persist for years.

SCLEREDEMA (SCLEREDEMA ADULTORUM, SCLEREDEMA OF BUSCHKE)

Etiology and Pathogenesis

The cause of scleredema is unknown. There are three types. **Type 1** (55% of cases) is preceded by a febrile illness, often related to an upper or lower respiratory infection (most commonly streptococcus). **Type 2** (25%) is associated with paraproteinemia, including multiple myeloma. **Type 3** (20%) is seen in diabetes mellitus.

Clinical Manifestations

Fifty percent of patients with scleredema are younger than 20 years old. Onset of type 1 is sudden, with brawny edema of the face and neck that spreads rapidly to involve the thorax and arms in a sweater distribution; the abdomen and legs are usually spared. The face acquires a waxy, masklike appearance. The involved areas feel indurated and woody, are nonpitting, and are not sharply demarcated from normal skin. The overlying skin is normal in color and is not atrophic.

Type 2 and type 3 scleredema may occur insidiously. Systemic involvement, which is uncommon and usually associated with types 2 and 3, is marked by thickening of the tongue, dysarthria, dysphagia, restriction of eye and joint movements, and pleural, pericardial, and peritoneal effusions. Electrocardiographic changes may also be observed. Laboratory data are not helpful.

Differential Diagnosis

Scleredema must be differentiated from scleroderma (see Chapter 201), morphea, myxedema, trichinosis, dermatomyositis, sclerema neonatorum, and subcutaneous fat necrosis.

Histology

Skin biopsy demonstrates an increase in dermal thickness due to swelling and homogenization of the collagen bundles, which are separated by large interfibrous spaces. Special stains can identify increased amounts of mucopolysaccharides in the dermis of patients with scleredema.

Treatment

In type 1 scleredema, the active phase of the disease persists for 2-8 weeks. Spontaneous and complete resolution usually occurs after 6 months to 2 years. Recurrent attacks are unusual. In types 2 and 3, the disease is slowly progressive. There is no specific therapy.

LIPOID PROTEINOSIS (URBACH-WIETHE DISEASE, HYALINOSIS CUTIS ET MUCOSAE)

Etiology and Pathogenesis

Lipoid proteinosis is an autosomal recessive disorder caused by pathogenic variants in the *ECM-1* gene, which encodes ECM-1. ECM-1 has a functional role in the structural organization of the dermis by binding to perlecan, matrix metalloproteinase 9, and fibulin. Pathogenesis involves infiltration of hyaline material into the skin, oral cavity, larynx, and internal organs.

Clinical Manifestations

Lipoid proteinosis presents initially in early infancy as hoarseness due to vocal cord involvement. Skin lesions appear during childhood and consist of yellowish papules and nodules that may coalesce to form plaques. The classic sign is a string of beaded papules on the eyelids. Lesions also occur on the face, forearms, neck, genitals, dorsum of the fingers, and scalp, where they result in patchy alopecia. Similar deposits are found on the lips, leading to eversion of the lips, as well as the undersurface of the tongue, fauces, uvula, epiglottis,

and vocal cords. The tongue becomes enlarged and feels firm on palpation. The patient may be unable to protrude the tongue. Pocklike, atrophic scars may develop on the face. Hypertrophic, hyperkeratotic nodules and plaques occur at sites of friction, such as the elbows and knees; the palms may be diffusely thickened. The disease progresses until early adult life, but the prognosis is good. Symmetric calcification lateral to the sella turcica in the medial temporal region, identifiable roentgenographically as bilateral bean-shaped opacities, is pathognomonic but is not always present. Involvement of the larynx can lead to respiratory compromise, particularly in infancy, necessitating tracheostomy. Associated anomalies include dental abnormalities, epilepsy, and recurrent parotitis because of infiltrates in the Stensen duct. Virtually any organ can be involved.

Histology

The distinctive histologic pattern in lipoid proteinosis includes dilation of dermal blood vessels and infiltration of homogeneous eosinophilic extracellular hyaline material along capillary walls and around sweat glands. Hyaline material in homogeneous bundles, diffusely arranged in the upper dermis, produces a thickened dermis. The infiltrates appear to contain both lipid and mucopolysaccharide substances.

Treatment

There is no specific treatment for lipoid proteinosis.

MACULAR ATROPHY (ANETODERMA)

Etiology and Pathogenesis

Anetoderma is characterized by circumscribed areas of slack skin associated with loss of dermal substance. This disorder may have no associated underlying disease (primary macular atrophy) or may develop after an inflammatory skin condition. Secondary macular atrophy may be a result of direct destruction of dermal elastin or elastolysis on an immunologic basis, especially in the presence of antiphospholipid antibodies, which are related to autoimmune disorders. The elastolysis may then be a result of release of elastase from inflammatory cells.

Clinical Manifestations

Lesions vary from 0.5 to 1.0 cm in diameter and, if inflammatory, may initially be erythematous. They subsequently become thin, wrinkled, and blue-white or hypopigmented. The lesions often protrude as small outpouchings that, on palpation, may be readily indented into the subcutaneous tissue because of the dermal atrophy. Sites of predilection include the trunk, thighs, upper arms, and, less commonly, the neck and face. Lesions remain unchanged for life; new lesions often continue to develop for years.

Histology

All types of macular atrophy show focal loss of elastic tissue on histopathologic examination, a change that may not be recognized unless special stains are used.

Differential Diagnosis

Lesions of anetoderma occasionally resemble morphea, LS, focal dermal hypoplasia, atrophic scars, or end-stage lesions of chronic bullous dermatoses.

Treatment

There is no effective therapy for macular atrophy.

PSEUDOXANTHOMA ELASTICUM

Etiology and Pathogenesis

Pseudoxanthoma elasticum (PXE) is a genetic metabolic disease linked to pathogenic variants in the *ABCC6* gene. The primary abnormality seen in PXE is mineralization of tissue in the skin, Bruch membrane in the retina, and vessel walls. Cutaneous manifestations of PXE may be present in generalized arterial calcification of infancy.

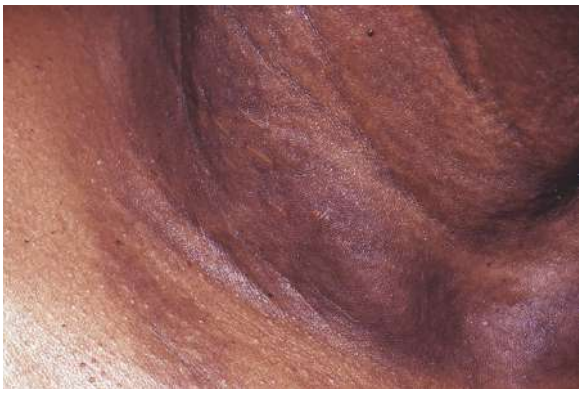

Fig. 700.8 Confluent plaque of pebbly skin in pseudoxanthoma elasticum.

Clinical Manifestations

Onset of skin manifestations often occurs during childhood, but the changes produced by early lesions are subtle and may not be recognized. The characteristic pebbly, "plucked chicken skin" cutaneous lesions are 1- to 2-mm, asymptomatic, yellow papules arranged in a linear or reticulated pattern or in confluent plaques. Preferred sites are the flexural neck (Fig. 700.8), axillary and inguinal folds, umbilicus, thighs, and antecubital and popliteal fossae. As the lesions become more pronounced, the skin acquires a velvety texture and droops in lax, inelastic folds. The face is usually spared. Mucous membrane lesions may involve the lips, buccal cavity, rectum, and vagina. There is involvement of the connective tissue of the media and intima of blood vessels, Bruch membrane of the eye, and endocardium or pericardium, which may result in visual disturbances, angioid streaks in the Bruch membrane, irregular mottling of the retinal epithelium, intermittent claudication, cerebral and coronary occlusion, hypertension, and hemorrhage from the gastrointestinal tract, uterus, or mucosal surfaces. Women with PXE have an increased risk of miscarriage in the first trimester. Arterial involvement generally manifests in adulthood, but claudication and angina have occurred in early childhood.

Pathology

Histopathologic examination shows fragmented, swollen, and clumped elastic fibers in the middle and lower third of the dermis. The fibers stain positively for calcium. Collagen near the altered elastic fibers is reduced in amount and is split into small fibers. Aberrant calcification of the elastic fibers of the internal elastic lamina of arteries in PXE leads to narrowing of vessel lumina.

Treatment

There is no effective treatment for PXE, although laser therapy, with or without intravitreal injection of vascular endothelial growth factor antagonists, may help prevent retinal hemorrhage. The use of oral phosphate binders has shown mixed results in decreasing calcification of elastic fibers.

ELASTOSIS PERFORANS SERPIGINOSA

Etiology and Pathogenesis

Elastosis perforans serpiginosa (EPS) is characterized by the extrusion of altered elastic fibers through the epidermis. The primary abnormality is probably in the dermal elastin, which provokes a cellular response that ultimately leads to extrusion of the abnormal elastic tissue.

Clinical Manifestations

This is an unusual skin disorder in which 1- to 3-mm, firm, skin-colored, keratotic papules tend to cluster in arcuate and annular patterns on the posterolateral neck and limbs (Fig. 700.9) and occasionally on the face and trunk. Onset usually occurs in childhood or

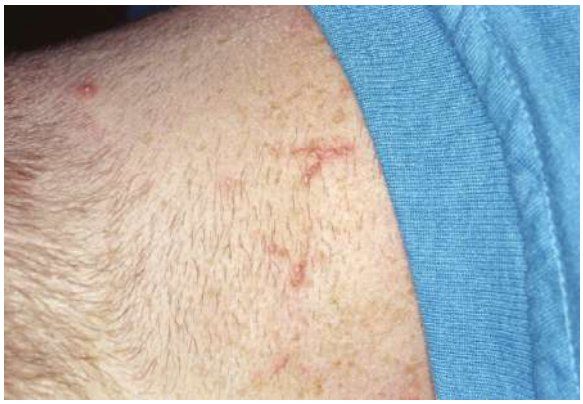

Fig. 700.9 Arcuate keratotic papule of elastosis perforans serpiginosa.

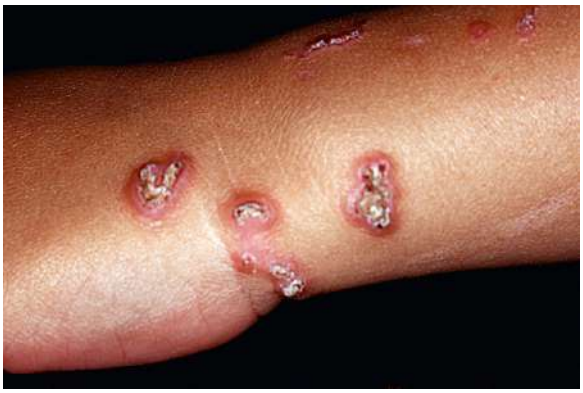

Fig. 700.10 Hyperkeratotic papules in reactive perforating collagenosis.

adolescence. A papule consists of a circumscribed area of epidermal hyperplasia that communicates with the underlying dermis by a narrow channel. There is a great increase in the amount and size of elastic fibers in the upper dermis, particularly in the dermal papillae. Approximately 30% occur in association with osteogenesis imperfecta, Marfan syndrome, PXE, Ehlers-Danlos syndrome, Rothmund-Thomson syndrome, scleroderma, acrogeria, and Down syndrome. EPS has also occurred in association with penicillamine therapy.

Histology
Histopathology reveals a hyperplastic epidermis with extrusion of abnormal elastic fibers and a lymphocytic superficial infiltrate.

Differential Diagnosis
The differential diagnosis of EPS includes tinea corporis, perforating GA, reactive perforating collagenosis, lichen planus, creeping eruption, and porokeratosis of Mibelli.

Treatment
Treatment of EPS is ineffective; however, the lesions are asymptomatic and may disappear spontaneously.

REACTIVE PERFORATING COLLAGENOSIS
Etiology and Pathogenesis
The primary process in reactive perforating collagenosis represents transepidermal elimination of altered collagen. A familial autosomal recessive form has been described.

Clinical Manifestations
Reactive perforating collagenosis usually manifests in early childhood as small papules on the dorsal areas of the hands and forearms, elbows, knees, and, sometimes, the face and trunk. Over a period of several weeks, the papules enlarge to 5-10 mm, become umbilicated, and develop keratotic plugs centrally (Fig. 700.10). Individual lesions resolve spontaneously in 2-4 months, leaving hypopigmented macules or scars. Lesions may recur in crops, linearly as a part of the Koebner phenomenon, or in response to cold temperatures or superficial trauma such as abrasions, insect bites, and acne lesions.

Histology
Collagen in the papillary dermis is engulfed within a cup-shaped perforation in the epidermis. The central crater contains pyknotic inflammatory cells and keratinous debris.

Differential Diagnosis
EPS and Kyrle disease may mimic reactive perforating collagenosis.

Treatment
Reactive perforating collagenosis resolves spontaneously in 6-8 weeks. Narrow-band ultraviolet B (UVB) light may help with pruritus and hasten resolution.

XANTHOMAS
See Chapter 105.

FABRY DISEASE
See Chapter 653.6.

MUCOPOLYSACCHARIDOSES
See Chapter 109.

Several of the mucopolysaccharidoses are characterized by thickened, rough, inelastic skin, particularly on the extremities, and generalized hypertrichosis but are nonspecific features. Extensive and persistent dermal melanocytosis has been described in children with Hurler and Hunter syndromes. Telangiectasias on the face, forearms, trunk, and legs have been observed in Scheie and Morquio syndromes. In some patients with Hunter syndrome, ivory-colored, distinctive, firm dermal papules and nodules with corrugated surface texture are grouped into symmetric plaques on the upper trunk (Fig. 700.11), arms, and thighs. Onset of these unusual lesions occurs in the first decade of life, and spontaneous disappearance has been noted.

MASTOCYTOSIS
Etiology and Pathogenesis
Mastocytosis encompasses a clinical spectrum of disorders that range from solitary cutaneous nodules to diffuse infiltration of skin associated with involvement of internal organs (Table 700.1). All of the disorders are characterized by aggregates of mast cells in the dermis. There are four types of mastocytosis: mastocytomas (three or fewer lesions), urticaria pigmentosa (more than three lesions, also known as *maculopapular cutaneous mastocytosis*), diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans (TMEP). Increased expression of stem cell factor (also called *kit ligand* or *mast cell growth factor*) stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. Some forms of mastocytosis are associated with activating pathogenic variants (most commonly the *D816V* variant) in the *KIT* gene. The local and systemic manifestations of the disease are at least partly a result of the release of histamine and heparin from mast cell granules; although heparin is present in significant amounts in mast cells, coagulation disturbances occur only rarely. The vasodilator prostaglandin D_2 or its metabolite appears to exacerbate the flushing response. Serum tryptase values may be elevated, but not consistently.

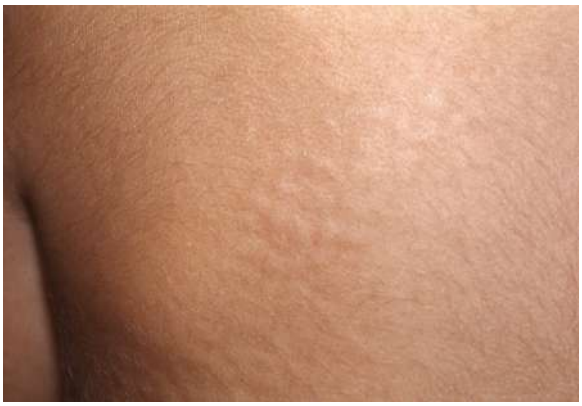

Fig. 700.11 Ivory-colored papules on the upper back in Hunter syndrome.

Table 700.1	Mastocytosis Classification
CUTANEOUS MASTOCYTOSIS	
Urticaria pigmentosa/maculopapular cutaneous mastocytosis	
Diffuse cutaneous mastocytosis	
Solitary mastocytoma	
SYSTEMIC MASTOCYTOSIS	
Indolent mastocytosis	
Smoldering mastocytosis	
Aggressive mastocytosis	
Systemic mastocytosis with associated hematologic non–mast cell lineage (AHN) disease	
Mast cell leukemia	
MAST CELL SARCOMA	

Modified from Valent P, Akin C, Metcalfe D. Mastocytosis: 2016 Updated WHO classification and novel emerging treatment concepts. *Blood.* 2017;129:1420–1427, Table 2.

Clinical Manifestations

Mastocytomas are usually 1-5 cm in diameter. Lesions may be present at birth or may arise in early infancy at any site. The lesions may manifest as recurrent, evanescent wheals or bullae; in time, an infiltrated, pink, yellow, or tan, rubbery plaque develops at the site of whealing or blistering (Fig. 700.12). The surface acquires a pebbly, orange peel–like texture, and hyperpigmentation may become prominent. Mechanical irritation of the lesion may lead to urtication (Darier sign) within a few minutes due to local histamine release; rarely, systemic signs of histamine release become apparent.

Urticaria pigmentosa is the most common form of mastocytosis in children. In the first type of urticaria pigmentosa, the **classic infantile type**, lesions may be present at birth but more often erupt in crops in the first several months to 2 years of age. New lesions seldom arise after age 3-4 years. In some cases, early bullous or urticarial lesions fade, only to recur at the same site, ultimately becoming fixed and hyperpigmented. In others, the initial lesions are hyperpigmented. Vesiculation usually abates by 2 years of age. Individual lesions range in size from a few millimeters to several centimeters and may be macular, papular, or nodular. They range in color from yellow-tan to red-brown and often have ill-defined borders (see Fig. 700.12). Larger nodular lesions, like solitary mastocytomas, may have a characteristic *peau d'orange* (orange peel–like) texture. Lesions of urticaria pigmentosa may be sparse or numerous and are often symmetrically distributed. Palms, soles, and face are usually spared, as are the mucous membranes. The rapid appearance of erythema and wheals in response to vigorous stroking of a lesion can usually be elicited; dermographism of intervening normal skin is also common. Affected children can have intense pruritus. Systemic signs of histamine release, such as anaphylaxis-like episodes, hypotension, syncope, headache, episodic flushing, tachycardia, wheezing, colic, and diarrhea, are uncommon and occur most frequently in the more severe types of mastocytosis. Flushing is by far the most common symptom.

The **second type** of urticaria pigmentosa may begin in childhood but typically develops in adulthood. This type does not resolve, and new lesions continue to develop throughout life. Patients with this type of mastocytosis may develop systemic involvement.

Systemic mastocytosis is marked by an abnormal increase in the number of mast cells in numerous organ systems and is uncommon in children. Bone lesions are often silent (but may be painful) and are detectable radiologically as osteoporotic or osteosclerotic areas, principally in the axial skeleton. Gastrointestinal tract involvement may lead to abdominal pain, nausea, vomiting, diarrhea, steatorrhea, and bloating. Mucosal infiltrates may be detectable by barium studies or by small bowel biopsy. Peptic ulcers also occur. Hepatosplenomegaly due to mast cell infiltrates and fibrosis has been described, as has mast cell proliferation in lymph nodes, kidneys, periadrenal fat, and bone marrow. Abnormalities in the peripheral blood, such as anemia, leukocytosis, and eosinophilia, are noted in approximately 30% of patients. Mast cell leukemia may occur.

Diffuse cutaneous mastocytosis is characterized by diffuse involvement of the skin rather than discrete hyperpigmented lesions. Affected patients are usually normal at birth and demonstrate features of the disorder after the first few months of life. Rarely, the condition may present with intense generalized pruritus in the absence of visible skin changes. The skin usually appears thickened, pink to yellow in color, doughy, or with a *peau d'orange* texture. Surface changes are accentuated in flexural areas. Recurrent bullae (see Fig. 700.12), intractable pruritus, and flushing attacks are common, as is systemic involvement.

Telangiectasia macularis eruptiva perstans (TMEP) is a variant of mastocytosis that consists of telangiectatic, hyperpigmented macules usually localized to the trunk. These lesions do not urticate when stroked. This form of the disease is seen primarily in adolescents and adults.

Differential Diagnosis

The differential diagnosis of solitary mastocytomas includes recurrent bullous impetigo, herpes simplex, congenital melanocytic nevi, and juvenile xanthogranuloma.

Urticaria pigmentosa can be confused with drug eruptions, postinflammatory pigmentary change, juvenile xanthogranuloma, pigmented nevi, ephelides, xanthomas, chronic urticaria, insect bites, and bullous impetigo. Diffuse cutaneous mastocytoma may be confused with epidermolytic hyperkeratosis. TMEP must be differentiated from other causes of telangiectasia.

The systemic manifestations of mastocytosis may mimic pheochromocytoma, carcinoid syndrome, vasoactive intestinal peptide–secreting tumors, vasculitis, autoinflammatory diseases, hyper-IgE syndrome, somatization disorder, autonomic dysfunction, angioedema, chronic urticaria, and anaphylaxis.

Prognosis

Spontaneous involution usually occurs in patients with solitary mastocytomas and classic infantile urticaria pigmentosa. The incidence of systemic manifestations in these patients is very low. The mean duration of urticaria pigmentosa is around 10 years. A larger number of lesions early in life may lead to later resolution.

Treatment

Solitary mastocytomas usually do not require treatment. Lesions that blister may be treated with topical steroids after each blistering episode.

In urticaria pigmentosa, flushing can be precipitated by excessively hot baths, vigorous rubbing of the skin, and certain drugs, such as

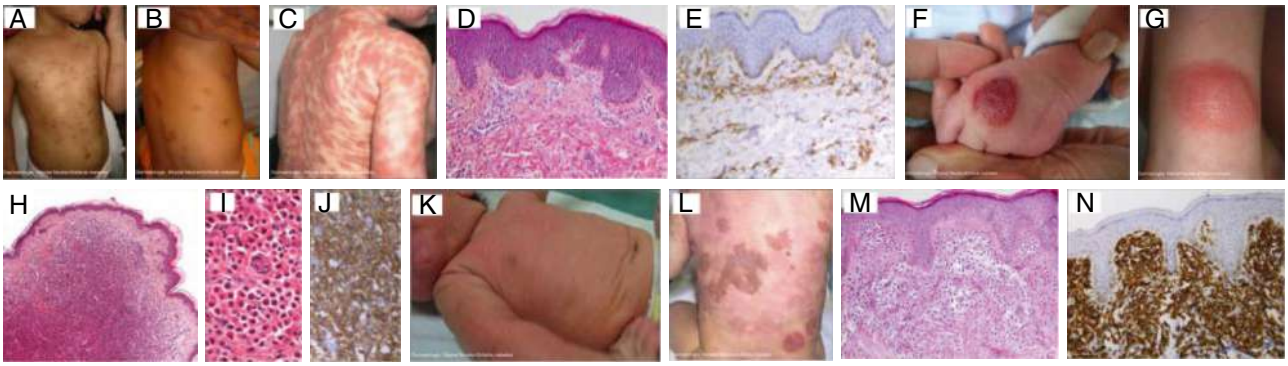

Fig. 700.12 Clinical features and histologic findings in childhood mastocytosis. Diagnosis of mastocytosis in children is often obvious, and skin biopsy is rarely performed. The histologic diagnosis of cutaneous mastocytosis must consider the increased number and proportion of mast cells compared to other inflammatory cells. Mast cells can be rounded, cuboidal, fusiform, or histiocyte-like. Eosinophils may be observed in all mastocytosis subtypes. The epidermis may be hyperpigmented in urticaria pigmentosa (UP) and diffuse cutaneous mastocytosis (DCM), whereas it is normal in mastocytoma. **A-E,** Types of urticaria pigmentosa. **A,** Maculopapular UP. **B,** Plaque-type UP. **C,** Extensive UP with plaques and macules. **D,** Skin biopsy: increased number and proportion of mast cells around the vessels or scattered into the dermis, dilatation of the capillaries of the superficial dermis. **E,** c-Kit staining. **F-J,** Mastocytoma. **F,** Mastocytoma localized on the hand. **G,** Mastocytoma localized on the forearm. **H, I,** Skin biopsy: abundant and diffuse infiltration of mast cells throughout the dermis. Mast cells are always recognizable, with a large, pink, and granular cytoplasm and a round, dense, central nucleus. **J,** c-Kit staining. **K-N,** DCM. **K,** Diffuse infiltration of skin. **L,** Extensive bullous lesions associated with infiltration on the back. **M,** Skin biopsy: diffuse dermal infiltration of mast cells associated with some fibrosis and dilated capillaries. **N,** c-Kit staining. *(From Méni C, Bruneau J, Georgin-Lavialle S, et al. Paediatric mastocytosis: a systematic review of 1747 cases. Br J Dermatol. 2015;172:642–651, Fig. 1, p. 643.)*

Table 700.2 Pharmacologic Agents and Physical Stimuli that May Exacerbate Mast Cell Mediator Release in Patients with Mastocytosis

Venoms (bee stings, jellyfish stings, snake bites)
Complement-derived anaphylatoxins
Biologic peptides (substance P, somatostatin, vasoactive intestinal polypeptide)
Polymers (dextran)
Physical stimuli (heat, cold, exertion, friction, trauma, vibration, sunlight)
Acetylsalicylic acid (aspirin), ibuprofen, and related nonsteroidal analgesics*
Alcohol
General anesthetics (D-tubocurarine, scopolamine, decamethonium, gallamine, pancuronium)
Polymyxin B
Local anesthetics (lidocaine, tetracaine procaine, methylparaben preservative)
Sympathomimetics
Opiates (codeine, morphine)*
Radiographic dyes (iodine-containing)
Other drugs (papaverine, dipyridamole, trimethaphan, amphotericin B, quinine, thiamine, dextromethorphan, lactam, antibiotics, vancomycin)
Stress (sleep deprivation, anxiety, pain)

*Appears to be a problem in <10% of patients.
Modified from Carter MC, Metcalfe DD. Paediatric mastocytosis. *Arch Dis Child.* 2002;86:315–319, Table 4.

codeine, aspirin, morphine, atropine, ketorolac, alcohol, tubocurarine, iodine-containing radiographic dyes, and polymyxin B (Table 700.2). Avoidance of these triggering factors is advisable; it is notable that general anesthesia may be safely performed with appropriate precautions.

For patients who are symptomatic, oral antihistamines may be palliative. H_1 receptor antagonists are the initial drugs of choice for systemic signs of histamine release. If H_1 antagonists are unsuccessful, H_2 receptor antagonists may be helpful in controlling pruritus or gastric hypersecretion. Topical steroids are of benefit in controlling skin urtication and blistering. Oral mast cell–stabilizing agents, such as cromolyn sodium or ketotifen, may also be effective for diarrhea or abdominal cramping and with systemic symptoms such as headache or muscle pain. Midostaurin, an inhibitor of receptor tyrosine kinase KIT, may be effective in patients with systemic mastocytosis associated with hematologic malignancy. A premeasured epinephrine pen kit may be considered for those individuals at higher risk for anaphylaxis such as systemic disease, extensive cutaneous disease, high baseline tryptase levels, and known allergies.

For patients with diffuse cutaneous mastocytosis, treatment is similar to urticaria pigmentosa. Phototherapy with narrow-band UV (UVB or UVA-1) or psoralen with UVA treatment may be useful.

Lesions of TMEP may be cautiously treated with vascular pulsed dye lasers.

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700.1 Mast Cell Activation Syndrome

James J. Nocton

Mast cell activation (MCA) occurs in several defined conditions, including primary mast cell disorders, allergic reactions, systemic inflammatory diseases, and drug reactions, and results in the release of multiple proinflammatory mediators, including tryptase, histamine, prostaglandins, and leukotrienes. The effects of these mediators lead to the clinical symptoms of MCA, which may range from mild to severe and may involve multiple organ systems, including the cutaneous, gastrointestinal, respiratory, and cardiovascular systems (Table 700.3). The term *mast cell activation syndrome (MCAS)* has been used to describe a condition associated with symptoms, signs, and laboratory abnormalities that are consistent with the effects of mast cell mediators; it is recurrent, usually severe, and involves multiple organ systems and responds to treatment with medications that are known to inhibit mast cells or secreted mast cell mediators. Consensus criteria for the diagnosis and

Table 700.3 Common Symptoms in Patients with Mast Cell Mediator Disorders

Cardiovascular: chest pain, hypotension, hypotensive syncope, tachycardia
Dermatologic: angioedema, dermatographism, flushing, pruritus, urticaria pigmentosa
Gastrointestinal: abdominal cramping/pain, bloating, diarrhea, esophagitis, nausea, vomiting
Musculoskeletal: bone/muscle pain, degenerative disc disease, osteoporosis/osteopenia
Naso-ocular: nasal congestion, pruritus, tearing
Neurologic: headache, memory and concentration difficulties (brain fog), paresthesia, peripheral neuropathy
Respiratory: hoarseness, sore throat, stridor, throat swelling, wheezing
Systemic: anaphylaxis, fatigue

From Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders? *Expert Rev Clin Immunol.* 2019;15(6):639–656, Table 1.

Table 700.4 Consensus Criteria for the Diagnosis of Mast Cell Activation Syndrome (MCAS)*

Criterion A: Typical clinical signs of severe, recurrent (episodic) systemic MCA are present (often in the form of anaphylaxis) (definition of systemic: involving at least two organ systems)
Criterion B: Involvement of MC is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to plus 20% + 2 ng/mL†
Criterion C: Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production or drugs blocking mediator release or effects of MC-derived mediators‡

*All three MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS.
†Other MC-derived markers of MCA (histamine and histamine metabolites, PGD_2 metabolites, and heparin) have also been proposed but are less specific compared to tryptase.
‡Example: histamine receptor blockers.
From Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome (MCAS). *J Allergy Clin Immunol Pract.* 2019;7(4):1125–1133, Table I, p. 1126.

Table 700.5 Facial Flushing Etiologies

FLUSHING WITH FOOD
- Alcohol
- Monosodium glutamate (MSG)
- Sulfites
- Scrombroidosis
- Auriculotemporal syndrome (Frey syndrome gustatory flushing)
- Postherpetic gustatory flushing
- Nitrates
- Capsaicin
- Tyramine-containing foods

ENDOCRINE
- Carcinoid
- Pheochromocytoma and paraganglioma
- Medullary thyroid carcinoma
- Pancreatic neuroendocrine tumors (VIP)
- Cushing syndrome
- Perimenopause
- Thyrotoxicosis

OTHER
- Mastocytosis
- Urticaria pigmentosa
- Mast cell activation syndrome
- Harlequin syndrome
- Congenital Horner syndrome
- Idiopathic anaphylaxis
- Panic attacks
- Blushing/anxiety
- Spinal cord injury/autonomic dysregulation
- Niacin supplements

classification of MCAS have been developed (Table 700.4). Under this classification, MCAS is designated primary when it is associated with a defined mast cell disorder such as systemic or cutaneous **mastocytosis**; it is termed secondary when it is recognized in the context of an allergen or another disease known to be associated with MCA; and it is designated idiopathic when neither a primary mast cell disorder nor another associated disease is present.

Patients fulfilling the consensus criteria for MCAS must have *recurrent* clinical manifestations *consistent with MCA*. Cutaneous symptoms have included urticaria, angioedema, itching, and frequent skin **flushing** (Table 700.5). Gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea are common. Tachycardia, sometimes with hypotension and syncope, may be frequent, and some patients have wheezing episodes and rhinitis. Nonspecific and constitutional symptoms have also been described, including headache, fatigue, chronic pain, paresthesias, anxiety, and depression. These nonspecific symptoms most likely represent comorbidities.

Patients diagnosed with MCAS have biochemical evidence indicating mast cell mediator release. **Laboratory abnormalities** that might indicate MCA include elevated serum tryptase and increases in 24-hour urinary histamine metabolites (N-methylhistamine), the prostaglandin D_2 metabolite 2,3-dinor-11-β-$PGF_{2\text{-}\alpha}$, or the leukotriene metabolite LTE_4. The current consensus criteria for the diagnosis of MCAS includes an increase in serum tryptase as the preferred measurement documenting mast cell mediator release (see Table 700.4). Additional biochemical markers have been proposed but remain either of unknown or questionable reliability as markers of MCA.

MCAS has been classified into three groups: primary, secondary, and idiopathic. Primary MCAS refers to patients with *clonal proliferation* of mast cells resulting from pathogenic variants in the *KIT* gene and is usually associated with systemic or cutaneous mastocytosis. A small percentage of those with primary MCAS have clonal proliferation of mast cells but may not completely fulfill the criteria to diagnose systemic or cutaneous mastocytosis. Secondary MCAS refers to patients with either an IgE-dependent allergy, a non–IgE-mediated hypersensitivity disorder, or another inflammatory disease associated with MCA. Idiopathic MCAS refers to patients who do not have clonal mast cells and who do not have an underlying disorder but who nonetheless fulfill the consensus criteria for MCAS with characteristic clinical symptoms and signs, specific abnormal laboratory test results, and a response to treatment that inhibits mast cells or the effect of mast cell mediators.

The **differential diagnosis** of MCAS is broad, reflecting the protean symptoms and signs that have been associated with the syndrome. Cardiovascular conditions may be considered in those with syncope; thyroid disease, adrenal insufficiency, infectious diseases, intoxications, chronic pain syndromes, somatization secondary to anxiety or depression, hypereosinophilic syndromes, hereditary angioedema, and dysautonomias are also considerations in patients with symptoms that appear to be potentially related to MCA. There is also an overlap with idiopathic anaphylaxis and MCAS (see Chapter 190 and Fig. 190.4).

When episodes of cutaneous flushing are the primary symptom and sign, the differential diagnosis is likewise broad. Flushing refers to transient episodes of erythema, most commonly on the face, accompanied by a sensation of warmth. Wet flushing is associated with *increased sweating* and is typical of autonomic nervous system activation, whereas dry flushing occurs without sweating. Wet flushing is more likely caused by panic attacks, pain syndromes, dysautonomia, medications, or toxins. Dry flushing is associated with a more extensive list of

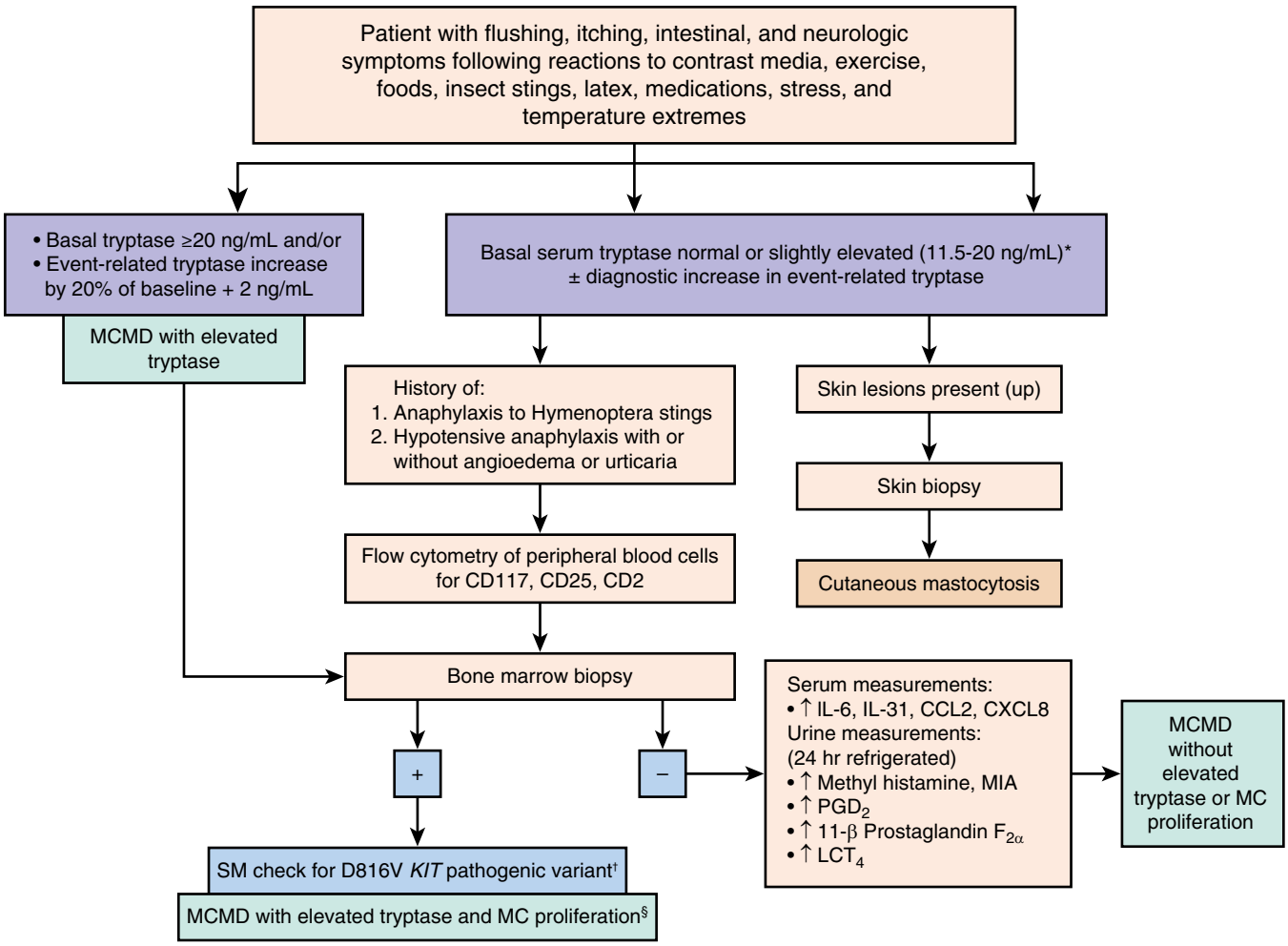

Fig. 700.13 Diagnostic algorithm for mast cell disorders. Diagrammatic representation of a proposed diagnostic rubric for mast cell mediator disorders with emphasis on clonal and nonclonal subtypes and the presence or absence of elevated serum tryptase. MC, Mast cells; MCMD, mast cell mediator disorder; SM, systemic mastocytosis. *This range varies among different laboratories. †KIT pathogenic variants should be investigated. §A patient with elevated basal tryptase should also have BM biopsy; most of these patients have SM. *(From Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders? Expert Rev Clin Immunol. 2019;15[6]:639–656, Fig. 1.)*

possible diagnoses, including MCAS, thyroid disease, foods and other ingestions, some interferonopathies and channelopathies, and tumors such as pheochromocytoma, neuroendocrine tumors, and medullary carcinoma of the thyroid.

When evaluating a patient with symptoms consistent with MCA, if the symptoms are severe, episodic, and respond to mast cell–directed therapy, then the likelihood of MCAS is high. In this setting, further evaluation with serum tryptase measurements should be performed. If the patient fulfills all three diagnostic criteria for MCAS (see Table 700.4), a potential underlying cause should then be sought. This investigation might include genetic analysis of the *KIT* gene in those suspected of having clonal disease such as cutaneous or systemic mastocytosis, a search for potential allergens, or further evaluation for an underlying chronic inflammatory disease (Fig. 700.13). The MCAS can then be classified as primary, secondary, or idiopathic and appropriate management initiated.

The management of MCAS includes medications that interfere with the effects of mast cell mediators, such as the antihistamines cetirizine, loratadine, and fexofenadine; the antileukotrienes montelukast and zafirlukast; and medications that interfere with degranulation such as the mast cell stabilizer cromolyn. Recently, the tyrosine kinase inhibitor midostaurin has also demonstrated efficacy by inhibiting histamine release and increasing apoptosis of mast cells. Management of any identified associated disease is paramount. Prognosis is favorable for most individuals with MCAS but is also dependent on potential associated disease and comorbidities.

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Chapter 701

Diseases of Subcutaneous Tissue

Jacquelyn R. Sink and Yvonne E. Chiu

Diseases involving the subcutis are usually characterized by necrosis and/or inflammation; they may occur either as a primary event or as a secondary response to various stimuli or disease processes. The principal diagnostic criteria relate to the appearance and distribution of the lesions, associated symptoms, results of laboratory studies, histopathology, and natural history and exogenous provocative factors of these conditions.

CORTICOSTEROID-INDUCED ATROPHY

Intradermal or subcutaneous injection of a corticosteroid can produce deep atrophy accompanied by surface pigmentary changes and telangiectasia (Fig. 701.1). These changes occur approximately 2-8 weeks after injection and may last for months.

RAYNAUD PHENOMENON

An exaggerated vascular response to cold temperatures or emotional stress, Raynaud phenomenon is characterized by sudden-onset, sharply demarcated, transient color changes of the skin of the digits (see Chapter 201). This condition can occur as a primary condition or may be associated with an underlying disorder, such as systemic lupus erythematosus (SLE) or systemic sclerosis. It is thought to be caused by abnormal vasoconstriction of the digital blood vessels.

701.1 Panniculitis and Erythema Nodosum

Jacquelyn R. Sink and Yvonne E. Chiu

Inflammation of the fibrofatty subcutaneous tissue may primarily involve the fat lobule (lobular panniculitis) or the fibrous septum that compartmentalizes the fatty lobules (septal panniculitis). Histopathologic evaluation is usually necessary to confirm the diagnosis. Lobular panniculitis that spares the subcutaneous vasculature includes infectious panniculitis, traumatic panniculitis (including cold and post-steroid panniculitis), connective tissue disease panniculitis, pancreatic panniculitis, α_1 antitrypsin deficiency, subcutaneous fat necrosis (SCFN) of the newborn, sclerema neonatorum, subcutaneous sarcoidosis, and factitial panniculitis. Lobular panniculitis associated with vasculitis occurs in erythema induratum and occasionally as a feature of Crohn's disease (see Chapter 382.2). Septal panniculitis, sparing the vasculature, may be seen in erythema nodosum (Table 701.1 and Fig. 701.2), necrobiosis lipoidica, progressive systemic sclerosis (see Chapter 201), and subcutaneous granuloma annulare (see Chapter 700). Septal panniculitis that includes inflammation of the vessels is found primarily in leukocytoclastic vasculitis and polyarteritis nodosa (see Chapter 210).

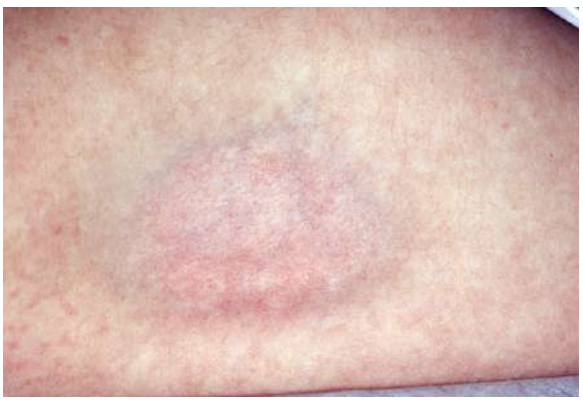

Fig. 701.1 Localized fat atrophy with overlying erythema after steroid injection.

ERYTHEMA NODOSUM

Etiology and Pathogenesis

No underlying cause is found in 30–50% of pediatric cases of erythema nodosum; Table 701.1 lists numerous potential etiologies. The most common etiology in children is group A β-hemolytic streptococcal infection. Other causes include *Yersinia enterocolitica* gastroenteritis, medications (cephalosporins, penicillins, macrolides), and inflammatory disorders (inflammatory bowel disease); sarcoidosis should be considered in young adults.

Clinical Manifestations

Erythema nodosum is a nodular erythematous hypersensitivity reaction that typically appears as multiple lesions on the lower legs (favoring the pretibial area) and less often in other areas, including the extensor surfaces of the arms and thighs. The lesions vary in size from 1 to 6 cm and are symmetric and oval, with the longer axis parallel to the extremity. Lesions initially appear bright or dull red but progress to a brown or purple; they are painful and usually do not ulcerate (see Fig. 701.2). Initial lesions may resolve in 1-2 weeks, but new lesions may continue to appear for 2-6 weeks. Repeat episodes may occur over weeks to months. Before or immediately at the onset of lesions, there may be systemic manifestations, including fever, malaise, arthralgias (50–90%), and rheumatoid factor–negative arthritis.

Histology

A septal panniculitis occurs acutely with thickening of the septa and an inflammatory cell infiltrate composed of neutrophils. Monocytes and histiocytes predominate in chronic erythema nodosum.

Treatment

Treatment is directed at the underlying cause. Nonsteroidal antiinflammatory agents (ibuprofen, naproxen, salicylates) may be prescribed for symptomatic relief, along with bed rest and leg elevation. Supersaturated solution of potassium iodide (oral), colchicine, and intralesional corticosteroids can be considered as alternative treatments for persistent symptoms. Oral steroids have been employed for the treatment of severe, persistent, or recurrent lesions. The idiopathic form

Table 701.1 Etiology of Erythema Nodosum

VIRUSES
Epstein-Barr, hepatitis B, mumps
FUNGI
Coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis, *Trichophyton mentagrophytes*
BACTERIA AND OTHER INFECTIOUS AGENTS
Group A streptococcus,* tuberculosis,* *Yersinia, Shigella, Escherichia coli,* cat-scratch disease, leprosy, leptospirosis, tularemia, mycoplasma, Whipple disease, lymphogranuloma venereum, psittacosis, brucellosis, meningococcosis, neisserial infection, syphilis
OTHER
Sarcoidosis, inflammatory bowel disease,* estrogen-containing oral contraceptives,* systemic lupus erythematosus, Behçet syndrome, severe acne, celiac disease, Hodgkin disease, lymphoma, sulfonamides, bromides, echinacea, Sweet syndrome, pregnancy, idiopathic*

*Common.

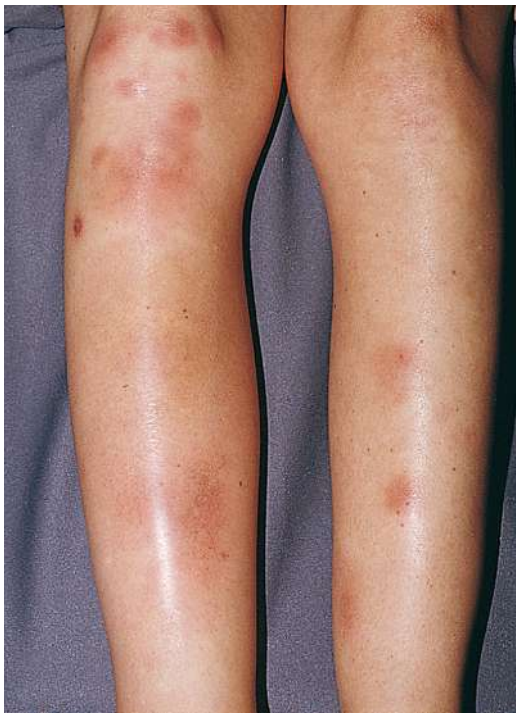

Fig. 701.2 Tender red nodules with indistinct borders in a teenage girl with erythema nodosum. *(From Weston WL, Lane AT, Morelli J. Color Textbook of Pediatric Dermatology, 3rd ed. St. Louis: Mosby; 2002, p. 212.)*

is a self-limited disorder. Protracted or recurrent cases may warrant further workup, including antistreptolysin O/deoxyribonuclease ASO/(DNase) B titer, complete blood count (CBC), throat culture, QuantiFERON-TB gold assay but not a tuberculosis (TB) skin test, chest radiograph, erythrocyte sedimentation rate, and C-reactive protein.

POST-STEROID PANNICULITIS

Etiology and Pathogenesis

The mechanism of the inflammatory reaction in the fat in post-steroid panniculitis is unknown.

Clinical Manifestations

Most cases of post-steroid panniculitis have been reported in children. The disorder occurs in children who have received high-dose corticosteroids, particularly after rapid discontinuation. Within 1-2 weeks after discontinuation of the drug, multiple subcutaneous nodules usually appear on the cheeks, although other areas may be involved. Nodules range in size from 0.5 to 4.0 cm, are erythematous or skin-colored, and may be pruritic or painful.

Histology

A lobular panniculitis is seen with a mixed infiltrate of lymphocytes, histiocytes, and neutrophils. Scattered, swollen adipocytes with eosinophilic, needle-shaped crystals are also seen. The epidermis, dermis, and fibrous septa of the fat are normal. Vasculitis is not seen.

Treatment

Treatment of post-steroid panniculitis is unnecessary because the lesions remit spontaneously over a period of months without scarring.

LUPUS ERYTHEMATOSUS PROFUNDUS (LUPUS ERYTHEMATOSUS PANNICULITIS)

Etiology and Pathogenesis

The pathophysiology of lupus erythematosus profundus is largely unknown. This variant of chronic cutaneous lupus erythematosus is rare in childhood. Only 2–5% of patients with lupus erythematosus profundus have associated SLE. It can occur in association with other forms of cutaneous lupus or as an isolated condition. The mean age of onset in reported pediatric cases is 9.8 years.

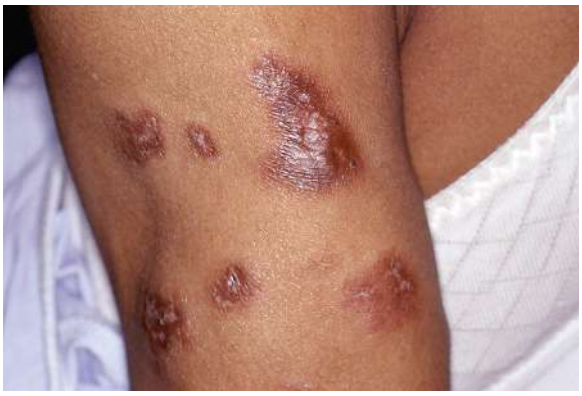

Fig. 701.3 Deep nodule of lupus profundus with overlying hyperkeratotic lesion of discoid lupus erythematosus.

Clinical Manifestations

Lupus erythematosus profundus manifests as one to several firm, tender, well-defined, purple plaques or nodules 1-3 cm in diameter. Most pediatric cases involve the head/neck and proximal extremities. This condition may precede or follow the development of other cutaneous lesions and/or SLE. The overlying skin is usually normal but may be erythematous, atrophic, poikilodermatous, ulcerated, or hyperkeratotic (Fig. 701.3). On healing, a shallow depression generally remains or, rarely, soft pink areas of anetoderma result.

Histology

The histopathologic changes in lupus erythematosus profundus are distinctive and may allow the clinician to make the diagnosis in the absence of other cutaneous features of lupus erythematosus. The panniculitis is characterized by a mostly nodular, dense infiltrate of lymphocytes and plasma cells. Necrosis of the fat lobule is characteristic. A dense perivascular and periappendiceal lymphocytic infiltrate is seen in the dermis. Lichenoid changes may be identified at the epidermal-dermal junction. Histopathologic differentiation from subcutaneous panniculitis–like T-cell lymphoma may be difficult and requires T-cell rearrangement studies.

Treatment

Nodules tend to be persistent and frequently ulcerate. Long-term follow-up to evaluate for systemic disease is warranted; approximately 5–10% of patients with lupus erythematosus profundus will have SLE. There is no consensus on the utility of laboratory testing. Antinuclear antibody is positive in only a small subset of patients. A few case reports show slight neutropenia, leukopenia, and mildly elevated liver function tests. Hydroxychloroquine (2-5 mg/kg/day) is the treatment of choice for lupus erythematosus profundus. Systemic corticosteroids may be helpful, but topical corticosteroids are typically ineffective. Intralesional corticosteroids may worsen the lipoatrophy and lead to ulceration. Immunosuppressive agents are indicated only for the treatment of other severe manifestations of SLE. Avoidance of sun exposure and trauma is also important.

α_1-ANTITRYPSIN DEFICIENCY

Etiology and Pathogenesis

Individuals with α_1-antitrypsin deficiency have severe homozygous deficiency (ZZ genotype) or, rarely, a partial deficiency of the protease inhibitor α_1-antitrypsin, which inhibits trypsin activity and the activity of elastase, serine proteases, collagenase, factor VIII, and kallikrein (see Chapter 442). Panniculitis is rare and usually occurs with severe α_1-antitrypsin deficiency.

Clinical Manifestations

Cellulitis-like areas or one or more warm, tender, red nodules occur on the trunk or proximal extremities. Nodules tend to ulcerate

spontaneously and discharge an oily yellow fluid. Panniculitis may be associated with other manifestations of the disease, such as panacinar emphysema, noninfectious hepatitis, cirrhosis, persistent cutaneous vasculitis, cold contact urticaria, and acquired angioedema. Diagnosis can be substantiated by a decreased level of serum α_1-antitrypsin activity.

Histology
Extensive septal and lobular neutrophilic infiltrate with necrosis of the fat is observed.

Treatment
Panniculitis associated with α_1-antitrypsin deficiency typically resolves over several weeks after treatment with intravenous exogenous enzyme replacement therapy.

PANCREATIC PANNICULITIS
Etiology and Pathogenesis
The pathogenesis of pancreatic panniculitis appears to be multifactorial, involving liberation of the lipolytic enzymes lipase, trypsin, and amylase into the circulation, which leads to adipocyte membrane damage and intracellular lipolysis. There is no correlation, however, between the occurrence of panniculitis and the serum concentration of pancreatic enzymes.

Clinical Manifestations
Pancreatic panniculitis manifests most commonly on the pretibial regions, thighs, or buttocks as tender, erythematous nodules that may be fluctuant and occasionally discharge an oily brown or yellowish liquid. It appears most often in males with alcoholism but may also occur in patients with pancreatitis because of cholelithiasis or abdominal trauma, rupture of pancreatic pseudocysts, pancreatic ductal adenocarcinoma, or pancreatic acinar cell carcinoma. Associated features may include polyarthritis **(pancreatitis-panniculitis-polyarthritis syndrome)**. In almost 65% of patients, abdominal signs are absent or mild, making the diagnosis difficult.

Histology
Characteristic histopathologic changes include lobular panniculitis with necrosis of fat cells and ghost cells with thick, shadowy walls and no nuclei.

Treatment
The primary pancreatic disorder must be treated. The arthritis may be chronic and responds poorly to treatment with nonsteroidal antiinflammatory drugs and oral corticosteroids.

SUBCUTANEOUS FAT NECROSIS
Etiology and Pathogenesis
SCFN in infants may be a result of ischemic injury from various perinatal complications, such as maternal preeclampsia, birth trauma, asphyxia, meconium aspiration, and prolonged hypothermia. Whole-body cooling for neonatal hypoxemic-ischemic encephalopathy is increasingly associated with SCFN. Susceptibility is attributed to differences in composition between the subcutaneous tissue of young infants and that of older infants, children, and adults. Neonatal fat solidifies at a relatively high temperature because of its relatively greater concentration of high-melting-point saturated fatty acids, such as palmitic and stearic acids.

Clinical Manifestations
This benign, self-limited inflammatory disorder of adipose tissue occurs primarily in the first few days to weeks of life in apparently healthy, full-term or postterm infants. Some lesions may be present at birth. Typical lesions are asymptomatic, indurated, erythematous to violaceous, sharply demarcated plaques or nodules located primarily on the cheeks, buttocks, back, thighs, or upper arms (Fig. 701.4). Lesions may be focal or extensive and are generally asymptomatic, although they may be tender during the acute phase. Uncomplicated

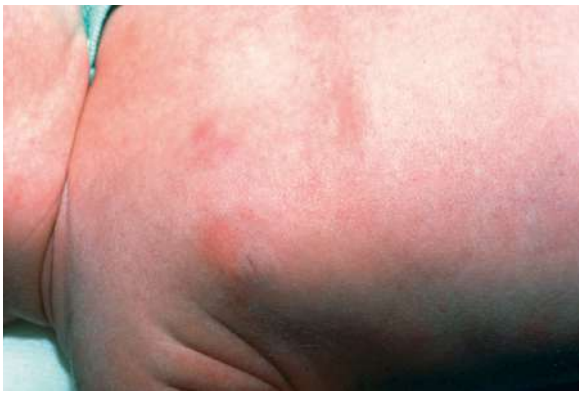

Fig. 701.4 Red-purple nodular infiltration of the skin of the chest caused by subcutaneous fat necrosis.

lesions involute spontaneously within weeks to months, usually without scarring or atrophy. Calcium deposition may occasionally occur within areas of fat necrosis, which may sometimes result in rupture and drainage of liquid material. These areas may heal with atrophy. A potentially serious complication of SCFN is **hypercalcemia**. It typically manifests before 2 months of age, but can present up to 6 months of age, with lethargy, poor feeding, vomiting, failure to thrive, irritability, seizures, shortening of the QT interval on electrocardiography, and/or renal failure. The origin of the hypercalcemia is unknown, but an accepted hypothesis is that macrophages produce 1,25-dihydroxyvitamin D_3 which, in turn, increases calcium uptake. Infants with SCFN should be monitored for several months after lesion resolution for delayed-onset hypercalcemia.

Histology
Histopathologic changes in SCFN are diagnostic, consisting of necrosis of fat; a granulomatous cellular infiltrate composed of lymphocytes, histiocytes, multinucleated giant cells, and fibroblasts; and radially arranged clefts of crystalline triglyceride within fat cells and multinucleated giant cells. Calcium deposits are commonly found in areas of fat necrosis.

Differential Diagnosis
SCFN can be confused with sclerema neonatorum, panniculitis, cellulitis, and hematoma.

Treatment
Because the lesions are self-limited, therapy is not required for uncomplicated cases of SCFN. Needle aspiration of fluctuant lesions may prevent rupture and subsequent scarring but is rarely needed. Treatment of hypercalcemia is aimed at enhancing renal calcium excretion with hydration and furosemide (1-2 mg/kg/dose) and at limiting dietary intake of calcium and vitamin D. Reduction of intestinal calcium absorption and alteration of vitamin D metabolism may be accomplished by administering corticosteroids (0.5-1.0 mg/kg/day). Bisphosphonates have been used in severe cases.

SCLEREMA NEONATORUM
Etiology and Pathogenesis
Although the cause of sclerema neonatorum remains unknown, multiple theories have been proposed. The hardening of the subcutaneous fat may occur as a response to a decrease in body temperature because of circulatory shock, a defect in lipolytic enzymes or in lipid transport, association with an underlying severe disease, or a special form of edema affecting the connective tissue supporting the adipocytes.

Clinical Manifestations
This uncommon panniculitis manifests abruptly in preterm, gravely ill infants as diffuse, yellowish white, woody indurations of the skin. It begins on the legs and buttocks and then quickly progresses to other areas, sparing the palms and soles. Affected skin becomes stony in

consistency, cold, and nonpitting. The face assumes a masklike expression, and joint mobility may be compromised because of inflexibility of the skin.

Histology
Histopathologic changes in sclerema neonatorum consist of increased size of fat cells and width of the fibrous connective tissue septa. In contrast to SCFN, fat necrosis, inflammation, giant cells, and calcium crystals are generally absent.

Treatment
Sclerema neonatorum is almost always associated with serious illness, such as sepsis, congenital heart disease, multiple congenital anomalies, or hypothermia. The appearance of sclerema in a sick infant should be regarded as an ominous prognostic sign. There is no specific therapy for the condition. The outcome depends on the response of the underlying disorder to treatment.

COLD PANNICULITIS
Etiology and Pathogenesis
The pathogenic mechanism of cold panniculitis may be likened to that of SCFN, involving a greater propensity of fat to solidify in infants than in older children and adults because of the higher percentage of saturated fatty acids in the subcutaneous fat of infants. Lesions occur in infants after prolonged cold exposure, especially on the cheeks, or after prolonged application of a cold object such as an ice cube, ice bags, cooling blankets, or popsicles to any area of the skin.

Clinical Manifestations
Ill-defined, erythematous to bluish, painful, indurated plaques or nodules arise within hours to a few days in areas exposed to cold (face, arms, legs); the lesions persist for 2-3 weeks and heal without residua.

Histology
Histopathologic examination reveals an infiltrate of lymphoid and histiocytic cells around blood vessels at the dermal-subdermal junction and in the fat lobules; by the third day, some of the fat cells in the subcutis may have ruptured and coalesced into cystic structures.

Differential Diagnosis
Cold panniculitis may be confused with facial cellulitis caused by *Haemophilus influenzae* type b. As opposed to buccal cellulitis, the area may be cold to the touch, and the patient is afebrile and appears well. **Familial cold autoinflammatory syndrome** manifests with urticaria on exposure to cold environments; associated features include conjunctivitis, myalgias, fatigue, and elevated inflammatory markers. **Cold urticaria**, in contrast, occurs on direct contact with cold objects, resulting in urticaria at the site, which can be reproduced with the ice cube test.

Treatment
Treatment is unnecessary because cold panniculitis resolves spontaneously. Recurrence of the lesions is common, emphasizing the importance of parental education.

CHILBLAINS (PERNIO)
Etiology and Pathogenesis
Vasospasm of arterioles from damp cold exposure with resultant hypoxemia and localized perivascular mononuclear inflammation appears to be responsible for chilblains (see Chapter 90). The disease is most commonly idiopathic but may be associated with cryoglobulins, antiphospholipid antibodies, anorexia nervosa, or a thin body habitus. There are reports of chilblain-like rash occurring during the COVID-19 pandemic.

Clinical Manifestations
The condition is characterized by initial blanching followed by localized, symmetric, erythematous to violaceous, edematous plaques and nodules in areas exposed to cold, typically acral sites (distal hands and feet, ears, face). Lesions develop 12-24 hours after cold exposure and may be associated with numbness, tingling, itching, burning, or pain. Blister formation and ulceration are rare (see Chapter 90).

Histology
Histopathologic examination reveals marked dermal edema and a perivascular and periappendiceal, predominantly T-cell lymphocytic infiltrate in the papillary and reticular dermis.

Differential Diagnosis
Raynaud phenomenon is a more acute condition than chilblains, with characteristic color changes and no chronic lesions. Frostbite due to extreme cold exposure is painful and involves freezing of the tissue, with resultant tissue necrosis.

Treatment
Most cases of chilblains resolve spontaneously, but the condition can last up to 2-3 weeks. Prevention is the treatment of choice. Nifedipine (0.25-0.5 mg/kg 3 times a day, maximum 10 mg/dose) may be used in severe cases. Unusual or persistent cases of perniosis in children may warrant further workup, including antinuclear antibody titer, cryoglobulins, antiphospholipid antibodies, CBC with differential, and cold agglutinins.

FACTITIAL PANNICULITIS
Etiology and Pathogenesis
Factitial panniculitis results from subcutaneous injection of a foreign substance by the patient or a proxy. The most common substances are organic materials such as milk and feces; drugs, such as the opiates and pentazocine; oily materials, such as mineral oil and paraffin; and the synthetic polymer povidone.

Clinical Manifestations
Indurated plaques, ulcers, or nodules that liquefy and drain may be noted clinically in factitial panniculitis.

Histology
The histopathology is variable, depending on the injected substance, but may include the presence of birefringent crystals, oil cysts surrounded by fibrosis and inflammation, and an acute inflammatory reaction with fat necrosis. Vessels are characteristically spared.

Treatment
Treatment of factitial panniculitis must address the primary reason for the performance of this self-destructive act. Munchausen syndrome by proxy should be considered in young children (see Chapter 17.2).

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701.2 Lipodystrophy
Leah Lalor

Lipodystrophies are conditions that share a common finding of reduction in subcutaneous fat, often with accompanying lipohypertrophy in other areas. They may be inherited or acquired. Several lipodystrophy syndromes have been described, which are extremely rare disorders of deficient body fat associated with many metabolic complications. Lipoatrophy is selective loss of fat (whereas lipodystrophy is redistribution of fat) and is associated with medications, HIV infection, trauma or pressure, autoimmune disorders, and after inflammation of fat.

Lipodystrophies are defined by etiology (congenital or acquired) and distribution of fat loss (generalized or partial). This results in four main types of lipodystrophy: congenital generalized lipodystrophy, familial partial lipodystrophy, acquired generalized lipodystrophy, and acquired partial lipodystrophy.

GENERALIZED LIPODYSTROPHY
Generalized lipodystrophy may be congenital or acquired and is characterized by loss of fat affecting the whole body.

Congenital generalized lipodystrophy (CGL): This is an autosomal recessive disorder characterized by nearly complete lack of subcutaneous fat starting at birth or in infancy with prominent musculature, phlebomegaly, acanthosis nigricans, hepatomegaly, umbilical prominence, and voracious appetite in childhood. There are several known genetic causes, each with unique clinical features. Metabolic complications are frequent and may be severe.

Acquired generalized lipodystrophy (AGL): This typically presents before adolescence with progressive fat loss of the whole body, including palms and soles, and is more common in females (3:1 female:male). There may be fat accumulation in the face, neck, and/or axillae. There are frequent and often severe metabolic complications, and this is associated with autoimmune disease.

PARTIAL LIPODYSTROPHY

Partial lipodystrophy is when part of the body has loss of fat with frequent excess fat accumulation elsewhere in the body. It may be inherited or acquired.

Familial partial lipodystrophy (FPLD): This is a group of autosomal dominant disorders in which fat loss affects the limbs, buttocks, and hips with excess fat accumulation in other areas dependent on particular subtype. Fat distribution is often normal in childhood with development of progressive loss of fat around puberty. There is often associated muscular hypertrophy and metabolic complications in adulthood, particularly cardiac.

Acquired partial lipodystrophy (APL): As in AGL, this is more common in females (4:1 female:male) and begins in childhood with progressive loss of fat in a cranial-to-caudal distribution. Fat accumulation may appear in the hips, buttocks, and legs. Metabolic complications are uncommon, but it is associated with autoimmune diseases, in particular, membranoproliferative glomerulonephritis.

Diagnosis

Diagnosis of lipodystrophy is based on history, physical examination, body composition, and metabolic status, and confirmatory genetic testing may be helpful in suspected familial cases, but formal diagnostic criteria have not been established. Lipodystrophy should be suspected in patients with regional or generalized lack of adipose tissue outside the normal range and in children with failure to thrive. Additional physical features include prominent muscles and veins; severe acanthosis nigricans; eruptive xanthomas; and Cushingoid, acromegaloid, or progeroid appearance. Familial forms can be suspected when there is a clear familial pattern.

Differential diagnosis includes other conditions that present with severe weight loss, including malnutrition, eating disorders, uncontrolled diabetes mellitus, thyrotoxicosis, adrenocortical deficiency, cancer cachexia, HIV-associated wasting, and chronic infections.

Screening for Comorbidities

Metabolic comorbidities are common in many forms of lipodystrophy, and all patients should be screened for dyslipidemia, diabetes, nonalcoholic fatty liver disease, and cardiovascular and reproductive dysfunction. Those with APL are at lower risk for metabolic issues.

Dyslipidemia: Triglycerides should be measured at least annually and with new-onset abdominal pain or appearance of cutaneous xanthomas. Fasting lipid panel should be measured at diagnosis and yearly after age 10 years.

Diabetes mellitus: Screening should be formed annually following the guidelines of the American Diabetes Association, which includes fasting plasma glucose, oral glucose tolerance test, or glycosylated hemoglobin.

Liver disease: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be measured yearly with liver ultrasound performed at diagnosis and then clinically as indicated based on symptoms or laboratory abnormalities. Liver biopsy should be performed as indicated clinically.

Reproductive dysfunction: Early adrenarche, true precocious puberty, or central hypogonadism may occur in children with generalized lipodystrophy, and oligo/amenorrhea, decreased fertility, and polycystic ovary syndrome are common in women with lipodystrophy. Measurement of gonadal steroids and gonadotropins, and pelvis ultrasonography should be performed as clinically indicated with pubertal staging performed annually for children.

Cardiac disease: Hypertension is common in lipodystrophy syndromes, even in children. Blood pressure should be measured at least yearly. ECG and echocardiogram should be done yearly in CGL and progeroid disorders and at diagnosis and as clinically indicated in FPLD and AGL.

Kidney disease: Protenuria is common. Urine protein should be measured yearly using 24-hour collection or spot urine protein-to-creatinine ratio. Kidney biopsy should be done as indicated clinically.

Malignancy: Lymphomas occur in AGL. Appropriate screening has not been established but could include yearly skin and lymph node exam. Generalized lipodystrophy has been reported as a paraneoplastic phenomenon in pilocytic astrocytoma in some children who recovered body fat after treatment. Some progeroid syndromes are associated with increased malignancy risk.

Treatment of Lipodystrophy

There is no cure for lipodystrophy, and no treatment that can regrow lost adipose tissue; however, there are some ways to prevent or improve the associated comorbidities. Diet is the cornerstone of therapy for the metabolic complications of lipodystrophies, and a dietician should be consulted for children with these diagnoses. Medium-chain triglyceride oil formulas can provide energy and reduce triglycerides in infants. Most patients with lipodystrophy should be encouraged to be physically active, though some should have a cardiac evaluation before engaging in an intense exercise regimen.

Metreleptin is recombinant human methionyl leptin and is the only approved medication for lipodystrophy. It is a first-line treatment for metabolic and endocrine abnormalities in generalized lipodystrophy and may be used for prevention of these complications in children. Treatment for specific metabolic complications can be reviewed elsewhere.

Consideration should be given to referral to plastic surgeons and/or cosmetic dermatologists for patients with distress related to their body appearance. Mental health professionals may also be helpful.

HIV/ART-ASSOCIATED LIPODYSTROPHY

This is the most common form of *nonlocalized* lipodystrophy and is linked to protease inhibitors and nucleoside analogue reverse transcriptase inhibitors. It may affect up to 40% of patients within 1-2 years of antiretroviral therapy (ART) initiation. Typical manifestations include lipoatrophy of peripheral sites (face, limbs, heel pads, buttocks), central lipohypertrophy (particularly dorsocervical, supraclavicular, breast, intraabdominal, and visceral), and metabolic abnormalities (insulin resistance, type 2 diabetes mellitus, dyslipidemia, hypertension, lactic acidosis). These changes are progressive and largely irreversible, can be disfiguring and stigmatizing, and may result in a lack of adherence to treatment.

LOCALIZED LIPOATROPHY

Localized lipoatrophy can be idiopathic or secondary to subcutaneous medication injections, pressure, and panniculitis. Unlike generalized or partial lipodystrophy, localized lipoatrophy involves a small part of the body and has no accompanying metabolic derangements. Idiopathic and pressure-induced lipoatrophy manifest as annular atrophy at the ankles; a bandlike semicircular depression 2-4 cm in diameter on the thighs, abdomen, and/or upper groin; or a centrifugally spreading, depressed, bluish plaque with an erythematous margin. Medication-induced lipoatrophy is most common with insulin and injected corticosteroids, though others have been reported. **Insulin lipoatrophy** usually occurs approximately 6 months to 2 years after the initiation of relatively high doses of insulin. A dimple or well-circumscribed depression at or surrounding the site of injection is typically seen. Lesions may be prevented by frequent rotation of injection sites or a switch to insulin pump.

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Chapter 702

Disorders of the Sweat Glands

Kari L. Martin

Eccrine glands are found over nearly the entire skin surface and provide the primary means, through evaporation of the water in sweat, of cooling the body. These glands, which have no anatomic relationship to hair follicles, secrete a relatively large amount of odorless aqueous sweat. In contrast, apocrine sweat glands are limited in distribution to the axillae, anogenital skin, mammary glands, ceruminous glands of the ear, Moll glands in the eyelid, and selected areas of the face and scalp. Each apocrine gland duct enters the pilosebaceous follicle at the level of the infundibulum and secretes a small amount of a complex, viscous fluid that, on alteration by microorganisms, produces a distinctive body odor. Some disorders of these two types of sweat glands are similar pathogenetically, whereas others are unique to a given gland.

ANHIDROSIS

Neuropathic anhidrosis results from a disturbance in the neural pathway from the control center in the brain to the peripheral efferent nerve fibers that activate sweating. Disorders in this category, which are characterized by generalized anhidrosis, include **congenital insensitivity to pain with anhidrosis (CIPA)**, tumors of the hypothalamus, and damage to the floor of the third ventricle. Pontine or medullary lesions may produce anhidrosis of the ipsilateral face or neck and ipsilateral or contralateral anhidrosis of the rest of the body. Peripheral or segmental neuropathies, caused by leprosy, amyloidosis, diabetes mellitus, alcoholic neuritis, or syringomyelia, may be associated with anhidrosis of the innervated skin. Various autonomic disorders are also associated with altered eccrine sweat gland function.

At the level of the sweat gland, anticholinergics (drugs such as atropine and scopolamine) may paralyze the sweat glands. Acute intoxication with barbiturates or diazepam has produced necrosis of sweat glands, resulting in anhidrosis with or without erythema and bullae. Eccrine glands are largely absent throughout the skin or are present in a localized area among patients with **hypohidrotic ectodermal dysplasia (HED)** or **localized congenital absence of sweat glands**, respectively. Infiltrative or destructive disorders that may produce atrophy of sweat glands by pressure or scarring include scleroderma, acrodermatitis chronica atrophicans, radiodermatitis, burns, Sjögren syndrome, multiple myeloma, and lymphoma. Obstruction of sweat glands may occur in miliaria and in a number of inflammatory and hyperkeratotic disorders, such as the ichthyoses, psoriasis, lichen planus, pemphigus, porokeratosis, atopic dermatitis, and seborrheic dermatitis. Occlusion of the sweat pore may also occur with the topical agents aluminum and zirconium salts, formaldehyde, or glutaraldehyde.

Diverse disorders that are associated with anhidrosis by unknown mechanisms include dehydration, uremia, cirrhosis, endocrine disorders such as Addison disease, diabetes mellitus, diabetes insipidus, and hyperthyroidism, toxic overdose with lead, arsenic, thallium, fluorine, or morphine, and inherited conditions such as autonomic neuropathies, Fabry disease, Franceschetti-Jadassohn syndrome, which combines features of incontinentia pigmenti and HED, CIPA, and familial anhidrosis with neurolabyrinthitis.

Anhidrosis may be complete, but in many cases, what appears clinically to be anhidrosis is actually hypohidrosis caused by anhidrosis of many, but not all, eccrine glands. Compensatory, localized hyperhidrosis of the remaining functional sweat glands may occur, particularly in diabetes mellitus and miliaria. The primary complication of anhidrosis is *hyperthermia,* seen primarily in anhidrotic ectodermal dysplasia or in otherwise normal preterm or full-term neonates who have immature eccrine glands.

HYPERHIDROSIS

Etiology and Pathogenesis

Hyperhidrosis is excessive sweating beyond what is physiologically necessary for temperature control and occurs in 3% of the population, with about half having axillary hyperhidrosis. The numerous disorders that can be associated with increased production of eccrine sweat may also be classified into those with neural mechanisms involving an abnormality in the pathway from the neural regulatory centers to the sweat gland and those that are nonneurally mediated and occur by direct effects on the sweat glands (Table 702.1).

Clinical Manifestations

The average age at onset of hyperhidrosis is 14-25 years. The excess sweating may be continuous or may occur in response to emotional stimuli. In severe cases, sweat may be seen to drip constantly from the hands.

Treatment

Excessive sweating of the palms and soles (volar hyperhidrosis) and axillary sweating may respond to 20% aluminum chloride in anhydrous ethanol applied under occlusion for several hours, iontophoresis, injection with botulinum toxin, therapy with oral anticholinergics and antimuscarinic drugs (oxybutynin), or in severe, refractory cases, cervicothoracic or lumbar sympathectomy. Reports of successful treatment of hyperhidrosis with ultrasound and microwave technology are available, but studies are faulted with small sample size and/or lack of controls.

MILIARIA

Etiology and Pathogenesis

Miliaria results from retention of sweat in occluded eccrine sweat ducts. The eruption is most often induced by hot, humid weather, but it may also be caused by high fever. Infants who are dressed too warmly may demonstrate this eruption indoors, even during the winter.

Clinical Manifestations

In miliaria crystallina, asymptomatic, noninflammatory, pinpoint, clear vesicles may suddenly erupt in profusion over large areas of the body surface, leaving brawny desquamation on healing (Fig. 702.1). This type of miliaria occurs most frequently in newborn infants because of the relative immaturity and delayed patency of the sweat duct and the tendency for infants to be nursed in relatively warm, humid conditions. It may also occur in older patients with hyperpyrexia or hypernatremia.

Miliaria rubra is a less superficial eruption characterized by erythematous, minute papulovesicles that may impart a prickling sensation. The lesions are usually localized to sites of occlusion or to flexural areas, such as the neck, groin, and axillae, where friction may have a role in their pathogenesis. Involved skin may become macerated and eroded. However, lesions of miliaria rubra are extrafollicular.

Repeated attacks of miliaria rubra may lead to miliaria profunda, which is caused by rupture of the sweat duct deeper in the skin, at the level of the dermal-epidermal junction. Severe, extensive miliaria rubra or miliaria profunda may result in disturbance of heat regulation. Lesions of miliaria rubra may become infected, particularly in malnourished or debilitated infants, leading to development of **periporitis staphylogenes**, which involves extension of the process from the sweat duct into the sweat gland.

Histology

Histologically, miliaria crystallina reveals an intracorneal or subcorneal vesicle in communication with the sweat duct, whereas in miliaria rubra, one sees focal areas of spongiosis and spongiotic vesicle formation in close proximity to sweat ducts that generally contain a keratinous plug.

Table 702.1 Causes of Hyperhidrosis

CORTICAL
- Emotional
- Familial dysautonomia
- Congenital ichthyosiform erythroderma
- Epidermolysis bullosa
- Nail-patella syndrome
- Jadassohn-Lewandowsky syndrome
- Pachyonychia congenita
- Palmoplantar keratoderma
- Stroke

HYPOTHALAMIC

Drugs
- Alcohol
- Antipyretics
- Cocaine
- Emetics
- Insulin
- Opiates (including withdrawal)
- Ciprofloxacin
- Exercise

Infection
- Defervescence
- Chronic illness

Metabolic
- Carcinoid syndrome
- Debility
- Diabetes mellitus
- Hyperpituitarism
- Hyperthyroidism
- Hypoglycemia
- Obesity
- Pheochromocytoma
- Porphyria
- Pregnancy
- Rickets
- Infantile scurvy

Cardiovascular
- Heart failure
- Shock
- Vasomotor
- Cold injury
- Raynaud phenomenon
- Rheumatoid arthritis

Neurologic
- Abscess
- Familial dysautonomia
- Postencephalitic
- Tumor
- Absence of corpus callosum

Miscellaneous
- Chédiak-Higashi syndrome
- Compensatory
- Lymphoma
- Phenylketonuria
- Vitiligo
- Frey syndrome

MEDULLARY
- Physiologic gustatory sweating
- Encephalitis
- Granulosis rubra nasi
- Syringomyelia
- Thoracic sympathetic trunk injury

SPINAL
- Cord transection
- Syringomyelia

CHANGES IN BLOOD FLOW
- Maffucci syndrome
- Arteriovenous fistula
- Klippel-Trénaunay syndrome
- Glomus tumor
- Blue rubber-bleb nevus syndrome

Differential Diagnosis

The clarity of the fluid, superficiality of the vesicles, and absence of inflammation permit differentiation of miliaria crystalline from other blistering disorders. Miliaria rubra may be confused with or superimposed on other diaper area eruptions, including candidiasis and folliculitis.

Treatment

All forms of miliaria respond dramatically to cooling of the patient by regulation of environmental temperatures and by removal of excessive clothing; administration of antipyretics is also beneficial to patients with fever. Topical agents are usually ineffective and may exacerbate the eruption.

BROMHIDROSIS

Bromhidrosis, characterized by excessive odor, may result from alteration of either apocrine or eccrine sweat. Apocrine bromhidrosis develops after puberty as a result of the formation of short-chain fatty acids and ammonia by the action of anaerobic diphtheroids on axillary apocrine sweat. Eccrine bromhidrosis is caused by microbiologic degradation of stratum corneum that has become softened by excessive eccrine sweat. The soles of the feet and the intertriginous areas are the primary affected sites. Hyperhidrosis, warm weather, obesity, intertrigo, and diabetes mellitus are predisposing factors. Treatments that may be helpful include cleansing with germicidal soaps, topical clindamycin or erythromycin, or topical application of aluminum or zirconium. In addition, more invasive surgical and laser treatments have been used. Treatment of any associated hyperhidrosis is mandatory.

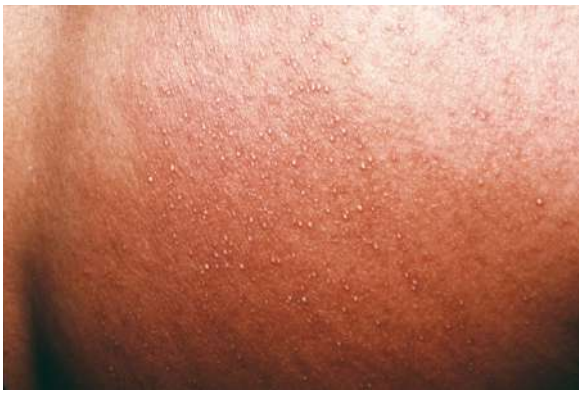

Fig. 702.1 Superficial clear vesicles of miliaria crystallina.

HIDRADENITIS SUPPURATIVA

Etiology and Pathogenesis

Hidradenitis suppurativa (HS) is a disease of the apocrine gland–bearing areas of the skin. The pathogenesis of hidradenitis suppurativa is controversial. It is believed that it is a primary inflammatory disorder of the hair follicle and not solely an alteration of apocrine glands. It is considered a part of the follicular occlusion tetrad, along with acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus. The natural history of the disease involves progressive dilation below the follicular obstruction, leading to rupture of the duct, inflammation, sinus tract formation, and destructive scarring. It has been associated with Sjögren syndrome, inflammatory bowel disease, obesity, smoking, diabetes mellitus, and thyroid disease. It is also known to occur in other family members and may be associated with loss-of-function pathogenic variants in multiple genes in some patients (Fig. 702.2). HS has been one manifestation of autoinflammatory syndromes, including pyoderma gangrenosum-acne-HS (PASH) (*PSTPIP1* promoter), pyoderma gangrenosum-acne-pyogenic arthritis-HS (PAPASH) (*PSTPIP1*), and psoriatic arthritis-pyoderma gangrenosum-acne-HS (PsAPASH).

Clinical Manifestations

HS is a chronic, inflammatory, suppurative disorder of the follicular units in the axillae, anogenital area, and, occasionally, the scalp, posterior aspect of the ears, inframammary folds (female), and periumbilical area (Fig. 702.3). Onset of clinical manifestations is sometimes preceded by pruritus or discomfort and usually occurs during puberty or early adulthood. Solitary or multiple painful erythematous nodules, deep abscesses, and contracted scars are sharply confined to areas of skin containing apocrine glands. When the disease is severe and chronic, sinus tracts, ulcers, and thick, linear fibrotic bands develop. HS tends to persist for many years, punctuated by relapses and partial remissions. Complications include cellulitis, ulceration, and burrowing abscesses that may perforate adjacent structures, forming fistulas to the urethra, bladder, rectum, or peritoneum. Episodic inflammatory arthritis develops in some patients. Obesity and smoking may worsen or trigger symptoms. Patients with HS have an increased risk of adverse cardiovascular outcomes and a long-term risk of squamous cell carcinoma.

The autoinflammatory associated disorders present with fever, joint pain, cutaneous lesions (severe painful acne), and elevated inflammatory markers (ESR, CRP).

Differential Diagnosis

Early lesions of HS are often mistaken for infected epidermal cysts, furuncles, scrofuloderma, actinomycosis, cat-scratch disease, granuloma inguinale, or lymphogranuloma venereum. However, sharp localization to areas of the body that bear apocrine glands should suggest hidradenitis. When involvement is limited to the anogenital region, the condition may be difficult to distinguish from Crohn's disease.

Treatment

Conservative management includes cessation of smoking, weight loss, and avoidance of irritation of the affected area. Warm compresses and topical antiseptic or antibacterial soaps may also be helpful. For mild, early disease, topical clindamycin 1% may be helpful. For more severe disease, therapy may be initiated with doxycycline (100 mg bid) or minocycline (100 mg bid) in adolescents and young adults. Some patients require intermittent or long-term antibiotic treatment. Combination therapy with clindamycin and rifampin is helpful in some patients. Oral retinoids for 5-6 months may also be effective, although disease may recur. Oral contraceptive agents, which contain a high estrogen:progesterone ratio and low androgenicity of the progesterone, are another alternative along with spironolactone. Laser hair ablation has proven helpful in some studies as well. Systemic immunosuppressants (infliximab, adalimumab, cyclosporine, anakinra) and medications targeted at glucose metabolism and metabolic syndrome (metformin) have been helpful in patients resistant to more traditional measures. Adalimumab, a tumor necrosis factor-alpha (TNF-α) inhibitor, is the only FDA-approved medication for the treatment of moderate-to-severe HS. Surgical measures, including deroofing procedures and full excision, may be a helpful adjuvant to medical therapy, especially in recalcitrant cases.

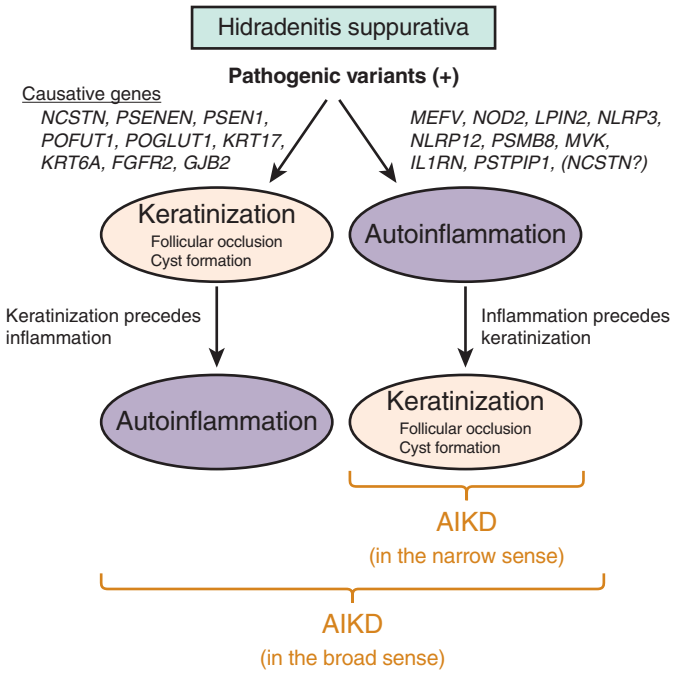

Fig. 702.2 Hidradenitis suppurativa and autoinflammatory keratinization disease (AIKD). Genes responsible for hidradenitis suppurativa can be divided into two groups. One includes *NCSTN, PSENEN, PSEN1, POFUT1, POGLUT1, KRT17, KRT6A, FGFR2,* and *GJB2*, whose pathogenic variants result in autoinflammation preceded by keratinization. This hidradenitis suppurativa subtype can be regarded as an autoinflammatory keratinization disease in the broad sense. The other group includes *MEFV, NOD2, LPIN2, NLRP3, NLRP12, PSMB8, MVK, IL1RN, PSTPIP1,* and possibly *NCSTN*, whose pathogenic variants lead to keratinization preceded by autoinflammation. This hidradenitis suppurativa subtype can be regarded as an autoinflammatory keratinization disease in the narrow sense. *(From Nomura T. Hidradenitis suppurativa as a potential subtype of autoinflammatory keratinization disease. Front Immunol. 2020;11:847, Fig. 1.).*

FOX-FORDYCE DISEASE

Etiology and Pathogenesis

The cause of Fox-Fordyce disease is unknown, but it is related to blockage of apocrine sweat glands.

Clinical Manifestations

This disease is most common in females and manifests during puberty to the third decade of life as pruritus primarily in the axillae, although the areolae, pubic, and perineal regions can also be affected. Pruritus is exacerbated by emotional stress and stimuli that induce apocrine sweating. Dome-shaped, skin-colored to slightly hyperpigmented, follicular papules develop in the pruritic areas.

Treatment

Fox-Fordyce disease is difficult to treat. Oral contraceptive pills and topical treatments, including corticosteroids, antibiotics, or retinoids, may help some patients. Systemic isotretinoin and ablative lasers have shown varying efficacy. Mechanical destruction and removal of apocrine glands have been used in recalcitrant cases. Partial response has been seen in one study using botulinum toxin type A.

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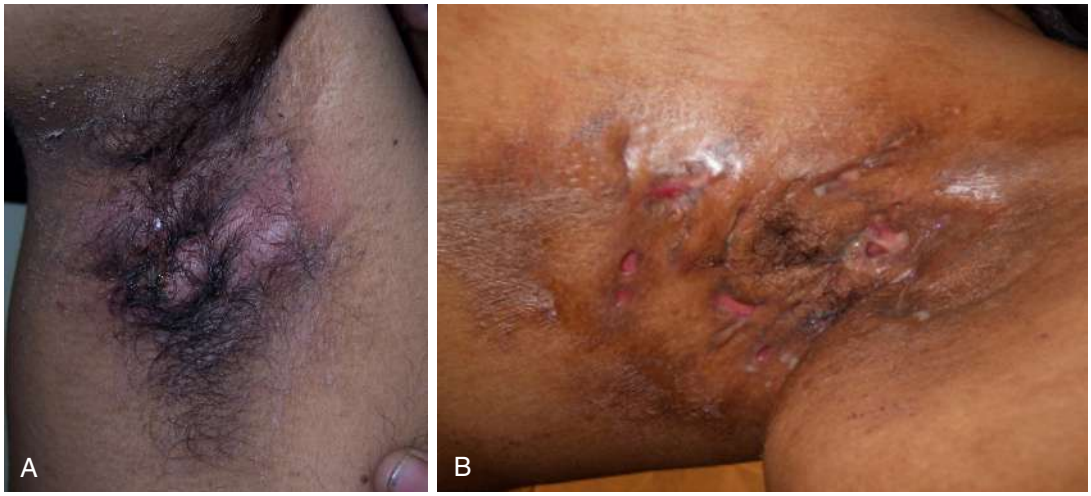

Fig. 702.3 Hidradenitis suppurativa. **A,** This young man had recurrent inflammatory papules and nodulocystic lesions in the axillae and groin for 5 years. Although lesions initially improved with oral antibiotics, he subsequently developed draining sinus tracts. **B,** This young woman had multiple indurated sinus tracts, nodules, and ulcers with purulent and necrotic drainage in her axillae. *(From Rachidi S, Bender AM, Cohen BA. Disorders of the hail and nails. In: Cohen BA, ed. Pediatric Dermatology, 5th ed. Philadelphia: Elsevier; 2022, Fig. 8.42.)*

Chapter 703

Disorders of Hair

Kari L. Martin

Disorders of hair in infants and children may be a result of intrinsic disturbances of hair growth, underlying biochemical or metabolic defects, inflammatory dermatoses, or structural anomalies of the hair shaft. Excessive and abnormal hair growth is referred to as hypertrichosis or hirsutism. **Hypertrichosis** is excessive hair growth at inappropriate locations; **hirsutism** is an androgen-dependent male pattern of hair growth in women (see Chapter 589). **Hypotrichosis** is deficient hair growth. Hair loss, partial or complete, is called **alopecia**. Alopecia may be classified as nonscarring or scarring; the latter type is rare in children and, if present, is most often caused by prolonged or untreated inflammatory conditions such as pyoderma and tinea capitis.

HYPERTRICHOSIS

Hypertrichosis is rare in children and may be localized or generalized and permanent or transient. Tables 703.1 and 703.2 list some of the many causes of hypertrichosis.

HYPOTRICHOSIS AND ALOPECIA

Table 703.3 lists some of the disorders associated with hypotrichosis and alopecia. True alopecia is rarely congenital; it is more often related to an inflammatory dermatosis, mechanical factors, drug ingestion, infection, endocrinopathy, nutritional disturbance, or disturbance of the hair cycle. Any inflammatory condition of the scalp, such as atopic dermatitis or seborrheic dermatitis, if severe enough, may result in partial alopecia. Unless the hair follicle has been permanently damaged, hair growth returns to normal if the underlying condition is treated successfully.

Hair loss in childhood should be divided into the following four categories: congenital diffuse, congenital localized, acquired diffuse, and acquired localized.

Table 703.1 Causes of Hypertrichosis and Associated Conditions

INTRINSIC FACTORS
Racial and familial forms such as hairy ears, hairy elbows, intraphalangeal hair, or generalized hirsutism
EXTRINSIC FACTORS
Local trauma Malnutrition Anorexia nervosa Long-standing inflammatory dermatoses Drugs: Diazoxide, phenytoin, corticosteroids, Cortisporin, cyclosporine, androgens, anabolic agents, hexachlorobenzene, minoxidil, psoralens, penicillamine, streptomycin, danazol, omeprazole, valproic acid
HAMARTOMAS OR NEVI
Congenital pigmented nevocytic nevus, hair follicle nevus, Becker nevus, congenital smooth muscle hamartoma, fawn-tail nevus associated with diastematomyelia
ENDOCRINE DISORDERS
Virilizing ovarian tumors, Cushing syndrome, acromegaly, hyperthyroidism, hypothyroidism, congenital adrenal hyperplasia, adrenal tumors, gonadal dysgenesis, male pseudohermaphroditism, nonendocrine hormone–secreting tumors, polycystic ovary syndrome, pigmentary hypertrichosis with non-autoimmune diabetes mellitus *(SLC29A3)*
CONGENITAL AND GENETIC DISORDERS (SEE TABLE 703.2)

Acquired localized hair loss is the most common type of hair loss in childhood. Three conditions—traumatic alopecia, alopecia areata, and tinea capitis—are predominantly seen (Tables 703.4 and 703.5).

TRAUMATIC ALOPECIA (TRACTION ALOPECIA, HAIR PULLING, TRICHOTILLOMANIA)

Traction Alopecia

Traction alopecia is common and is seen in almost 20% of school-aged females with coily or kinky hair. It is caused by trauma to the hair follicles from tight braids or ponytails, headbands, rubber bands, curlers, weaves, or rollers (Fig. 703.1). There is a greater risk of traction alopecia if hair trauma is combined with chemically relaxed hair. Broken hairs and inflammatory follicular papules in circumscribed patches at the scalp margins are characteristic and may be accompanied by regional lymphadenopathy. Children and parents must be encouraged to avoid devices that cause trauma to the hair and, if necessary, to alter the hairstyle. Otherwise scarring of hair follicles may occur. Treatment with topical phenylephrine, an α_1-adrenergic receptor agonist, facilitates contraction of arrector pili smooth muscle and shows promise in decreasing hair loss and increasing the force needed for epilation.

Hair Pulling

Hair pulling in childhood is usually an acute reactional process related to emotional stress, or it may be a habit (especially in young children). It may also be seen in trichotillomania (obsessive-compulsive disorder) and as part of more severe psychiatric disorders, usually in adolescents.

Table 703.2 Congenital Syndromes Associated with Generalized Hypertrichosis

Acromegaloid facial appearance syndrome (affected genes: *PGM1, GLO1, IGHG3, HP*)
Barber-Say syndrome *(KMT2A)*
Cantú syndrome (hypertrichosis with osteochondrodysplasia) (*ABCC9, KCNJ8*)
Coffin-Siris syndrome (BAF complex genes)
Cornelia de Lange (Brachmann-de Lange) syndrome (*NIPBL, SMC1A, SMC3, RAD21, HDAC8*)
Craniofacial dysostosis
Eye disorders • With amaurosis congenital, cone-rod type • With congenital lamellar cataracts and mental retardation • With pigmentary retinopathy
Gorlin-Chaudhry-Moss (oculo-facio-cardio-dental) syndrome *(BCOR)*
Gingival hyperplasia • Congenital generalized hypertrichosis with gingival hyperplasia • Zimmerman-Laband syndrome
Hemimaxillofacial dysplasia
Lipodystrophies • Berardinelli-Seip syndrome (*BSCL*) • Donohue syndrome (leprechaunism) (*INSR*)
Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome
Mucopolysaccharidoses • Hunter syndrome • Hurler syndrome • Sanfilippo syndrome
Porphyrias • Erythropoietic porphyria (Gunther disease) • Familial porphyria cutanea tarda • Hepatoerythropoietic porphyria
Rubinstein-Taybi syndrome (*CREBBP, EP300*)
Schinzel-Giedion syndrome (*SETBP1* [MAJ359])
Stiff skin syndrome
Toxin exposure • Fetal alcohol syndrome • Fetal hydantoin syndrome
Weidemann-Steiner syndrome (*KMT2A*)
Winchester (Torg-Winchester) syndrome (*MMP2*)

From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022, Box 7.8, p. 191.

Trichotillomania

Etiology and Pathogenesis. The *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5) classifies trichotillomania in the category of obsessive-compulsive and related disorders. The diagnostic criteria for trichotillomania include visible hair loss attributable to pulling; mounting tension preceding or during hair pulling; gratification or release of tension after hair pulling; and absence of hair pulling attributable to hallucinations, delusions, or an inflammatory skin condition.

Clinical Manifestations. Compulsive pulling, twisting, and breaking of hair produces irregular areas of incomplete hair loss, most often on the crown and in the occipital and parietal areas of the scalp. Occasionally eyebrows, eyelashes, and body hair are traumatized. Trichotillomania often begins during periods of inactivity (going to bed, watching TV) and is frequently unobserved by the parents. Some plaques of alopecia may have a linear outline. The hairs remaining within the areas of loss are of various lengths (Fig. 703.2) and are typically blunt-tipped because of breakage. The scalp usually appears normal, although hemorrhage, crusting (Fig. 703.3), and chronic folliculitis may also occur. Long-term repeated trauma may result in irreversible damage and permanent alopecia. Trichophagy, resulting in trichobezoars, may complicate this disorder.

Differential Diagnosis. Acute reactional hair pulling, tinea capitis, and alopecia areata must be considered in the differential diagnosis of trichotillomania (see Tables 703.4 and 703.5).

Treatment. Trichotillomania is closely related to obsessive-compulsive disorder and may be an expression of it for some children. When trichotillomania occurs secondary to obsessive-compulsive disorder, clomipramine 50-150 mg/day or a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine may be helpful, particularly when combined with behavioral interventions (see Chapter 37). *N*-Acetylcysteine may also be helpful.

Table 703.3 Disorders Associated with Alopecia and Hypotrichosis

Congenital total alopecia: Atrichia with papules, Moynahan alopecia syndrome
Congenital localized alopecia: Aplasia cutis, triangular alopecia, sebaceous nevus
Hereditary hypotrichosis: Marie-Unna syndrome, hypotrichosis with juvenile macular dystrophy, hypotrichosis (Mari type), ichthyosis with hypotrichosis, cartilage-hair hypoplasia, Hallermann-Streiff syndrome, trichorhinophalangeal syndrome, ectodermal dysplasia, "pure" hair and nail and other ectodermal dysplasias
Diffuse alopecia of endocrine origin: Hypopituitarism, hypothyroidism, hypoparathyroidism, hyperthyroidism
Alopecia of nutritional origin: Marasmus, kwashiorkor, iron deficiency, zinc deficiency (acrodermatitis enteropathica), gluten-sensitive enteropathy, essential fatty acid deficiency, biotinidase deficiency
Disturbances of the hair cycle: Telogen effluvium
Toxic alopecia: Anagen effluvium
Autoimmune alopecia: Alopecia areata
Traumatic alopecia: Traction alopecia, trichotillomania
Cicatricial alopecia: Lupus erythematosus, lichen planopilaris, pseudopelade, morphea (*en coup de sabre*) dermatomyositis, infection (kerion, favus, tuberculosis, syphilis, folliculitis, leishmaniasis, herpes zoster, varicella), acne keloidalis, follicular mucinosis, sarcoidosis
Hair shaft abnormalities: Monilethrix, pili annulati, pili torti, trichorrhexis invaginata, trichorrhexis nodosa, woolly hair syndrome, Menkes disease, trichothiodystrophy, trichodento-osseous syndrome, uncombable hair syndrome (spun-glass hair, pili trianguli et canaliculi)

ALOPECIA AREATA

Etiology and Pathogenesis

Alopecia areata is a T-cell–driven autoimmune disorder producing nonscarring alopecia. The cause is unknown. It is hypothesized that in genetically susceptible individuals, loss of immune privilege of the hair follicle allows for T-cell inflammation against anagen hairs and follicles, leading to stoppage of hair growth.

Clinical Manifestations

Alopecia areata is characterized by rapid and complete loss of hair in round or oval patches on the scalp (Fig. 703.4), eyebrows, eyelashes, and on other body sites. In alopecia totalis, all the scalp hair is lost (Fig. 703.5); alopecia universalis involves all body and scalp hair. The lifetime incidence of alopecia areata is 0.1–0.2% of the population. More than half of affected patients are younger than 20 years of age.

The skin within the plaques of hair loss appears normal. Alopecia areata is associated with atopy and with nail changes such as pits (Fig. 703.6), longitudinal striations, and leukonychia. Autoimmune diseases such as Hashimoto thyroiditis, Addison disease, pernicious anemia, ulcerative colitis, myasthenia gravis, collagen vascular diseases, and vitiligo may also be seen. An increased incidence of alopecia areata has been reported in patients with Down syndrome (5–10%).

Differential Diagnosis

Tinea capitis, seborrheic dermatitis, trichotillomania, traumatic alopecia, and lupus erythematosus should be considered in the differential diagnosis of alopecia areata (see Tables 703.4 and 703.5).

Treatment

The course is unpredictable, but spontaneous resolution in 6-12 months is usual, particularly when relatively small, stable patches of alopecia are present. Recurrences are common. Onset at a young age, extensive or prolonged hair loss, and numerous episodes are usually poor prognostic signs. Alopecia universalis, alopecia totalis, and alopecia ophiasis (Fig. 703.7)—a type of alopecia areata in which hair loss is circumferential—are also less likely to resolve. Therapy is difficult to evaluate because the course is erratic and unpredictable. The use of highly potent or superpotent topical corticosteroids is effective in

Table 703.4 Helpful Historical Clues in the Diagnosis of Hair Disorders

HISTORICAL CONSIDERATIONS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Are the spots itchy?	Negative	Negative	Positive	Usually negative
Do the spots come and go?	Negative	Sometimes positive	Negative	Sometimes positive
Is the hair falling out in clumps?	Positive	Negative	Negative	Usually negative
Are there any anxiety disorders or obsessive-compulsive tendencies?	Negative	Positive	Negative	Negative

From Lio PA. What's missing from this picture? An approach to alopecia in children. *Arch Dis Child Educ Pract Ed.* 2007;92:193–198.

Table 703.5 Helpful Physical Examination Clues in the Diagnosis of Hair Disorders

PHYSICAL FINDINGS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Scarring?	Negative	Negative	Usually negative	Negative
Exclamation-point hairs?	Negative	Negative	Negative	Positive
Irregular pattern with mixed length and stubbly hairs?	Negative	Positive	Negative	Negative
Scaling, pustules, or kerion?	Negative	Negative	Positive	Negative
Positive hair-pull test result?	Positive	Negative	Negative	Usually negative
Nail pitting or grooves?	Negative	Negative	Negative	Positive

From Lio PA. What's missing from this picture? An approach to alopecia in children. *Arch Dis Child Educ Pract Ed.* 2007;92:193–198.

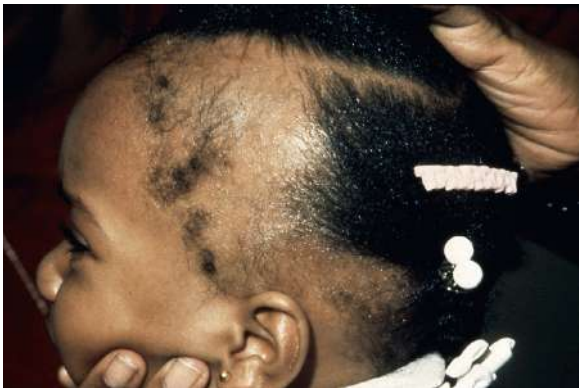

Fig. 703.1 Traction alopecia.

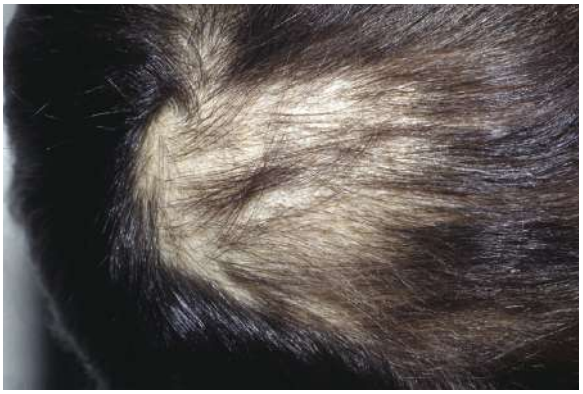

Fig. 703.2 Hair pulling. Hairs are broken off at various lengths.

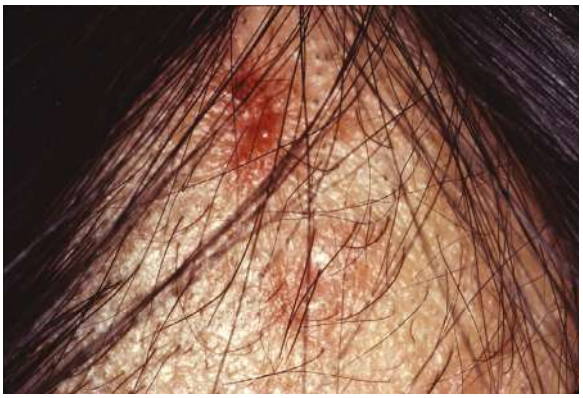

Fig. 703.3 Hemorrhage and crusting secondary to hair pulling.

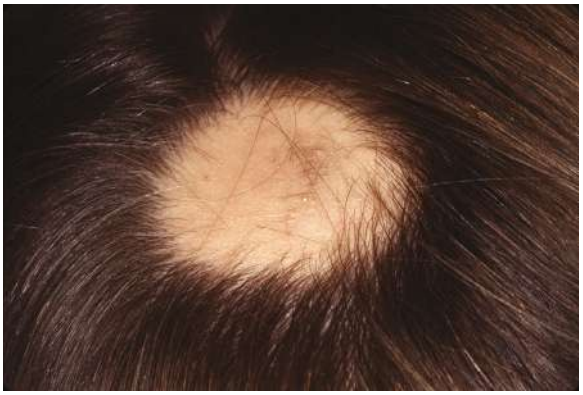

Fig. 703.4 Circular patch of alopecia areata with normal-appearing scalp.

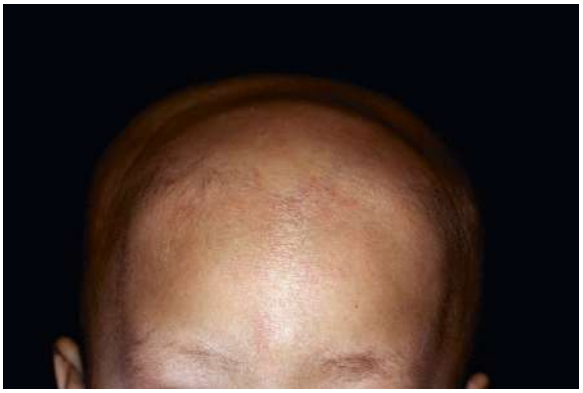

Fig. 703.5 Alopecia totalis: total loss of scalp hair.

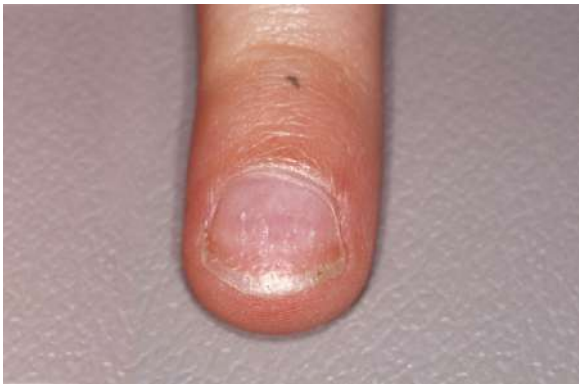

Fig. 703.6 Multiple nail pits in alopecia areata.

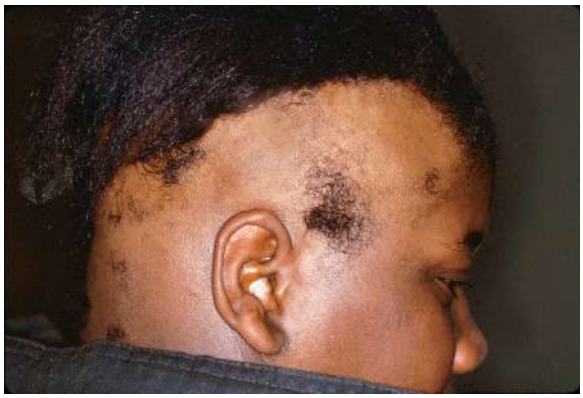

Fig. 703.7 Ophiasis pattern of alopecia areata.

some patients. Intradermal injections of steroid (triamcinolone 5 mg/mL) every 4-6 weeks may also stimulate hair growth locally, but this mode of treatment is impractical in young children or in patients with extensive hair loss. Systemic corticosteroid therapy (prednisone 1 mg/kg/day) is associated with good results; the permanence of cure is questionable, however, and the side effects of chronic oral corticosteroids are a serious deterrent. Some patients may maintain hair growth by switching to a more appropriate long-term immunosuppressant such as methotrexate. Additional therapies that are sometimes effective include short-contact anthralin, topical minoxidil, and contact sensitization with squaric acid dibutylester or diphenylcyclopropenone. Janus kinase inhibitors, both oral and topical, may also be used. In general, parents and patients can be reassured that spontaneous remission of alopecia areata usually occurs. New hair growth may initially be of finer caliber and lighter color, but replacement by normal terminal hair can be expected.

ACQUIRED DIFFUSE HAIR LOSS

Telogen Effluvium

Telogen effluvium manifests as sudden loss of large amounts of hair, often with brushing, combing, and washing of hair. Diffuse loss of scalp hair occurs from premature conversion of growing, or anagen, hairs, which normally constitute 80–90% of hairs, to resting, or telogen, hairs. Hair loss is noted 6 weeks to 3 months after the precipitating cause, which may include childbirth; a febrile episode; surgery; acute blood loss, including blood donation; sudden severe weight loss; discontinuation of high-dose corticosteroids or oral contraceptives; hypothyroidism or hyperthyroidism; and psychiatric stress. Telogen effluvium also accounts for the loss of hair by infants in the first few months of life; friction from bed sheets, particularly in infants with pruritic, atopic skin, may exacerbate the problem. There is no inflammatory reaction; the hair follicles remain intact, and telogen bulbs can be demonstrated microscopically on shed hairs. Because >50% of the scalp hair is rarely involved, alopecia is usually not severe. Parents should be reassured that normal hair growth will return within approximately 3-6 months.

Toxic Alopecia (Anagen Effluvium)

Anagen effluvium is an acute, severe, diffuse inhibition of growth of anagen follicles, resulting in the loss of >80–90% of scalp hair. Hairs become dystrophic, and the hair shaft breaks at the narrowed segment. Loss is diffuse, rapid (1-3 weeks after treatment), and temporary, as regrowth occurs after the offending agent is discontinued. Causes of anagen effluvium include radiation; cancer chemotherapeutic agents such as antimetabolites, alkylating agents, and mitotic inhibitors; thallium; thiouracil; heparin; the coumarins; boric acid; and hypervitaminosis A (see Table 703.6).

Table 703.6 Possible Etiology of Anagen Effluvin

CANCER THERAPY
Chemotherapy
Radiation therapy
TOXIC METAL (SEE CHAPTER 760)
Lead (see Chapter 761)
Mercury
Arsenic (rat, insect poison)
Thallium (rat poison)
Bismuth
TOXIC CHEMICALS
Boric acid (pesticide, cleaning agent)
Warfarin
Colchicine

CONGENITAL DIFFUSE HAIR LOSS

Congenital diffuse hair loss is defined as congenitally thin hair diffusely related to either hypoplasia of hair follicles or to structural defects in hair shafts.

Structural Defects of Hair

Structural defects of the hair shaft may be congenital, reflect known biochemical aberrations, or be related to damaging grooming practices. All the defects can be demonstrated by microscopic examination of affected hairs, particularly with scanning and transmission electron microscopy, although many can even be seen by simple trichography done in the office.

Trichorrhexis Nodosa

Congenital trichorrhexis nodosa is an autosomal dominant condition. The hair is dry, brittle, and lusterless, with irregularly spaced, grayish white nodes on the hair shaft. Microscopically, the nodes have the appearance of two interlocking brushes (Fig. 703.8A). The defect results from a fracture of the hair shaft at the nodal points caused by disruption of the cells in the hair cortex. Trichorrhexis nodosa has also been observed in some infants with Menkes syndrome, trichothiodystrophy, citrullinemia, and argininosuccinic aciduria.

Acquired Trichorrhexis Nodosa

Acquired trichorrhexis nodosa, the most common cause of hair breakage, occurs in two forms. Proximal defects are found most frequently in children with coily or kinky hair, whose complaint is not of alopecia but of failure of the hair to grow. The hair is short, and longitudinal splits, knots, and whitish nodules can be demonstrated in hair mounts. Easy breakage is demonstrated by gentle traction on the hair shafts. A history of other affected family members may be obtained. The problem may be caused by a combination of genetic predisposition and the cumulative mechanical trauma of rough combing and brushing, hair-straightening procedures, and "permanents." Patients must be cautioned to avoid damaging grooming techniques. A soft, natural-bristle brush and a wide-toothed comb should be used. The condition is self-limited, with resolution in 2-4 years, if patients avoid damaging practices. Distal trichorrhexis nodosa is seen more frequently in children with loose curly or straight hair types. The distal portion of the hair shaft is thinned, ragged, and faded; white specks, sometimes mistaken for nits, may be noted along the shaft. Hair mounts reveal the paintbrush defect and the sites of excessive fragility and breakage. Localized areas of the moustache or beard may also be affected. Avoidance of traumatic grooming, regular trimming of affected ends, and the use of cream rinses to lessen tangling ameliorate this condition.

Pili Torti

Patients with pili torti present with spangled, brittle, coarse hair of different lengths over the entire scalp. There is a structural defect in which the hair shaft is grooved and flattened at irregular intervals and is twisted on its axis to various degrees. Minor twists that occur in normal hair should not be misconstrued as pili torti. Curvature of the hair follicle apparently leads to the flattening and rotation of the

Fig. 703.8 A, Microscopic hair fracture in trichorrhexis nodosa. B, Beading of hair in monilethrix. C, Cuplike abnormality of hair in Netherton syndrome.

hair shaft. The genetic defect in isolated pili torti is unknown, and both autosomal dominant and recessive forms have been described. Syndromes in which the hair shaft abnormalities of pili torti are seen in association with other cutaneous and systemic abnormalities include Menkes kinky hair syndrome, Björnstad syndrome (pili torti with deafness; *BCS1L* gene), and multiple ectodermal dysplasia syndromes.

Menkes Kinky Hair Syndrome (Trichopoliodystrophy)

Males with Menkes kinky hair syndrome, an X-linked recessive trait, are born to an unaffected mother after a normal pregnancy. Neonatal problems include hypothermia, hypotonia, poor feeding, seizures, and failure to thrive. Hair is normal to sparse at birth but is replaced by short, fine, brittle, light-colored hair that may have features of trichorrhexis nodosa, pili torti, or monilethrix. The skin is hypopigmented and thin, cheeks typically appear plump, and the nasal bridge is depressed. Progressive psychomotor retardation is noted in early infancy. Pathogenic variants in the *ATP7A* gene, encoding a copper-transporting adenosine triphosphatase protein, cause Menkes kinky hair syndrome. It is a result of maldistribution of the copper in the body. Copper uptake across the brush border of the small intestine is increased, but copper transport from these cells into the plasma is defective, resulting in low total body copper stores. Parenteral administration of copper-histidine is helpful if begun in the first 2 months of life.

Monilethrix

The hair shaft defect known as monilethrix is inherited as an autosomal dominant trait with variable age of onset, severity, and course. Pathogenic variants in the hair keratins *KRT81* (hHb1), *KRT83* (hHb3), and *KRT86* (hHb6) have been identified in autosomal dominant cases, and pathogenic variants in desmoglein 4 are found in autosomal recessive cases. The hair appears dry, lusterless, and brittle, and it fractures spontaneously or with mild trauma. Eyebrows, lashes, body and pubic hair, and scalp hair may be affected. Monilethrix may be present at birth, but the hair is usually normal at birth and is replaced in the first few months of life by abnormal hairs; the condition is sometimes first apparent in childhood. Follicular papules may appear on the nape of the neck and the occiput and, occasionally, over the entire scalp. Short, fragile beaded hairs that emerge from the horny follicular plugs give a distinctive appearance. Keratosis pilaris and koilonychia of fingernails and toenails may also be present. Microscopically, a distinctive, regular beading pattern of the hair shaft is evident, characterized by elliptic nodes that are separated by narrower internodes (see Fig. 703.8B). Not all hairs have nodes, and both normal and beaded hairs may break. Patients should be advised to handle the hair gently to minimize breakage. Treatment is generally ineffective, although oral retinoids and topical minoxidil have produced some improvement.

Trichothiodystrophy

Hair in trichothiodystrophy is sparse, short, brittle, and uneven; the scalp hair, eyebrows, or eyelashes may be affected. Microscopically, the hair is flattened, folded, and variable in diameter; it has longitudinal grooving and nodal swellings that resemble those seen in trichorrhexis nodosa. Under a polarizing microscope, distinctive alternating dark and light bands are seen. The abnormal hair has a cystine content that is <50% of normal because of a major reduction in and altered composition of constituent high-sulfur matrix proteins. Trichothiodystrophy is caused by pathogenic variants in DNA repair/transcription genes (*XPD, XPB, TTDN1,* and *TTDA*) and may occur as an isolated finding or in association with various syndrome complexes that include intellectual impairment, short stature, ichthyosis, nail dystrophy, dental caries, cataracts, decreased fertility, neurologic abnormalities, bony abnormalities, and immunodeficiency. Some patients are photosensitive and have impaired DNA repair mechanisms, similar to that seen in groups B and D xeroderma pigmentosum; the incidence of skin cancers, however, is not increased. Patients with trichothiodystrophy tend to resemble one another, with a receding chin, protruding ears, raspy voice, and sociable, outgoing personality. Trichoschisis, a fracture perpendicular to the hair shaft, is characteristic of the many syndromes that are associated with trichothiodystrophy. Perpendicular breakage of the hair shaft has also been described in association with other hair abnormalities, particularly monilethrix.

Trichorrhexis Invaginata (Bamboo Hair)

Short, sparse, fragile hair without apparent growth is characteristic of trichorrhexis invaginata, which is found primarily in association with Netherton syndrome (see Chapter 699). It has also been reported in other ichthyosiform dermatoses. The distal portion of the hair is invaginated into the cuplike proximal portion, forming a fragile nodal swelling (see Fig. 703.8C).

Pili Annulati

Alternating light and dark bands of the hair shaft characterize pili annulati. When viewed under the light microscope, the region of the hair shaft that appeared bright in reflected light instead appears dark in the transmitted light as a result of focal aggregates of abnormal air-filled cavities within the shaft. The hair is not fragile. The defect may be autosomal dominant or sporadic in inheritance and usually begins after age 2. Pseudopili annulati is a variant of normal blond hair; an optical effect caused by the refraction and reflection of light from the partially twisted and flattened shaft creates the impression of banding.

Woolly Hair Disease

Woolly hair diseases manifest at birth as peculiarly tight, curly, abnormal hair in a person who is not Black. Autosomal dominant and recessive (*PKRY5* gene) types have been described along with the genodermatoses Naxos disease and Carvajal syndrome, which are associated with cardiomyopathy. Woolly hair nevus, a sporadic form, involves only a circumscribed portion of the scalp hair. The affected hair is fine, tightly curled, and light-colored, and it grows poorly. Microscopically, an affected hair is oval and shows twisting of 180 degrees on its axis.

Uncombable Hair Syndrome (Spun-Glass Hair)

The hair of patients with uncombable hair syndrome appears disorderly, is often silvery blond (Fig. 703.9), and may break because of

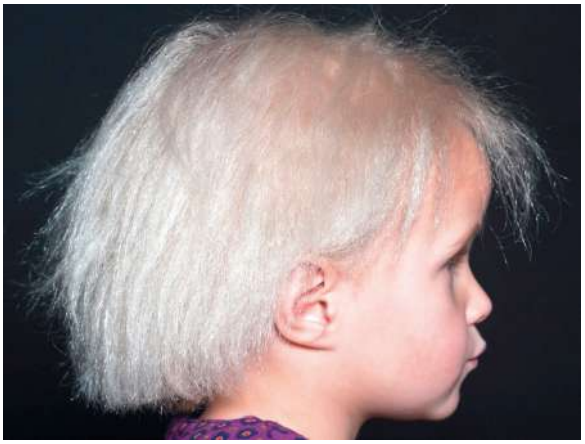

Fig. 703.9 Complicated combing. Blond, frizzy, and glistening hair in uncombable hair syndrome. *(From Drivenes JL, Betz RC, Bygum A. A girl with unruly locks: molecular genetics makes a diagnosis of uncombable hair syndrome. Lancet. 2022;399:1079.)*

repeated, futile efforts to control it. Eyebrows and eyelashes are normal. A longitudinal depression along the hair shaft is a constant feature, and most hair follicles and shafts are triangular (pili trianguli et canaliculi). The shape of the hair varies along its length, however, preventing the hairs from lying flat.

The disorder is associated with pathogenic variants in *PAD13, TCHH,* and *TGM3* genes. Most patients have no other findings, but in some there may be associated brachydactyly, ectodermal dysplasia, cataracts, and oligodontia.

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Table 704.1 White Nail or Nail Bed Changes

DISEASE	CLINICAL APPEARANCE
Anemia	Diffuse white
Arsenic	Mees lines: transverse white lines
Cirrhosis	Terry nails: most of nail, zone of pink at distal end (see Fig. 704.6)
Congenital leukonychia (autosomal dominant; variety of patterns)	Syndrome of leukonychia, knuckle pads, deafness; isolated finding; partial white
Darier disease	Longitudinal white streaks
Half-and-half nail	Proximal white, distal pink azotemia
High fevers (some diseases)	Transverse white lines
Hypoalbuminemia	Muehrcke lines: stationary paired transverse bands
Hypocalcemia	Variable white
Malnutrition	Diffuse white
Pellagra	Diffuse milky white
Punctate leukonychia	Common white spots
Tinea and yeast	Variable patterns
Thallium toxicity (rat poison)	Variable white
Trauma	Repeated manicure: transverse striations
Zinc deficiency	Diffuse white

From Habif TP, ed. *Clinical Dermatology,* 4th ed. Philadelphia: Mosby; 2004:887.

Table 704.2 Congenital Diseases with Nail Defects

Large nails	Pachyonychia congenita, Rubinstein-Taybi syndrome, hemihypertrophy
Smallness or absence of nails	Ectodermal dysplasias, nail-patella, dyskeratosis congenita, focal dermal hypoplasia, cartilage-hair hypoplasia, COIF, Ellis–van Creveld, Larsen, epidermolysis bullosa, incontinentia pigmenti, Rothmund-Thomson, Turner, Coffin-Siris, popliteal web, trisomies (8, 13, 18), Apert, Gorlin-Pindborg, long arm 21 deletion, otopalatodigital, elfin facies, anonychia, Noonan, acrodermatitis enteropathica, teratogens (alcohol, warfarin, hydantoin)
Other	Congenital malalignment of the great toenails, familial dystrophic shedding of the nails

COIF, Congenital onychodysplasia of index fingers.

Chapter 704
Disorders of the Nails

Kari L. Martin

Nail abnormalities in children may be manifestations of generalized skin disease, skin disease localized to the periungual region, systemic disease, drugs, trauma, or localized bacterial and fungal infections (Table 704.1). Nail anomalies are also common in certain congenital disorders (Table 704.2).

ABNORMALITIES IN NAIL SHAPE OR SIZE

Anonychia is absence of the nail plate, usually a result of a congenital disorder or trauma. It may be an isolated finding or may be associated with malformations of the digits. **Koilonychia** is flattening and concavity of the nail plate with loss of normal contour, producing a spoon-shaped nail (Fig. 704.1). Koilonychia occurs as an autosomal dominant trait or in association with iron-deficiency anemia, Plummer-Vinson syndrome, hemochromatosis, various genodermatoses, and occupational trauma. The nail plate is relatively thin for the first year or two of life and, consequently, may be spoon-shaped in otherwise normal children.

Congenital nail dysplasia, an autosomal dominant disorder, manifests at birth as longitudinal streaks and thinning of the nail plate. There is platyonychia and koilonychia, which may overgrow the lateral folds and involve all nails of the toes and fingers.

Nail-patella syndrome is an autosomal dominant disorder in which the nails are 30–50% of their normal size and often have triangular or pyramidal lunulae. The thumbnails are always involved, although in some cases only the ulnar half of the nail may be affected or may be missing. Nail involvement is symmetric, and the nails from the index finger to the little finger are progressively less damaged. The patella is also smaller than usual or absent, and this anomaly may lead to knee instability. Iliac horns, bony spines arising from the posterior aspect of the iliac bones; overextension of joints; skin laxity; ocular anomalies;

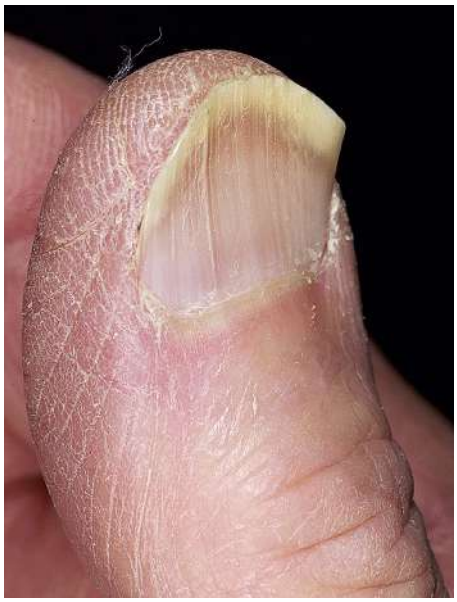

Fig. 704.1 Spoon nails (koilonychia). Most cases are a variant of normal. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:885.)*

Fig. 704.2 Finger clubbing. The distal phalanges are enlarged to a rounded bulbous shape. The nail enlarges and becomes curved, hard, and thickened. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:885.)*

Table 704.3 Clubbing in Children*

HISTORY	SYMPTOM	DISEASE
ACQUIRED		
Generalized	Pulmonary	Cystic fibrosis Bronchiectasis Tuberculosis, aspergillosis Asthma complicated by lung infections Sarcoidosis Pulmonary fibrosis Tumors
	Cardiovascular	Cyanotic congenital heart disease Subacute bacterial endocarditis Myxomas
	Gastrointestinal	Inflammatory bowel disease Gardner's syndrome Parasitosis Cirrhosis Chronic active hepatitis
	Endocrine	Diamond's syndrome (myxedema, exophthalmos and clubbing) Hypervitaminosis A Malnutrition
Limited to one or more digits		Aortic/subclavian artery aneurysm Brachial plexus injury Trauma Maffucci's syndrome Gout Sarcoidosis Severe herpetic whitlow
Hereditary		Pachydermoperiostosis Familial, isolated
Pseudoclubbing*		Apert's syndrome Pfeiffer's syndrome Rubinstein-Taybi syndrome

*Broad distal phalanges with normally shaped nails.
Modified from Baran R, Dawber RPR. *Diseases of the Nails and Their Management.* Oxford: Blackwell Science; 1984:29.

and nephropathy, the most serious feature, may also be present. Nail-patella syndrome is caused by pathogenic variants in the transcription factor *LMX1B* gene.

For a discussion of pachyonychia congenita, see Chapter 699.

Habit tic deformity consists of a depression down the center of the nail with numerous horizontal ridges extending across the nail from it. One or both thumbs are usually involved as a result of chronic rubbing and picking at the nail with an adjacent finger. Treatment aims at cessation of trauma to the nail via massaging with bland ointments, physical barriers, or cyanoacrylate adhesive.

Clubbing of the nails is characterized by swelling of each distal digit, an increase in the angle between the nail plate and the proximal nail fold (Lovibond angle) to >180 degrees, and a spongy feeling when one pushes down and away from the interphalangeal joint because of an increase in fibrovascular tissue between the matrix and the phalanx (Fig. 704.2). The pathogenesis is not known. Nail clubbing is seen in association with diseases of numerous organ systems, including pulmonary, cardiovascular (cyanotic heart disease), gastrointestinal (celiac disease, inflammatory bowel disease), and hepatic (chronic hepatitis) systems, and in healthy individuals as an idiopathic or familial finding (Table 704.3).

CHANGES IN NAIL COLOR

Leukonychia is a white opacity of the nail plate that may involve the entire plate or may be punctate or striate (see Table 704.1). The nail plate itself remains smooth and undamaged. Leukonychia can be traumatic or associated with infections such as leprosy and tuberculosis, dermatoses such as lichen planus and Darier disease, malignancies such as Hodgkin disease, anemia, and arsenic poisoning (Mees lines). Leukonychia of all nail surfaces is an uncommon hereditary autosomal dominant trait that may be associated with congenital epidermal cysts and renal calculi. Paired parallel white bands that do not change position with growth of the nail, fade with pressure, and thus reflect a change in the nail bed are associated with hypoalbuminemia and are called *Muehrcke lines.* When the proximal portion of the nail is white and the distal 20–50% of the nail is red, pink, or brown, the condition is called *half-and-half nails* or *Lindsay nails;* this is seen most commonly in patients with renal disease but may occur as a normal variant. White nails of cirrhosis, or Terry nails (Fig. 704.3), are characterized by a white ground-glass appearance of the entire or the proximal end of the nail and a normal pink distal 1-2 mm of the nail; this finding can also be associated with congestive heart failure and adult-onset diabetes and can be normal in children less than 4 years old.

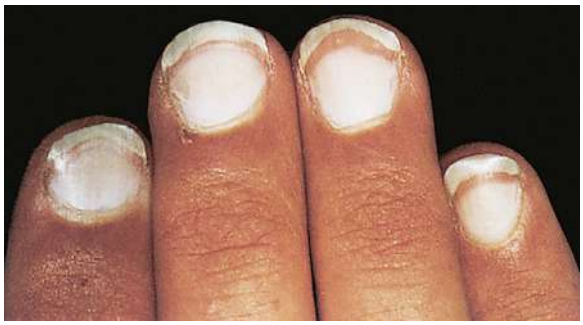

Fig. 704.3 Terry nails. The nail bed is white with only a narrow zone of pink at the distal end. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004:885.)*

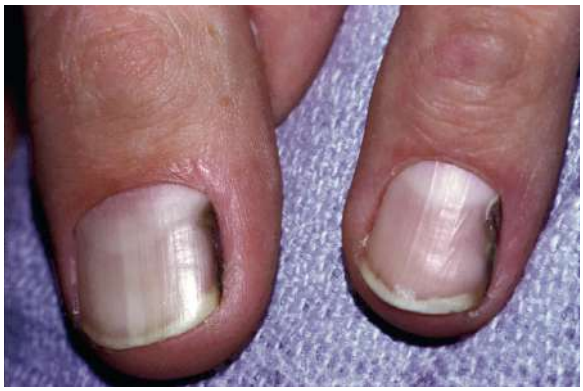

Fig. 704.4 Green/black discoloration at the edge of the nails secondary to *Pseudomonas* infection.

Black pigmentation of an entire nail plate or linear bands of pigmentation **(melanonychia striata)** is most common in individuals with Fitzpatrick type IV-VI skin. Most often, the pigment is melanin, which is produced by melanocytes of a junctional nevus in the nail matrix and nail bed and is of no consequence. Extension or alteration in the pigment should be evaluated by biopsy because of the possibility of malignant change.

Bluish black to greenish nails may be caused by *Pseudomonas* infection (Fig. 704.4), particularly in association with onycholysis or chronic paronychia. The coloration is caused by subungual debris and pyocyanin pigment from the bacterial organisms.

Yellow nail syndrome manifests as thickened, excessively curved, slow-growing yellow nails without lunulae. All nails are affected in most cases. Associated systemic diseases include bronchiectasis, recurrent bronchitis, chylothorax, and focal edema of the limbs and face. Deficient lymphatic drainage, caused by hypoplastic lymphatic vessels, is believed to lead to the manifestations of this syndrome.

Splinter hemorrhages most often result from minor trauma but may also be associated with subacute bacterial endocarditis, vasculitis, Langerhans cell histiocytosis, severe rheumatoid arthritis, peptic ulcer disease, hypertension, chronic glomerulonephritis, cirrhosis, scurvy, trichinosis, malignant neoplasms, and psoriasis (Fig. 704.5 and Table 704.4).

NAIL SEPARATION

Onycholysis indicates separation of the nail plate from the distal nail bed. Common causes are trauma, long-term exposure to moisture, hyperhidrosis, cosmetics, psoriasis, fungal infection (distal onycholysis), atopic or contact dermatitis, porphyria, drugs (bleomycin, vincristine, retinoid agents, indomethacin, chlorpromazine [Thorazine]), and drug-induced phototoxicity from tetracyclines (Fig. 704.6) or chloramphenicol (Table 704.5).

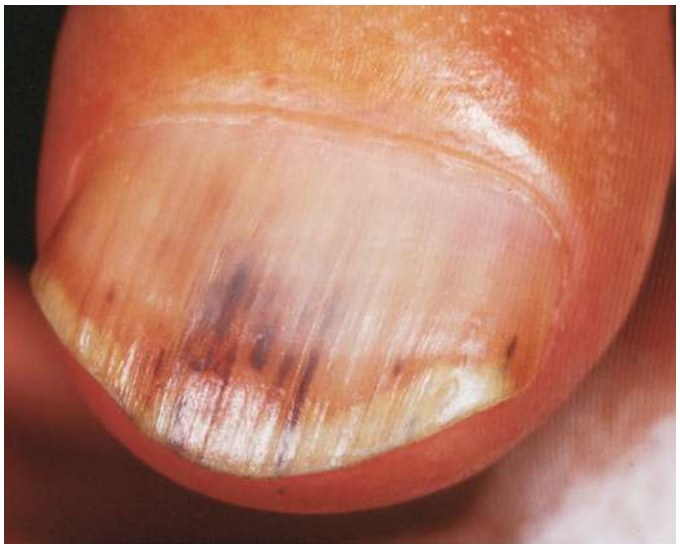

Fig. 704.5 Splinter hemorrhage of the distal nail bed due to trauma. *(From Hordinsky M, Sawaya ME, Scher RK. Atlas of Hair and Nails. London: Churchill Livingstone; 1999.)*

Table 704.4 Disorders Associated with Subungual Hemorrhage

	SPLINTER-SHAPED	HEMATOMAS
Normal variant	+	–
Blood dyscrasias	+	+
Collagen diseases (lupus erythematosus)	+	+
Trichinosis	+	–
Trauma	+	+
Child abuse	+	+
Cryoglobulinemia	+	–
Drug eruptions	+	–
Dialysis	+	–
Endocarditis (SBE)	+	–
Emboli	+	+
Langerhans cells histiocytosis	+	–
Arterial lines or punctures	+	–
Sarcoidosis	+	–
Sepsis	+	–
Thyroid disease	+	–
Vasculitis	+	–
Phototoxicity (tetracyclines)	+	–

From Silverman R, Baran R. Nail and appendageal abnormalities. In: Schachner LA, Hansen RC, eds. *Pediatric Dermatology,* 4th ed. Philadelphia: Mosby; 2011, Table 12.9, p. 813.

Beau lines are transverse grooves in the nail plate (Fig. 704.7) that represent a temporary disruption of formation of the nail plate. The lines first appear a few weeks after the event that caused the disruption in nail growth. A single transverse ridge appears at the proximal nail fold in most 4- to 6-week-old infants and works its way distally as the nail grows; this line may reflect metabolic changes after delivery. At

Fig. 704.6 Distal onycholysis secondary to oral tetracycline usage and ultraviolet light exposure.

Table 704.5 Underlying Causes of Onycholysis

CHEMICAL IRRITANTS
Cosmetics, especially with formaldehyde
Depilatories
Detergents
Nail polish removers
Organic solvents
INFLAMMATORY DISORDERS
Alopecia areata
Atopic dermatitis
Contact dermatitis
Lichen planus
Psoriasis
INFECTIOUS DISORDERS
Bacterial paronychia
Candidiasis
Herpes simplex (whitlow)
Onychomycosis
Verrucae
MEDICATIONS
Anticonvulsants (valproic acid)
Chemotherapeutic agents (especially taxanes)
Griseofulvin
Retinoids (isotretinoin)
Tetracyclines (photoonycholysis)
Thiazides (photoonycholysis)
SYSTEMIC DISORDERS
Iron-deficiency anemia
Rheumatic disease
Thyroid disease (hyperthyroidism or hypothyroidism)
Kawasaki disease
MIS-C
TRAUMA
Compulsive subungual cleaning
Sportsman toe

MIS-C, multisystem inflammatory syndrome in children.
From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022, Box 7.9, p. 201.

other ages, Beau lines are usually indicative of periodic trauma or episodic shutdown of the nail matrix secondary to a systemic disease such as hand-foot-and-mouth disease, measles, mumps, pneumonia, or zinc deficiency. Onychomadesis is an exaggeration of Beau lines leading to proximal separation of the nail bed (Fig. 704.8).

NAIL CHANGES ASSOCIATED WITH SKIN DISEASE

Nail changes may be particularly associated with various other diseases. Nail changes of psoriasis most characteristically include pitting, onycholysis, yellow-brown discoloration, and thickening. Nail changes in lichen planus include violaceous papules in the proximal nail fold and nail bed,

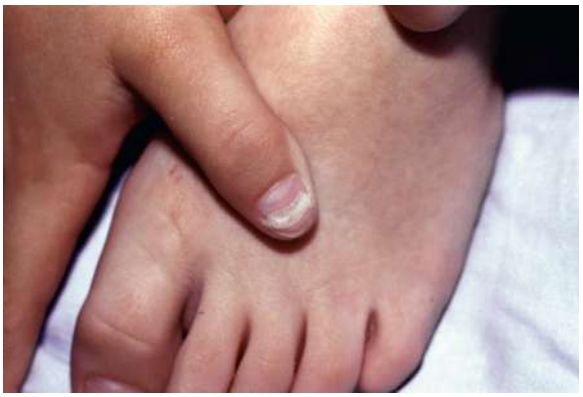

Fig. 704.7 Beau lines. Longitudinal disruption of the nail.

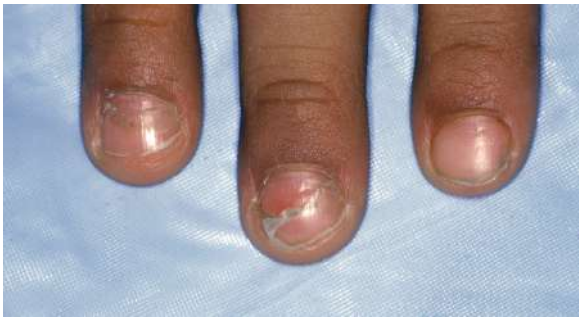

Fig. 704.8 Onychomadesis. Proximal nail bed separation.

leukonychia, longitudinal ridging, thinning of the entire nail plate, and pterygium formation, which is abnormal adherence of the cuticle to the nail plate or, if the plate is destroyed focally, to the nail bed. Postinfectious reactive arthritis syndromes may include painless erythematous induration of the base of the nail fold; subungual parakeratotic scaling; and thickening, opacification, or ridging of the nail plate. Dermatitis that involves the nail folds may produce dystrophy, roughening, and coarse pitting of the nails. Nail changes are more common in atopic dermatitis than in other forms of dermatitis that affect the hands. Darier disease is characterized by red or white streaks that extend longitudinally and cross the lunula. Where the streak meets the distal end of the nail, a V-shaped notch may be present. Total leukonychia may also occur. Transverse rows of fine pits are characteristic of alopecia areata. In severe cases, the entire nail surface may be rough. Patients with acrodermatitis enteropathica may have transverse grooves (Beau lines) and nail dystrophy as a result of periungual dermatitis.

TRACHYONYCHIA (20-NAIL DYSTROPHY)

Trachyonychia is characterized by longitudinal ridging, pitting, fragility, thinning, distal notching, and opalescent discoloration of all the nails (Fig. 704.9). Patients can have no associated skin or systemic diseases and no other ectodermal defects. Its occasional association with alopecia areata has led some authorities to suggest that trachyonychia may reflect an abnormal immunologic response to the nail matrix, whereas histopathologic studies have suggested that it may be a manifestation of lichen planus, psoriasis, or spongiotic (eczematous) inflammation of the nail matrix. The disorder must be differentiated from fungal infections, psoriasis, nail changes of alopecia areata, and nail dystrophy secondary to eczema. Eczema and fungal infections rarely produce changes in all the nails simultaneously. The disorder is self-limited, can be treated with potent topical steroids or topical retinoids, and eventually remits by adulthood.

NAIL INFECTION

Fungal infection **(onychomycosis)** of the nails has been classified into four types. White superficial onychomycosis manifests as diffuse or speckled white discoloration of the surface of the toenails. It is caused primarily by *Trichophyton mentagrophytes,* which invades the nail plate. The organism

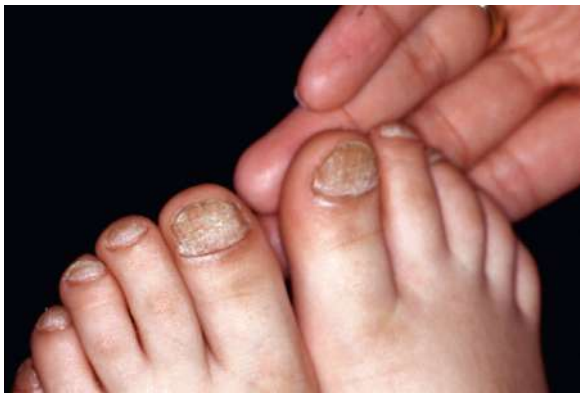

Fig. 704.9 Dystrophy of all nails in trachyonychia.

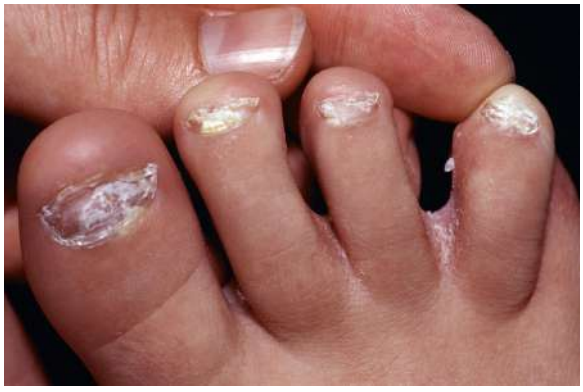

Fig. 704.10 Discoloration, hyperkeratosis, and crumbling of nail secondary to dermatophyte infection.

may be scraped off the nail plate with a blade, but treatment is best accomplished by the addition of a topical azole antifungal agent. Distal subungual onychomycosis, the most common type, involves foci of onycholysis under the distal nail plate or along the lateral nail groove, followed by development of hyperkeratosis and yellow-brown discoloration. The process extends proximally, resulting in nail plate thickening, crumbling (Fig. 704.10), and separation from the nail bed. *Trichophyton rubrum* and, occasionally, *T. mentagrophytes* infect the toenails; fingernail disease is almost exclusively caused by *T. rubrum,* which may be associated with superficial scaling of the plantar surface of the feet and often of one hand. The dermatophytes are found most readily at the most proximal area of the nail bed or adjacent ventral portion of the involved nail plates. Topical therapies such as ciclopirox 8% lacquer, amorolfine 5% lacquer, or bifonazole-urea 1%/40% ointment may be effective for solitary nail infection. Topical efinaconazole 10% and topical tavaborole 5% solution may also be effective; laser treatment is an expensive but safe alternative to oral therapy. Because of its long half-life in the nail, oral itraconazole may be effective when given as pulse therapy (1 week of each month for 3-4 months). Dosage is weight-dependent. Oral daily terbinafine is also quite effective. Either agent is superior to griseofulvin, fluconazole, or ketoconazole. The risks, the most concerning of which is hepatic toxicity, and costs of oral therapy are minimized with the use of pulsed dosing.

Proximal white subungual onychomycosis occurs when the organism, generally *T. rubrum,* enters the nail through the proximal nail fold, producing yellow-white discoloration of portions of the undersurface of the nail plate. The surface of the nail is unaffected. This occurs almost exclusively in immunocompromised patients and is a well-recognized manifestation of AIDS. Treatment includes oral terbinafine or itraconazole.

Candidal onychomycosis involves the entire nail plate in patients with chronic mucocutaneous candidiasis. It is also commonly seen in patients with AIDS. The organism, generally *Candida albicans,* enters distally or along the lateral nail folds; rapidly involves the entire thickness of the nail plate; and produces thickening, crumbling, and deformity of the plate. Topical azole antifungal agents may be sufficient for treatment of candidal onychomycosis in an immunocompetent host, but oral antifungal agents are necessary for treatment of patients with immune deficiencies. Table 704.6 outlines the differential diagnosis of onychomycosis.

Table 704.6 Differential Diagnosis of Onychomycosis

Psoriasis
- As in onychomycosis: onycholysis, subungual hyperkeratosis, splinter hemorrhages, leukonychia, dystrophy
- Pitting
- Oil drop sign (a translucent yellow-red discoloration seen in the nail bed)
- Other cutaneous features of psoriasis, family history of psoriasis

Lichen planus
- Cutaneous disease at other sites
- Thin nail plate and ridging
- Dorsal pterygium—scarring at proximal aspect of nail

Trauma
- Nail plate can appear abnormal
- Nail bed should be normal
- Distal onycholysis with repeated trauma
- Single nail affected, shape of nail changed, homogenous alteration of nail color

Eczema
- Irregular buckled nails with ridging
- Cutaneous signs of eczema

Yellow nail syndrome
- Nail plate is discolored green-yellow
- Nails are hard with elevated longitudinal curvature
- Nails may be shed, painful
- Associations with bronchiectasis, lymphedema, and chronic sinusitis

Lamellar onychoschizia (lamellar splitting)
- History of repeated soaking in water
- Usually distal portion of nail
- Periungual squamous cell carcinoma/Bowens disease
- Single nail, warty changes of nail fold; ooze from edge of nail

Malignant melanoma
- Black discoloration of nail plate or nail bed
- Pigment can extend onto nail fold
- Can get associated bleeding

Myxoid (mucous) cyst
- Cyst at base of nail, groove in nail extending length of nail

Alopecia areata
- Pits, longitudinal ridging, brittleness
- Hair loss

From Eisman S, Sinclair R. Fungal nail infection: diagnosis and management. *BMJ.* 2014;348:g1800.

PARONYCHIAL INFLAMMATION

Paronychial inflammation may be acute or chronic and generally involves one or two nail folds on the fingers. Acute paronychia manifests as erythema, warmth, edema, and tenderness of the proximal nail fold, most commonly as a result of pathogenic staphylococci, streptococci, or *Candida* (Fig. 704.11). Warm soaks and oral agents are generally effective; incision and drainage may occasionally be necessary. Development of chronic paronychia follows prolonged immersion in water (Fig. 704.12), such as occurs in finger or thumb sucking; exposure to irritating solutions; nail fold trauma; or diseases including Raynaud phenomenon, collagen vascular diseases, and diabetes. Swelling of the proximal nail fold is followed by separation of the nail fold from the underlying nail plate and suppuration. Foreign material, embedded in the dermis of the nail fold, becomes a nidus for inflammation and secondary infection with *Candida* species and mixed bacterial flora. A combination of attention to predisposing factors, meticulous drying of the hands, and long-term topical antifungal agents and potent topical corticosteroids may be required for successful treatment of chronic paronychia.

Ingrown nail occurs when the lateral edge of the nail, including spicules that have separated from the nail plate, penetrates the soft tissue of

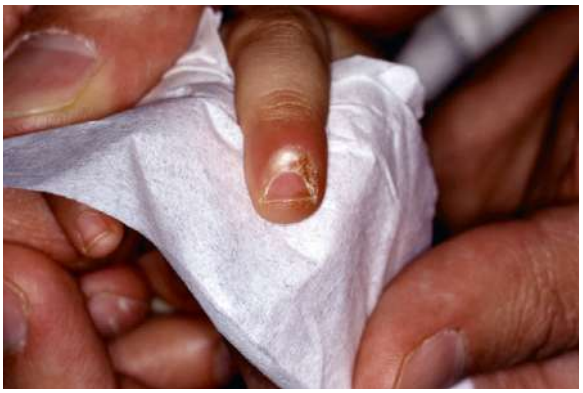

Fig. 704.11 Acute paronychia secondary to *Staphylococcus aureus.*

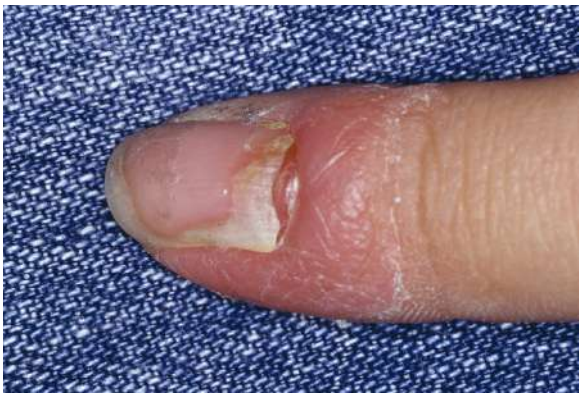

Fig. 704.12 Chronic paronychia with erythema and lateral nail fold separation.

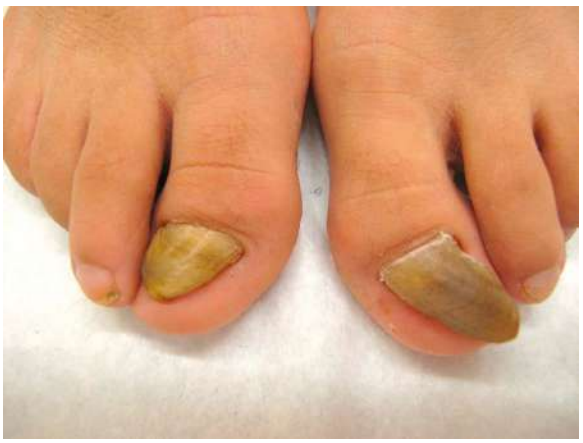

Fig. 704.13 Clinical features of an 8-yr-old boy upon initial presentation to a dermatology clinic. Findings included yellowish-brown discoloration, hyperkeratosis, transverse ridging, and lateral deviation of the bilateral great toenails. *(From Pollack K, Zlotoff B, Wilson B. Hyperkeratosis and discoloration of the toenails in an 8-year-old. J Pediatr. 2017;189:233.)*

the lateral nail fold. Erythema, edema, and pain, most often involving the lateral great toes, are noted acutely; recurrent episodes may lead to formation of granulation tissue. Predisposing factors include (1) congenital malalignment (especially of the great toes) (Fig.704.13); (2) compression of the side of the toe from poorly fitting shoes, particularly if the great toes are abnormally long and the lateral nail folds are prominent; and (3) improper cutting of the nail in a curvilinear manner rather than straight across. Management includes proper fitting of shoes; allowing the nail to grow out beyond the free edge before cutting it straight across; warm water soaks; oral antibiotics if cellulitis affects the lateral nail fold; and, in severe, recurrent cases, application of silver nitrate to granulation tissue, nail avulsion, or excision of the lateral aspect of the nail followed by matricectomy.

PARONYCHIAL TUMORS

Tumors in the paronychial area include pyogenic granulomas, mucous cysts, subungual exostoses, and junctional nevi. Periungual fibromas that appear in late childhood should suggest a diagnosis of tuberous sclerosis.

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Chapter 705
Disorders of the Mucous Membranes

Leah Lalor

The mucous membranes may be involved in developmental disorders, genodermatoses, infections, acute and chronic skin diseases, and benign or malignant tumors. This chapter includes some of the more common and more distinctive conditions of the mucous membranes, but is not exhaustive (see also Chapter 695 for erythema multiforme, Stevens-Johnson syndrome, and reactive infectious mucocutaneous eruption [RIME]).

ANGULAR CHEILITIS

Angular cheilitis **(perlèche)** is characterized by inflammation and fissuring at the corners of the mouth, often with associated erosion, maceration, and crusting (Fig. 705.1). Chapping or moisture collection at the angles of the mouth predispose children to developing angular cheilitis. Children who are chronic lip lickers or who have excessive salivation or drooling related to neurologic deficits, orthodontic appliances, or mouth breathing are at increased risk. Atopic dermatitis or contact dermatitis related to toothpaste, chewing gum, mouthwash, or cosmetics are also common causes. Nutritional deficiencies are a less frequent etiology. Protection can be provided by frequent application of a bland ointment such as petrolatum. Candidiasis should be treated with an appropriate antifungal agent, and contact dermatitis of the perioral skin should be treated with a low-potency topical corticosteroid ointment preparation and frequent use of petrolatum or a similar emollient along with avoidance of the offending agent. Correction of the underlying predisposing factors (if possible) will prevent recurrence.

APHTHOUS STOMATITIS (CANKER SORES)

Aphthous stomatitis consists of solitary or multiple painful ulcerations occurring on the labial (Fig. 705.2), buccal, lingual, sublingual, palatal, or gingival mucosa (see Chapter 361). Lesions may manifest initially as erythematous, indurated papules that erode rapidly to form sharply circumscribed, necrotic ulcers with a gray fibrinous exudate and an erythematous halo. Minor aphthous ulcers are 2-10 mm in diameter and heal spontaneously in 7-10 days. Major aphthous ulcers are >10 mm in diameter, take from 10 to 30 days to heal, and may heal with scarring. A third type of aphthous ulceration is herpetiform in appearance,

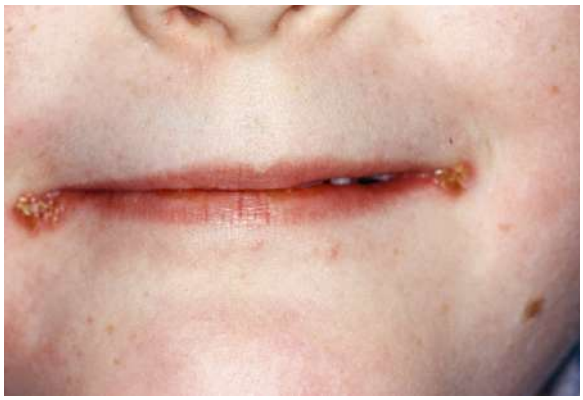

Fig. 705.1 Angular cheilitis.

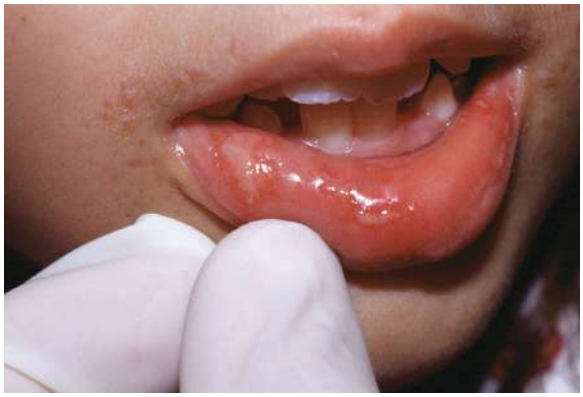

Fig. 705.2 Aphthous ulceration on lower lip.

manifesting as a few to numerous grouped 1- to 2-mm lesions, which tend to coalesce into plaques and heal over 7-10 days. Approximately 30% of patients with recurrent lesions have a family history of the disorder (see Chapter 361 for the differential diagnosis).

The etiology of aphthous stomatitis is multifactorial; the condition probably represents an oral manifestation of a number of conditions, including viral infection, inflammatory bowel disease, cyclic neutropenia, and others. Altered local regulation of the cell-mediated immune system, after activation and accumulation of cytotoxic T cells, may contribute to the localized mucosal breakdown. It is a common misconception that aphthous stomatitis is a manifestation of herpes simplex virus infection. Recurrent herpes infections remain localized to the lips and rarely cross the mucocutaneous junction; involvement of the oral mucosa occurs only in primary infections.

Treatment of aphthous stomatitis is supportive. The majority of mild cases do not require therapy. Relief of pain, particularly before eating, may be achieved with the use of a topical anesthetic such as viscous lidocaine or an oral rinse with a combined solution of elixir of diphenhydramine, viscous lidocaine, and an oral antacid. Caution must be taken to avoid hot food and drink after topical anesthetic use. A superpotent topical corticosteroid in a mucosa-adhering agent may help to reduce inflammation, and topical tetracycline mouthwash may also hasten healing. In severe, debilitating cases, systemic therapy with corticosteroids, colchicine, dapsone, or thalidomide may be helpful.

FORDYCE SPOTS

Fordyce spots (Fordyce granules) are clusters of asymptomatic, 1- to 3-mm, yellow-white macules and papules on the vermilion lips and buccal mucosa. They are a common clinical finding and represent a normal anatomic variant of sebaceous glands. They can present in either sex from infancy to adulthood and may become more prominent during puberty due to the influence of androgens. No therapy is required.

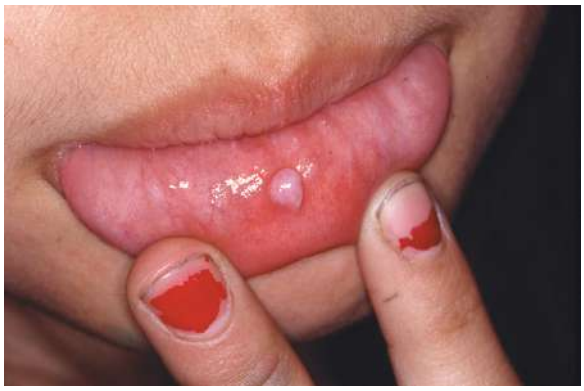

Fig. 705.3 Mucocele on lower lip.

EPSTEIN PEARLS (GINGIVAL CYSTS OF THE NEWBORN)

Epstein pearls are white, keratin-containing cysts on the palatal or alveolar mucosa of approximately 60–85% of neonates. They are epidermal inclusion cysts that form when the soft and hard palates fuse and are analogous to facial milia. They cause no symptoms and are generally shed within a few weeks; no therapy is necessary.

MUCOCELE

Mucus retention cysts are painless, fluctuant, tense, 2- to 10-mm, bluish papules on the lips (Fig. 705.3), tongue, palate, or buccal mucosa. Traumatic severance of the duct of a minor salivary gland leads to submucosal retention of mucus secretion. Lesions on the floor of the mouth are known as *ranulas* when the sublingual or submandibular salivary gland ducts are involved. Fluctuations in size are typical, and the lesions may disappear temporarily after traumatic rupture. Recurrence is prevented by surgical excision of the mucus deposit and associated salivary gland(s).

FISSURED TONGUE

Fissured tongue (scrotal tongue, or lingua plicata) is a common benign developmental anomaly of the tongue. The dorsal tongue has many folds with deep grooves and a pebbled appearance. Fissured tongue can be seen in individuals with Melkersson-Rosenthal syndrome and Down syndrome, and it is often seen in association with geographic tongue. Food particles and debris may become trapped in the fissures, resulting in irritation, inflammation, and halitosis. Careful cleansing with a mouth rinse and soft-bristled toothbrush is recommended.

GEOGRAPHIC TONGUE (BENIGN MIGRATORY GLOSSITIS)

Geographic tongue consists of single or multiple sharply demarcated, irregular, smooth, red patches surrounded by an elevated yellowish-white serpiginous border on the dorsum of the tongue. Onset is rapid, and the pattern may change over hours to days. The smooth patches correspond to atrophic filiform papillae, and the elevated margins represent hypertrophic papillae (Fig. 705.4). The etiology of this condition remains unclear, though it is associated with some inflammatory disorders of the skin like psoriasis. Lesions are typically asymptomatic, but some patients may experience a burning sensation or sensitivity to spicy, hot, or cold foods. No therapy other than reassurance is necessary.

Fig. 705.4 Geographic tongue.

BLACK HAIRY TONGUE

Black hairy tongue is a dark coating on the dorsum of the tongue caused by hyperplasia and elongation of the filiform papillae; overgrowth of chromogenic bacteria and fungi and entrapped pigmented residues that adsorb to microbial plaque and desquamating keratin may contribute to the dark coloration. Changes often begin posteriorly and extend anteriorly on the dorsum of the tongue. The condition is most common in adults but may also manifest during adolescence. Poor oral hygiene, lack of oral feeding, treatment with systemic antibiotics such as tetracycline (which promote the growth of *Candida* spp.), and smoking are predisposing factors. Improved oral hygiene and brushing with a soft-bristled toothbrush may be all that is necessary for treatment.

ORAL HAIRY LEUKOPLAKIA

Oral hairy leukoplakia occurs in approximately 25% of patients with AIDS but is rare in the pediatric population. It manifests as corrugated and shaggy white plaques on the lateral margins of the tongue, which cannot be removed by rubbing. The lesions occasionally may spread to the ventral tongue surface, floor of the mouth, tonsillar pillars, and pharynx. The condition is caused by Epstein-Barr virus, which is present in the upper layer of the affected epithelium. The plaques have no malignant potential. The disorder occurs predominantly in HIV-infected patients but may also be found in individuals who are immunosuppressed for other reasons, such as organ transplantation, leukemia, chemotherapy, and long-term use of inhaled steroids. The condition is generally asymptomatic and does not require therapy.

ACUTE NECROTIZING ULCERATIVE GINGIVITIS (VINCENT STOMATITIS, FUSOSPIROCHETAL GINGIVITIS, TRENCH MOUTH)

Acute necrotizing ulcerative gingivitis manifests as painful, punched-out ulceration, necrosis, and bleeding of the interdental papillae. A grayish-white pseudomembrane may cover the ulcerations. Lesions may spread to involve the buccal mucosa, lips, tongue, tonsils, and pharynx and may be associated with dental pain, a bad taste, low-grade fever, and lymphadenopathy. It occurs most commonly in the second or third decade, particularly in the context of poor dental hygiene, poor nutrition, smoking, and stress.

NOMA

Noma is a severe form of fusospirillary gangrenous stomatitis that occurs primarily in malnourished, impoverished children 2-5 years of age who have had a preceding illness such as measles, scarlet fever, tuberculosis, malignancy, or immunodeficiency. The disease is most prevalent in Africa but also occurs in Asia and Latin America. Sporadic cases associated with immunodeficiency have been reported in developed countries. It manifests as a painful, red, indurated papule on the alveolar margin, followed by ulceration and mutilating gangrenous destruction of tissue in the oronasal region. The process may also involve the scalp, neck, shoulders, perineum, and vulva. Noma neonatorum manifests in the first month of life as gangrenous lesions of the lips, nose, mouth, and anal regions. Affected infants are usually small for gestational age, malnourished, premature, and frequently ill (particularly with *Pseudomonas aeruginosa* sepsis). Care consists of nutritional support, conservative debridement of necrotic soft tissues, empirical broad-spectrum antibiotics such as penicillin and metronidazole, and, in the case of noma neonatorum, antipseudomonal antibiotics (see Chapter 62).

PTEN HAMARTOMA SYNDROME (COWDEN SYNDROME)

PTEN hamartoma syndrome is an autosomal dominant condition caused by loss-of-function pathogenic variants in the *PTEN* tumor-suppressor gene. Mucocutaneous lesions typically appear in the second or third decade. Oral papillomas are 1- to 3-mm, smooth, pink or whitish papules on the palatal, gingival, buccal, and labial mucosae and may coalesce into a cobblestone appearance. Numerous flesh-colored papules also develop on the face, particularly around the mouth, nose, and ears. These papules are most commonly trichilemmomas, a benign neoplasm of the hair follicle. Associated findings may include acral keratoses, thyroid adenoma, goiter, gastrointestinal polyps, fibrocystic breast nodules, and carcinoma of the breast or thyroid.

Herpes Simplex Virus Infection

Herpes simplex virus (HSV) types 1 and 2 commonly cause primary and recurrent infection, resulting in grouped vesicles on oral, nasal, and genital mucosae.

Erythema Multiforme

Erythema multiforme (EM) is an uncommon disorder of mucocutaneous blistering typically on the labial mucosa and acral skin as a reaction to HSV infection. Please see Chapter 695.1 for more detail.

Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) is an uncommon disorder of skin sloughing that occurs primarily after exposure to a medication. It can have extensive mucosal involvement in addition to skin. Please see Chapter 695.3 for more detail.

Reactive Infectious Mucocutaneous Eruption (Formerly Mycoplasma-Induced Rash and Mucositis)

This condition is on the spectrum of SJS and toxic epidermal necrolysis (TEN), but tends to be triggered by various infections and has more mucosal involvement than cutaneous. Please see Chapter 695.2 for more detail.

Lichen Sclerosus

Lichen sclerosus is a rare disorder of genital mucosa typically seen in young girls and elderly women. It manifests as pink and white atrophic genital mucosa that can be associated with pain, dysuria, constipation, and bleeding. Please see Chapter 586 for more details.

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Chapter 706

Cutaneous Bacterial Infections

706.1 Impetigo

Stephen R. Humphrey

ETIOLOGY/PATHOGENESIS

Impetigo is the most common skin infection in children throughout the world. Invasive *Staphylococcus aureus* has a global incidence of approximately 20-50 cases/100,000 population per year. There are two classic forms of impetigo: nonbullous and bullous.

S. aureus is the predominant organism of **nonbullous impetigo** in the United States (see Chapter 227); group A β-hemolytic streptococci (GABHS) are implicated in the development of some lesions (see Chapter 229). The staphylococcal types that cause nonbullous impetigo are variable but are not generally from phage group 2, the group that is associated with scalded skin and toxic shock syndromes. Staphylococci generally spread from the nose to normal skin and then infect the skin. In contrast, the skin becomes colonized with GABHS an average of 10 days before development of impetigo. The skin serves as the source for acquisition of GABHS and is the probable primary source for the spread of impetigo. Lesions of nonbullous impetigo that grow staphylococci in culture cannot be distinguished clinically from those that grow pure cultures of GABHS.

Bullous impetigo is always caused by *S. aureus* strains that produce exfoliative toxins. The staphylococcal exfoliative toxins (ETA, ETB, ETD) blister the superficial epidermis by hydrolyzing human desmoglein 1, resulting in a subcorneal vesicle. This is also the target antigen of the autoantibodies in pemphigus foliaceus.

CLINICAL MANIFESTATIONS

Nonbullous Impetigo

Nonbullous impetigo accounts for more than 70% of cases. Lesions typically begin on the skin of the face or on extremities that have been traumatized. The most common lesions that precede nonbullous impetigo are insect bites, abrasions, lacerations, chickenpox, scabies pediculosis, and burns. A tiny vesicle or pustule forms initially and rapidly develops into a honey-colored crusted plaque that is generally <2 cm in diameter (Fig. 706.1). The infection may be spread to other parts of the body by the fingers, clothing, and towels. Lesions are associated with little to no pain or surrounding erythema, and constitutional symptoms are generally absent. Pruritus occurs occasionally, regional adenopathy is found in up to 90% of cases, and leukocytosis is present in approximately 50%.

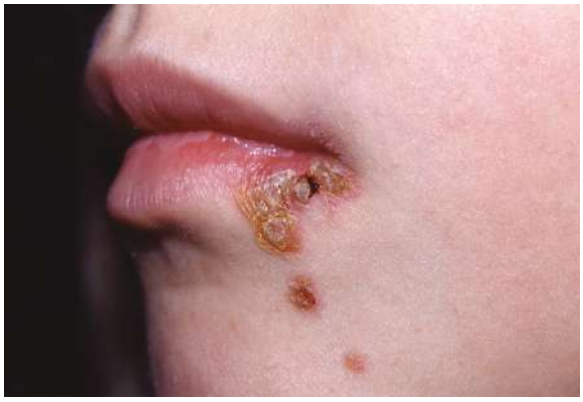

Fig. 706.1 Multiple crusted and oozing lesions of impetigo.

Bullous Impetigo

Bullous impetigo is mainly an infection of infants and young children. Flaccid, transparent bullae develop most commonly on skin of the face, buttocks, trunk, perineum, and extremities. **Neonatal bullous impetigo** can begin in the diaper area. Rupture of a bulla occurs easily, leaving a narrow rim of scale at the edge of a shallow, moist erosion. Surrounding erythema and regional adenopathy are generally absent. Unlike those of nonbullous impetigo, lesions of bullous impetigo are a manifestation of localized staphylococcal scalded skin syndrome and develop on intact skin.

Differential Diagnosis

The differential diagnosis of **nonbullous impetigo** includes viruses (herpes simplex, varicella-zoster), fungi (tinea corporis, kerion), arthropod bites, and parasitic infestations (scabies, pediculosis capitis), all of which may become impetiginized.

The differential diagnosis of **bullous impetigo** in neonates includes epidermolysis bullosa, bullous mastocytosis, herpetic infection, and early staphylococcal scalded skin syndrome. In older children, allergic contact dermatitis, burns, erythema multiforme, linear immunoglobulin A dermatosis, pemphigus, and bullous pemphigoid must be considered, particularly if the lesions do not respond to therapy.

COMPLICATIONS

Potential but *very rare* complications of either nonbullous or bullous impetigo include bacteremia with subsequent osteomyelitis, septic arthritis, pneumonia, and septicemia. Positive blood culture results are *very rare* in otherwise healthy children with localized lesions. Cellulitis has been reported in up to 10% of patients with nonbullous impetigo and rarely follows the bullous form. Lymphangitis, suppurative lymphadenitis, guttate psoriasis, and scarlet fever occasionally follow streptococcal disease. There is no correlation between the number of lesions and clinical involvement of the lymphatics or development of cellulitis in association with streptococcal impetigo.

Infection with nephritogenic strains of GABHS may result in **acute poststreptococcal glomerulonephritis** (see Chapter 559.4). The clinical character of impetigo lesions does not predict the development of poststreptococcal glomerulonephritis. Children 3-7 years of age are most commonly affected. The latent period from onset of impetigo to development of poststreptococcal glomerulonephritis averages 18-21 days, which is longer than the 10-day latency period after pharyngitis. Poststreptococcal glomerulonephritis occurs epidemically after either pharyngeal or skin infection. Impetigo-associated epidemics have been caused by M groups 2, 49, 53, 55, 56, 57, and 60. Strains of GABHS that are associated with endemic impetigo in the United States have little or no nephritogenic potential. Acute rheumatic fever does not occur as a result of impetigo.

TREATMENT

The decision on how to treat impetigo depends on the number of lesions and their locations. Topical therapy with mupirocin 2% and retapamulin 1% 2-3 times a day for 10-14 days is acceptable for localized disease caused by *S. aureus,* though there are resistant strains to these topical antibiotics.

Systemic therapy with oral antibiotics should be prescribed for patients with streptococcal or widespread involvement of staphylococcal infections; when lesions are near the mouth, where topical medication may be licked off; or in cases with evidence of deep involvement, including cellulitis, furunculosis, abscess formation, or suppurative lymphadenitis. Cephalexin 25-50 mg/kg/day in three to four divided doses for 7 days is an excellent choice for initial therapy. A culture should be performed, as the emergence of methicillin-resistant *S. aureus* (MRSA) typically requires a different antibiotic choice based on antibiotic susceptibility patterns. If MRSA is suspected, clindamycin, doxycycline, or sulfamethoxazole-trimethoprim is indicated. No evidence suggests that a 10-day course of therapy is superior to a 7-day course; twice-daily

sulfamethoxazole trimethoprim for 3 days has been comparable to once daily for 5 days. Benzathine benzylpenicillin IM has been used when compliance with multiple-dose and -day oral antibiotics may be poor.

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706.2 Subcutaneous Tissue Infections

Stephen R. Humphrey

The principal determinations for soft tissue infection are whether it is *nonnecrotizing* or *necrotizing* and *purulent* or *nonpurulent*. Nonnecrotizing, nonpurulent lesions respond to antibiotic therapy alone, whereas necrotizing or purulent (abscess) lesions require prompt surgical removal of all devitalized tissue in addition to antimicrobial therapy. Necrotizing soft tissue infections are life-threatening conditions that are characterized by rapidly advancing local tissue destruction and systemic toxicity, including shock. Tissue necrosis distinguishes soft tissue infections from cellulitis. In cellulitis, an inflammatory infectious process involves subcutaneous tissue but does not destroy it. Necrotizing soft tissue infections may initially manifest with a paucity of early cutaneous signs relative to the rapidity and degree of destruction of the subcutaneous tissues.

CELLULITIS

Etiology

Cellulitis is characterized by infection and inflammation of loose connective tissue, with limited involvement of the dermis and relative sparing of the epidermis. A break in the skin from previous trauma, insect bite, surgery, or an underlying skin lesion predisposes to cellulitis. Cellulitis is also more common in individuals with lymphatic stasis, diabetes mellitus, or immunosuppression.

S. aureus and *Streptococcus pyogenes* (group A streptococcus) are the most common etiologic agents. In patients who are immunocompromised or have diabetes mellitus, other bacterial or fungal agents may be involved, notably *Pseudomonas aeruginosa; Aeromonas hydrophila* and, occasionally, other Enterobacteriaceae; *Legionella* spp.; the Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp.; and *Cryptococcus neoformans.* Children with relapsed nephrotic syndrome may experience cellulitis caused by *Escherichia coli.* In children 3 months to 5 years of age, *Haemophilus influenzae* type b was once an important cause of facial cellulitis, but its incidence has declined significantly since the institution of immunization against this organism.

Environmental risk factors include exposure to fish, shellfish, and meats *(Erysipelothrix rhusiopathiae)*; salt water, or brackish inland waterways *(Vibrio vulnificus)*; penetrating trauma (mixed pathogens including *Clostridium perfringens*); and human or animal bites (see Chapter 765) (Table 706.1).

Table 706.1 Special Considerations for Causes of Cellulitis

SETTING OR EXPOSURE	CAUSES OF CELLULITIS
Cat or dog bites	*Pasteurella* species, *Capnocytophaga canimorsus*
Penetrating trauma	*Staphylococcus aureus*
Freshwater immersion	*Aeromonas hydrophila*
Saltwater immersion	*Vibrio* species
Freshwater, saltwater fish	*Streptococcus iniae*
Swine, poultry, fish	*Erysipelothrix rhusiopathiae*
Periorbital or facial cellulitis	*Haemophilus influenzae, Streptococcus pneumoniae*
Neutropenia	*Pseudomonas aeruginosa*, other gram-negative bacilli
Human immunodeficiency virus infection	*Helicobacter cinaedi*
Acute varicella	*Streptococcus pyogenes*
Immunosuppression	*Cryptococcus neoformans*

From Long SS, Prober CG, Fischer M. *Principles and Practice of Pediatric Infectious Diseases*, 5th ed. Philadelphia: Elsevier; 2018: Table 68.3, p. 444.

Clinical Manifestations

Cellulitis manifests clinically as a localized area of edema, warmth, erythema, and tenderness. The lateral margins tend to be indistinct because the process is deep in the skin, primarily involving the subcutaneous tissues in addition to the dermis. Application of pressure may produce pitting. Although distinction cannot be made with certainty in any particular patient, cellulitis due to *S. aureus* tends to be more localized and may suppurate, whereas infections caused by *S. pyogenes* (group A streptococci) tend to spread more rapidly and may be associated with lymphangitis. Regional adenopathy and constitutional signs and symptoms such as fever, chills, and malaise are common. Complications of cellulitis are uncommon but include subcutaneous abscess, bacteremia, osteomyelitis, septic arthritis, thrombophlebitis, endocarditis, and necrotizing fasciitis. Lymphangitis or glomerulonephritis can also follow infection with *S. pyogenes.*

Diagnosis

Cellulitis in a neonate should prompt assessment for invasive bacterial infection, including blood culture; lumbar puncture is also usually performed, though its necessity for mild cases of cellulitis is controversial in this age-group. In older children, cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended. However, blood cultures should be considered if the patient is younger than 1 year of age, if signs of systemic toxicity are present, if an adequate examination cannot be carried out, or if an immunocompromising condition (e.g., malignancy, neutropenia, or neutrophil functional defects) is present. Aspirates from the site of inflammation, skin biopsy, and blood cultures allow identification of the causal organism in approximately 25% of cases of cellulitis. Yield of the causative organism is approximately 30% when the site of origin of the cellulitis is apparent, such as an abrasion or ulcer. An aspirate taken from the point of maximum inflammation yields the causal organism more often than a leading-edge aspirate. Lack of success in isolating an organism stems primarily from the low number of organisms present within the lesion. Ultrasonography can be performed if an associated subcutaneous abscess is suspected and may be helpful in cases where there is uncertainty if there a drainable fluid collection is present.

The differential diagnosis includes an exuberant immune-allergic reaction to insect bites, particularly mosquito bites (Skeeter syndromes) (see Chapter 187). **Skeeter syndrome** is characterized by swelling disproportionate to erythema; there is pruritus but usually no tenderness. In addition, **cold panniculitis** may appear as an erythematous, but usually nontender, swelling after exposure to cold, such as sledding or eating a cold Popsicle (see Chapter 701.1).

Treatment

Empirical antibiotic therapy for cellulitis and the initial route of administration should be guided by the age and immune status of the patient, history of the illness, and location and severity of the cellulitis.

Neonates should receive an intravenous antibiotic with a β-lactamase–stable antistaphylococcal antibiotic such as nafcillin, cefazolin, or vancomycin, and an aminoglycoside such as gentamicin or a third-generation cephalosporin such as cefotaxime.

In infants and children older than 2 months with mild to moderate infections, particularly if fever, lymphadenopathy, and other constitutional signs are absent, treatment of cellulitis may be initiated orally on an outpatient basis with a penicillinase-resistant penicillin such as dicloxacillin or a first-generation cephalosporin such as cephalexin or, if MRSA is suspected, with clindamycin. Some recommend trimethoprim-sulfamethoxazole, although it does not provide ideal

coverage against *S. pyogenes,* a potential cause of cellulitis *without* abscess.

Intravenous antibiotics may be necessary if improvement is not noted or the disease progresses significantly in the first 24-48 hours of therapy. Infants and children older than 2 months with signs of systemic infection, including fever, lymphadenopathy, or constitutional signs, also require hospitalization and treatment with intravenous antibiotics effective against *S. pyogenes* and *S. aureus,* such as clindamycin or a first-generation cephalosporin (cefazolin). If the child is severely ill or toxic appearing, consideration should be given to the addition of clindamycin or vancomycin if these antibiotics were not started initially. Other agents for complicated skin and skin structure infections caused by MRSA or *S. pyogenes* have been approved by the U.S. Food and Drug Administration (FDA) in adults, including dalbavancin (IV given once weekly), ceftaroline (IV), telavancin (IV), linezolid (oral or IV), tedizolid (oral or IV), and oritavancin (IV). Dalbavancin also provides activity against vancomycin-resistant enterococci.

In unimmunized patients, antibiotic treatment may include a third-generation cephalosporin (cefepime, ceftriaxone, or, if available, cefotaxime) or a β-lactam/β-lactamase inhibitor combination (e.g., ampicillin-sulbactam), which provides coverage for *H. influenzae* type b and *Streptococcus pneumoniae*.

Once the erythema, warmth, edema, and fever have decreased significantly, a 5- to 7-day total course of treatment may be completed on an outpatient basis, though treatment should be extended if the infection has not substantially improved with this period. Elevation of an affected limb, particularly early in the course of therapy, may help reduce swelling and pain. If present, a subcutaneous abscess should be drained.

NECROTIZING FASCIITIS

Etiology

Necrotizing fasciitis is a subcutaneous tissue infection that involves the deep layer of superficial fascia but may spare adjacent epidermis, deep fascia, and muscle.

Relatively few organisms possess sufficient virulence to cause necrotizing fasciitis when acting alone. Most (55–75%) cases of necrotizing fasciitis are polymicrobial **(synergistic or type 1 necrotizing fasciitis)**, with an average of four different organisms isolated. The organisms most commonly isolated in polymicrobial necrotizing fasciitis are *S. aureus,* streptococcal species, *Klebsiella* species, *E. coli,* and anaerobic bacteria.

The rest of the cases **(type 2)** and the most fulminant infections, associated with toxic shock syndrome and a high case-fatality rate, are usually caused by *S. pyogenes* (group A streptococcus) (see Chapter 229). Streptococcal necrotizing fasciitis may occur in the absence of toxic shock-like syndrome and is potentially fatal and associated with substantial morbidity. Necrotizing fasciitis can occasionally be caused by *S. aureus; C. perfringens; Clostridium septicum; P. aeruginosa; Vibrio* spp., particularly *V. vulnificus;* and fungi of the order Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp. Necrotizing fasciitis has also been reported on rare occasions to result from nongroup A streptococci such as group B, C, F, or G streptococci; *S. pneumoniae;* or *H. influenzae* type b.

Infections caused by any organism or combination of organisms cannot be distinguished clinically from one another, although development of *crepitus* signals the presence of gas-forming organisms: *Clostridium* spp. or gram-negative bacilli such as *E. coli, Klebsiella, Proteus,* or *Aeromonas.*

Clinical Manifestations

Necrotizing fasciitis may occur anywhere on the body but most often on the extremities or areas of trauma. The incidence of necrotizing fasciitis is highest in hosts with systemic or local tissue immunocompromise, such as those with diabetes mellitus, neoplasia, or peripheral vascular disease, and those who have recently undergone surgery, who use IV drugs, or who are undergoing immunosuppressive treatment, particularly with corticosteroids. The infection can also occur in healthy individuals after minor puncture wounds, abrasions, or lacerations; blunt trauma; surgical procedures, particularly of the abdomen, gastrointestinal or genitourinary tracts, or the perineum; or hypodermic needle injection.

There is a resurgence of fulminant necrotizing soft tissue infections caused by *S. pyogenes,* which may occur in previously healthy individuals. Streptococcal necrotizing fasciitis is classically located on an extremity. There may be a history of recent trauma to or operation in the area. Necrotizing fasciitis due to *S. pyogenes* may also occur after superinfection of varicella lesions. Children with this disease have tended to display onset, recrudescence, or persistence of high fever and signs of toxicity after the third or fourth day of varicella. Common predisposing conditions in neonates are omphalitis and balanitis after circumcision.

Necrotizing fasciitis begins with acute onset of local, and at times tense, edema with erythema, tenderness, and heat. Fever is usually present, and pain, tenderness, and constitutional signs are disproportionate to cutaneous signs, especially with involvement of fascia and muscle. Tachycardia is out of proportion to the fever. Lymphangitis and lymphadenitis may or may not be present. The infection advances along the superficial fascial plane, and initially there may be few cutaneous signs to herald the serious nature and extent of the subcutaneous tissue necrosis that is occurring. Skin changes may appear over 24-48 hours as nutrient vessels are thrombosed and cutaneous ischemia develops. Early clinical findings include ill-defined cutaneous erythema and edema that extends beyond the area of erythema. *There is intense pain on movement.* Additional signs include formation of bullae filled initially with straw-colored and later bluish to hemorrhagic fluid and darkening of affected tissues from red to purple to blue. Skin anesthesia and, finally, frank tissue gangrene and slough develop owing to the ischemia and necrosis. Vesiculation or bulla formation, ecchymoses, crepitus, anesthesia, and necrosis are ominous signs indicative of advanced disease. Children with varicella lesions may initially show no cutaneous signs of superinfection with invasive *S. pyogenes,* such as erythema or swelling. Significant systemic toxicity may accompany necrotizing fasciitis, including shock, organ failure, and death. Advance of the infection in this setting can be rapid, progressing to death within hours. Patients with involvement of the superficial or deep fascia and muscle tend to be more acutely and systemically ill and have more rapidly advancing disease than those with infection confined solely to subcutaneous tissues above the fascia. There is often hyponatremia (<135 mg/L), an elevated CRP (>20 mg/L), and extreme leukocytosis. In an extremity, **compartment syndrome** may develop, manifesting as tight edema, pain on motion, and loss of distal sensation and pulses; this is a surgical emergency (see Chapter 80).

Diagnosis

Definitive diagnosis of necrotizing fasciitis is made by surgical exploration, which should be undertaken as soon as the diagnosis is suspected. Necrotic fascia and subcutaneous tissue are gray and offer little resistance to blunt probing. Although MRI aids in delineating the extent and tissue planes of involvement, these procedures should not delay surgical intervention. Frozen-section incisional biopsy specimens obtained early in the course of the infection can aid management by decreasing the time to diagnosis and helping to establish the margins of involvement. Gram staining of tissue can be particularly useful if chains of gram-positive cocci, indicative of infection with *S. pyogenes,* are seen.

Treatment

Early supportive care, surgical debridement, and parenteral antibiotic administration are mandatory for necrotizing fasciitis. All devitalized tissue should be removed to freely bleeding edges, and repeat exploration is generally indicated within 24-36 hours to confirm that no necrotic tissue remains. This procedure may need to be repeated on several occasions until devitalized tissue has ceased to form. Meticulous daily wound care is also paramount.

Parenteral antibiotic therapy should be initiated as soon as possible with broad-spectrum agents against all potential pathogens. Initial empirical therapy should be instituted with vancomycin, linezolid,

or daptomycin to cover gram-positive organisms and piperacillin-tazobactam to cover gram-negative organisms. An alternative is to add ceftriaxone with metronidazole to cover mixed aerobic-anaerobic organisms. Definitive therapy should then be based on sensitivity of isolated organisms. Penicillin with clindamycin is indicated for necrotizing fasciitis caused by either group A streptococcus or *Clostridium* spp. For group A streptococcus infections, clindamycin is administered until the patient is hemodynamically stable and no longer requires surgical debridement. Unlike penicillin, the effectiveness of clindamycin is not influenced by the infectious burden or bacterial stage of growth; thus its addition early in the course of infection may lead to more rapid bacterial killing. Doxycycline plus either ciprofloxacin or ceftazidime is recommended for *V. vulnificus* necrotizing fasciitis. Duration of therapy for necrotizing fasciitis depends on the course of the illness. Antibiotics are generally continued for at least 5 days after signs and symptoms of local signs and symptoms have resolved; the typical duration of therapy is 4 weeks. Many centers employ hyperbaric oxygen therapy, although it should not delay resuscitation of shock or surgical debridement.

Prognosis

The combined case-fatality rate among children and adults with necrotizing fasciitis and syndrome due to polymicrobial infection or *S. pyogenes* has been as high as 60%. However, death is less common in children and in cases not complicated by toxic shock–like syndrome.

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706.3 Staphylococcal Scalded Skin Syndrome (Ritter Disease)

Stephen R. Humphrey

ETIOLOGY AND PATHOGENESIS

Staphylococcal scalded skin syndrome is caused predominantly by phage group 2 staphylococci, particularly strains 71 and 55, which are present at localized sites of infection. Foci of infection include the nasopharynx and, less commonly, the umbilicus, urinary tract, a superficial abrasion, conjunctivae, and blood. The clinical manifestations of staphylococcal scalded skin syndrome are mediated by hematogenous spread in the absence of specific antitoxin antibody of staphylococcal epidermolytic or exfoliative toxins A or B. The toxins have reproduced the disease in both animal models and human volunteers. Decreased renal clearance of the toxins may account for the fact that the disease is most common in infants and young children, as well as a lack of protection from antitoxin antibodies. Epidermolytic toxin A is heat stable and is encoded by bacterial chromosomal genes. Epidermolytic toxin B is heat labile and is encoded on a 37.5-kb plasmid. The site of blister cleavage is subcorneal. The epidermolytic toxins produce the split by binding to and cleaving desmoglein 1. Intact bullae are consistently sterile, unlike those of bullous impetigo, but culture specimens should be obtained from all suspected sites of localized infection and from the blood to identify the source for elaboration of the epidermolytic toxins.

CLINICAL MANIFESTATIONS

Staphylococcal scalded skin syndrome, which occurs predominantly in infants and children younger than 5 years of age, includes a range of disease from localized bullous impetigo to generalized cutaneous involvement with systemic illness. Onset of the rash may be preceded by malaise, fever, irritability, and exquisite tenderness of the skin. **Scarlatiniform erythema** develops diffusely and is accentuated in flexural and periorificial areas. The conjunctivae are inflamed and occasionally become purulent. The brightly erythematous skin may rapidly acquire a wrinkled appearance, and in severe cases, sterile, flaccid blisters and erosions develop diffusely. Circumoral erythema is characteristically prominent, as is radial crusting and fissuring around the eyes, mouth, and nose. At this stage, areas of the epidermis may separate in response to gentle shear force (Nikolsky sign; Fig. 706.2). As large sheets of epidermis peel away, moist, glistening, denuded areas become apparent, initially in the flexures and subsequently over much of the body surface (Fig. 706.3). This development may lead to secondary cutaneous infection, sepsis, and fluid and electrolyte disturbances. The desquamative phase begins after 2-5 days of cutaneous erythema; healing occurs without scarring in 10-14 days. Patients may have pharyngitis, conjunctivitis, and superficial erosions of the lips, but intraoral mucosal surfaces are spared. Although some patients appear ill, many are reasonably comfortable except for the marked skin tenderness.

DIFFERENTIAL DIAGNOSIS

A presumed forme fruste of the disease manifests as diffuse, scarlatiniform, tender erythroderma that is accentuated in the flexural areas but does not progress to blister formation. In patients with this form, Nikolsky sign may be absent. Although the exanthem is similar to that of streptococcal scarlet fever, strawberry tongue and palatal petechiae are absent. Staphylococcal scalded skin syndrome may be mistaken for a number of other blistering and exfoliating disorders, including

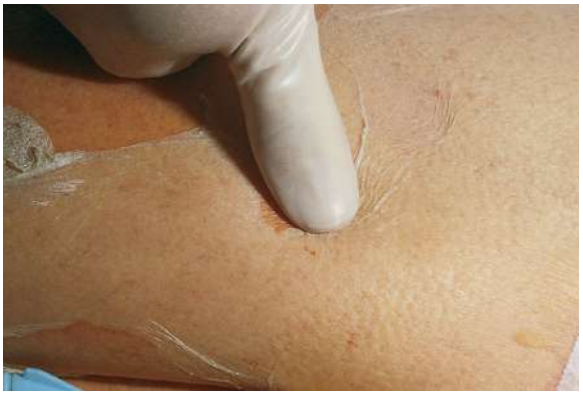

Fig. 706.2 Nikolsky sign. With slight thumb pressure the skin wrinkles, slides laterally, and separates from the dermis. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004.)*

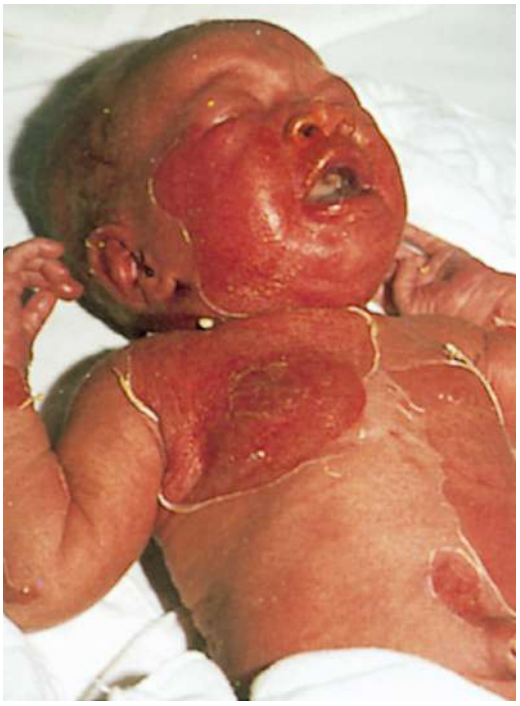

Fig. 706.3 Infant with staphylococcal scalded skin syndrome.

bullous impetigo, epidermolysis bullosa, epidermolytic hyperkeratosis, pemphigus, drug eruption, erythema multiforme, and drug-induced toxic epidermal necrolysis. Toxic epidermal necrolysis can often be distinguished by a history of drug ingestion, the presence of Nikolsky sign only at sites of erythema, the absence of perioral crusting, full-thickness epidermal necrosis, and a blister cleavage plane in the lowermost epidermis.

HISTOLOGY

A subcorneal, granular layer split can be identified on skin biopsy. Absence of an inflammatory infiltrate is characteristic. Histology is identical to that seen in pemphigus foliaceus, bullous impetigo, and subcorneal pustular dermatosis.

TREATMENT

Systemic therapy, given either orally in cases of localized involvement or parenterally with a semisynthetic antistaphylococcal penicillin (e.g., nafcillin), first-generation cephalosporin (e.g., cefazolin), clindamycin, or vancomycin if MRSA is considered, should be prescribed. Clindamycin is typically used *in addition* to other agents to inhibit bacterial protein (toxin) synthesis; however, it may not provide any additional coverage compared with cephalosporins unless there is high MRSA community prevalence. The skin should be gently moistened and cleansed. Application of an emollient provides lubrication and decreases discomfort. Topical antibiotics are unnecessary. In neonates, or in infants or children with severe infection, hospitalization is mandatory, with attention to fluid and electrolyte management, infection control measures, pain management, and meticulous wound care with contact isolation. In particularly severe disease, care in an intensive care or burn unit is required. Recovery is usually rapid, but complications, such as excessive fluid loss, electrolyte imbalance, faulty temperature regulation, pneumonia, septicemia, and cellulitis, may cause increased morbidity.

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706.4 Ecthyma

Stephen R. Humphrey

See also Chapters 227, 229, and 251.

Ecthyma resembles nonbullous impetigo in onset and appearance but gradually evolves into a deeper, more chronic infection. The initial lesion is a vesicle or vesicular pustule with an erythematous base that erodes through the epidermis into the dermis to form an ulcer with elevated margins. The ulcer becomes obscured by a dry, heaped-up, tightly adherent crust (Fig. 706.4) that contributes to the persistence of the infection and scar formation. Lesions may be spread by autoinoculation, may be as large as 4 cm, and occur most frequently on the legs. Predisposing factors include the presence of pruritic lesions, such as insect bites, scabies, or pediculosis, that are subject to frequent scratching; poor hygiene; and malnutrition. Complications include lymphangitis, cellulitis, and, rarely, poststreptococcal glomerulonephritis. The causative agent is usually GABHS; *S. aureus* is also cultured from most lesions but is probably a secondary pathogen. Crusts should be softened with warm compresses and removed. Systemic antibiotic therapy, as for impetigo, is indicated; almost all lesions are responsive to treatment with penicillin.

Ecthyma gangrenosum is a necrotic ulcer covered with a gray-black eschar. It is usually a sign of *P. aeruginosa* infection, most often occurring in immunosuppressed patients. Neutropenia is a risk factor for ecthyma gangrenosum, including variants such as chronic, cyclic, and transient neutropenia. Ecthyma gangrenosum occurs in up to 6% of patients with systemic *P. aeruginosa* infection but can also occur as a primary cutaneous infection by inoculation. The lesion begins as a red or purpuric macule that vesiculates and then ulcerates. There is a surrounding rim of pink to violaceous skin. The punched-out ulcer develops raised edges with a dense, black, depressed, crusted center.

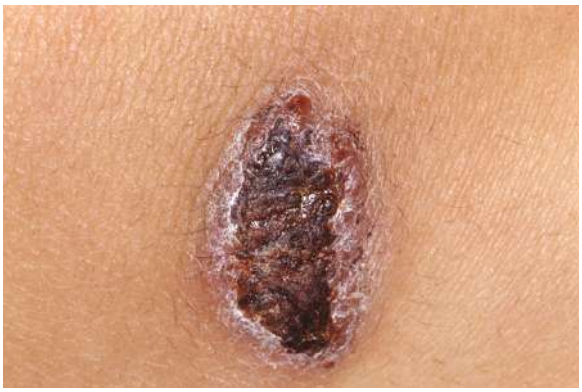

Fig. 706.4 Dry, tightly adherent crust in ecthyma.

Lesions may be single or multiple. Patients with bacteremia commonly have lesions in apocrine areas. Clinically similar lesions may also develop as a result of infection with other agents, such as *S. aureus, A. hydrophila, Enterobacter* spp., *Proteus* spp., *Burkholderia cepacia, Serratia marcescens, Aspergillus* spp., Mucorales, *E. coli,* and *Candida* spp. There is bacterial invasion of the adventitia and media of dermal veins but not arteries. The intima and lumina are spared. Blood and skin biopsy specimens for culture should be obtained, and empirical broad-spectrum, systemic therapy that includes coverage for *P. aeruginosa* (e.g., antipseudomonal penicillin or cephalosporin and an aminoglycoside) should be initiated as soon as possible.

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706.5 Other Cutaneous Bacterial Infections

Stephen R. Humphrey

BLASTOMYCOSIS-LIKE PYODERMA (PYODERMA VEGETANS)

Blastomycosis-like pyoderma is an exuberant cutaneous reaction to bacterial infection that occurs primarily in children who are malnourished and immunosuppressed. The organisms most commonly isolated from lesions are *S. aureus* and group A streptococcus, but several other organisms have been associated with these lesions, including *P. aeruginosa, Proteus mirabilis,* diphtheroids, *Bacillus* spp., and *C. perfringens.* Crusted, hyperplastic plaques on the extremities are characteristic, sometimes forming from the coalescence of many pinpoint, purulent, crusted abscesses (Fig. 706.5). Ulceration and sinus tract formation may develop, and additional lesions may appear at sites distant from the site of inoculation. Regional lymphadenopathy is common, but fever is not. Histopathologic examination reveals pseudoepitheliomatous hyperplasia and microabscesses composed of neutrophils and/or eosinophils. Giant cells are usually lacking. The differential diagnosis includes deep fungal infection, particularly blastomycosis (Fig. 706.6) and tuberculous and atypical mycobacterial infection. Underlying immunodeficiency should be ruled out, and the selection of antibiotics should be guided by susceptibility testing because the response to antibiotics is often poor.

BLISTERING DISTAL DACTYLITIS

Blistering distal dactylitis is a superficial blistering infection of the volar fat pad on the distal portion of the finger or thumb that typically affects infants and young children (Fig. 706.7). More than one finger may be involved, as may the volar surfaces of the proximal phalanges, palms, and toes. Blisters are filled with a watery purulent fluid; polymorphonuclear leukocytes and gram-positive cocci are identified on Gram stain. Patients commonly have no preceding history of trauma, and systemic symptoms are generally absent. Poststreptococcal

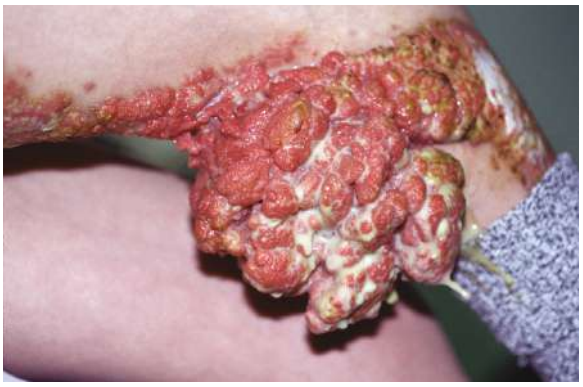

Fig. 706.5 Large vegetating lesion of pyoderma vegetans.

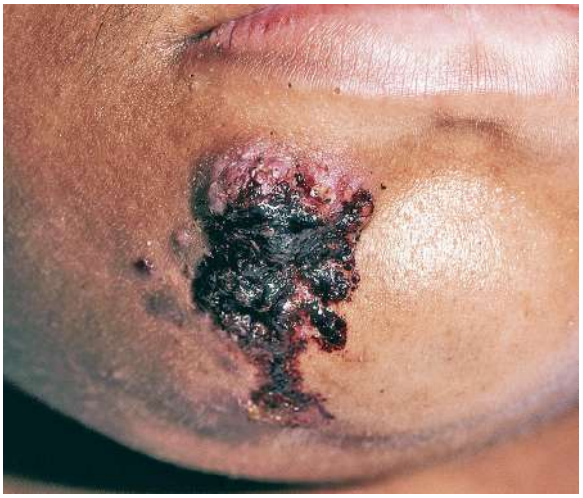

Fig. 706.6 Cutaneous blastomycosis. Verrucous, crusted, erythematous plaque on the chin in a 15-yr-old boy with respiratory symptoms and bone pain. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006, Fig. 14.13.)*

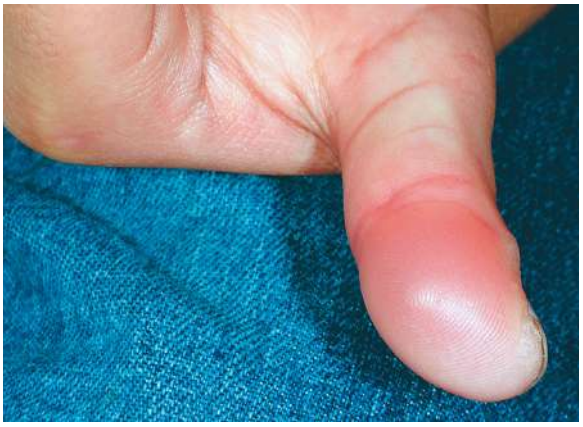

Fig. 706.7 Blistering dactylitis. Edema and a tense bulla on the thumb of this 7-yr-old girl. Culture of the blister fluid yielded *Staphylococcus aureus* rather than the more commonly seen group A β-hemolytic streptococcus. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006, Fig. 14.14.)*

glomerulonephritis has not occurred after blistering distal dactylitis. The infection is caused most commonly by group A streptococcus but has also occurred as a result of infection with *S. aureus.* If left untreated, blisters may continue to enlarge and extend to the paronychial area. The infection responds to incision and drainage and a 10-day course of an antibiotic effective against group A streptococcus and *S. aureus* (e.g., amoxicillin-clavulanate, clindamycin, cephalexin); patients may require initial IV antibiotic therapy.

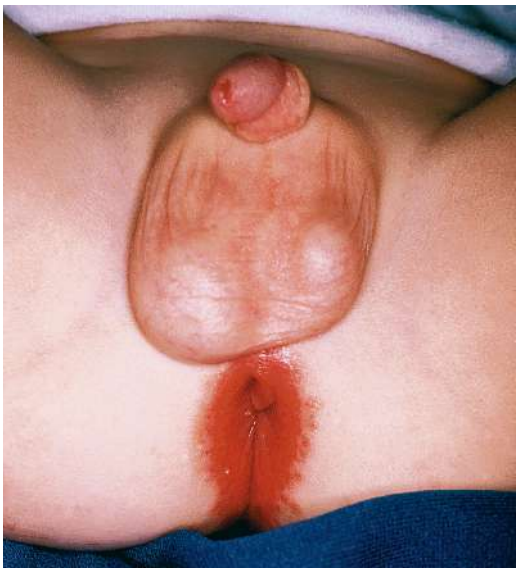

Fig. 706.8 Perianal streptococcal dermatitis. Bright red erythema with a moist, tender surface. *(From Paller AS, Mancini AJ, eds. Hurwitz Clinical Pediatric Dermatology, 3rd ed. Philadelphia: Saunders; 2006, Fig. 17.38.)*

PERIANAL INFECTIOUS DERMATITIS

Perianal infectious dermatitis presents most commonly in boys (70% of cases) between the ages of 6 months and 10 years as perianal dermatitis (90% of cases) and pruritus (80% of cases; Fig. 706.8). The incidence of perianal infectious dermatitis is not known precisely but ranges from 1 in 2,000 to 1 in 218 patient visits. When GABHS is suspected, it is often referred to as *perianal streptococcal dermatitis.* The rash is superficial, erythematous, well marginated, nonindurated, and confluent from the anus outward. Acutely (<6 weeks), the rash tends to be bright red, moist, and tender to touch. At this stage, a white pseudomembrane may be present. As the rash becomes more chronic, the perianal eruption may consist of painful fissures, a dried mucoid discharge, or psoriasiform plaques with yellow peripheral crust. In girls, the perianal rash may be associated with vulvovaginitis. In boys, the penis may be involved. Approximately 50% of patients have rectal pain, most commonly described as burning inside the anus during defecation, and 33% have blood-streaked stools. Fecal retention is a frequent behavioral response to the infection. Patients also have presented with guttate psoriasis. Although local induration or edema may occur, constitutional symptoms, such as fever, headache, and malaise, are absent, suggesting that subcutaneous involvement, as in cellulitis, is absent. Familial spread of perianal infectious dermatitis is common, particularly when family members bathe together or use the same water.

Perianal infectious dermatitis is usually caused by GABHS, but it may also be caused by *S. aureus.* The index case and family members should undergo culture; follow-up cultures to document bacteriologic cure after a course of treatment are recommended.

The differential diagnosis of perianal infectious dermatitis includes psoriasis, seborrheic dermatitis, candidiasis, pinworm infestation, sexual abuse, and inflammatory bowel disease.

For GABHS perianal infectious dermatitis, treatment with a 7-day course of cefuroxime (20 mg/kg/day in two divided doses) is superior to treatment with penicillin. Concomitant topical mupirocin ointment two to three times a day also may be used. If *S. aureus* is cultured, treatment should be based on sensitivities.

ERYSIPELAS

See Chapter 229.

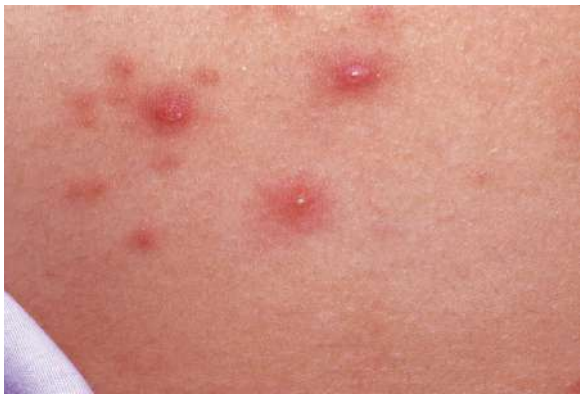

Fig. 706.9 Folliculitis. Multiple follicular pustules.

FOLLICULITIS

Folliculitis, or superficial infection of the hair follicle, is most often caused by *S. aureus*. The lesions are typically small, discrete, dome-shaped pustules with an erythematous base, located at the ostium of the pilosebaceous canals (Fig. 706.9). Hair growth is unimpaired, and the lesions heal without scarring. Favored sites include the scalp, buttocks, and extremities. Poor hygiene, maceration, drainage from wounds and abscesses, and shaving of the legs can be provocative factors. Folliculitis can also occur as a result of tar therapy or occlusive wraps. The moist environment encourages bacterial proliferation. In HIV-infected patients, *S. aureus* may produce confluent erythematous patches with satellite pustules in intertriginous areas and violaceous plaques composed of superficial follicular pustules in the scalp, axillae, or groin. The differential diagnosis includes *Candida,* which may cause satellite follicular papules and pustules surrounding erythematous patches of intertrigo (particularly in groin/buttocks), and *Malassezia furfur,* which produces 2- to 3-mm, pruritic, erythematous, perifollicular papules and pustules on the back, chest, and extremities, particularly in patients who have diabetes mellitus or are taking corticosteroids or antibiotics. Diagnosis is made by examining potassium hydroxide–treated scrapings from lesions. Detection of *Malassezia* may require a skin biopsy, demonstrating clusters of yeast and short, branching hyphae ("macaroni and meatballs") in widened follicular ostia mixed with keratinous debris.

Topical antibiotic therapy (e.g., clindamycin 1% lotion or solution twice a day) is usually all that is needed for mild cases, but more severe cases may require the use of a systemic antibiotic such as dicloxacillin or cephalexin. Bacterial culture should be performed in treatment-resistant cases. In chronic recurrent folliculitis, daily application of a benzoyl peroxide 5% gel or wash may facilitate resolution. Dilute bleach baths may also be effective in reducing recurrence.

Folliculitis barbae (sycosis barbae) is a deeper, more severe recurrent inflammatory form of folliculitis caused by *S. aureus* that involves the entire depth of the follicle. Erythematous follicular papules and pustules develop on the chin, upper lip, and angle of the jaw, primarily in young Black males. Papules may coalesce into plaques, and healing may occur with scarring. Affected individuals are frequently found to be *S. aureus* carriers. Treatment with warm saline compresses and topical antibiotics, such as mupirocin, generally clear the infection. More extensive, recalcitrant cases may require therapy with β-lactamase–resistant systemic antibiotics for several weeks and elimination of *S. aureus* from the sites of carriage.

Pseudomonal folliculitis (hot tub folliculitis) is attributable to *P. aeruginosa,* predominantly serotype O-11. It occurs after exposure to poorly chlorinated hot tubs/whirlpools and swimming pools and to a contaminated water slide or loofah sponge. The lesions are pruritic papules and pustules or deeply erythematous to violaceous nodules that develop 8-48 hours after exposure and are most dense in areas covered by a bathing suit (Fig. 685.10). Patients occasionally experience fever, malaise, and lymphadenopathy. The organism is readily cultured from pus. The eruption usually resolves spontaneously in 1-2 weeks, often leaving postinflammatory hyperpigmentation. Consideration should be given to the use of systemic antibiotics (ciprofloxacin) in adolescent patients with constitutional symptoms. Immunocompromised children are susceptible to complications of *Pseudomonas* folliculitis (cellulitis) and should avoid hot tubs.

ABSCESSES AND FURUNCLES

Etiology

The causative agent in furuncles ("boils") and carbuncles is usually *S. aureus,* which penetrates abraded perifollicular skin. Furuncles are nodules that develop from a single follicle, whereas carbuncles are a coalescence of multiple follicles and are more extensive. Conditions predisposing to furuncle formation include obesity, hyperhidrosis, maceration, friction, and preexisting dermatitis. Furunculosis is also more common in individuals with low serum iron levels, diabetes, malnutrition, HIV infection, or other immunodeficiency states. Recurrent furunculosis is frequently associated with carriage of *S. aureus* in the nares, axillae, or perineum or close contact with someone such as a family member who is a carrier. Other bacteria or fungi may occasionally cause furuncles or carbuncles.

Community-acquired MRSA **abscesses** can also complicate folliculitis-related carbuncles or are acquired from penetrating cutaneous trauma unrelated to folliculitis. Community-acquired MRSA infections commonly affect children and young adults, especially athletes, where spread of the infection is enhanced by skin-to-skin contact. Infection can also be spread by crowding conditions, shared personal hygiene items, and a compromised skin barrier. They may occur in any location; however, they are most common on the lower abdomen, buttocks, and legs.

Clinical Manifestations

This follicular lesion may originate from a preceding folliculitis or may arise initially as a deep-seated, tender, erythematous, perifollicular nodule. Although lesions are initially indurated, central necrosis and suppuration follow, leading to rupture and discharge of a central core of necrotic tissue and destruction of the follicle (Fig. 706.11). Healing occurs with scar formation. Sites of predilection are the hair-bearing areas on the face, neck, axillae, buttocks, and groin. Pain may be intense if the lesion is situated in an area where the skin is relatively fixed, such as in the external auditory canal or over the nasal cartilages. Patients with furuncles usually have no constitutional symptoms; bacteremia may occasionally ensue. Rarely, lesions on the upper lip or cheek may lead to cavernous sinus thrombosis. Infection of a group of contiguous follicles, with multiple drainage points, accompanied by inflammatory changes in surrounding connective tissue is a carbuncle. Carbuncles may be accompanied by fever, leukocytosis, and bacteremia. Hidradenitis suppurativa should be considered in individuals who have recurrent abscesses.

Treatment

Treatment for furuncle and carbuncle includes regular bathing with antimicrobial soaps (chlorhexidine) and wearing of loose-fitting clothing to minimize predisposing factors for furuncle formation. Frequent application of a hot, moist compress may facilitate the drainage of lesions. Large lesions should be drained by a small incision. Carbuncles and large or numerous furuncles should be treated with systemic antibiotics chosen based on culture and sensitivity testing results.

Abscesses are treated with incision and drainage and oral antibiotics for 7-10 days. Antibiotics with coverage against MRSA are recommended and commonly include oral clindamycin (10-30 mg/kg/day in divided doses) or trimethoprim-sulfamethoxazole (8-10 mg trimethoprim/kg/day in divided doses every 12 hours). Children older than 8 years may receive doxycycline. To reduce colonization and hence reinfection in children with recurrent infections, mupirocin intranasally (twice daily) and either chlorhexidine (in lieu of soap during showers) or diluted bleach baths (1 teaspoon per gallon of water or 1/4 cup per 1/4 tub [~13 gallons] of water) once daily for 5 days in patients and in family members has been recommended. Recolonization often occurs, typically within 3 months of the decolonization attempt.

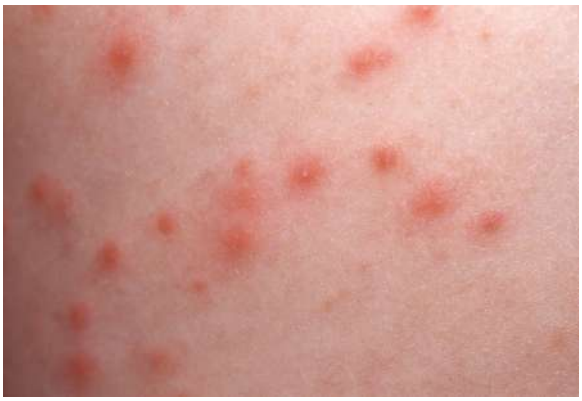

Fig. 706.10 Papules and pustules in hot tub folliculitis.

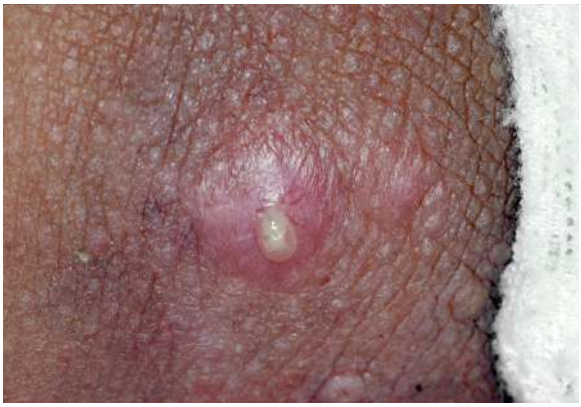

Fig. 706.11 Rupture and discharge of pus in a furuncle.

PITTED KERATOLYSIS

Pitted keratolysis occurs most frequently in humid tropical and subtropical climates, particularly in individuals whose feet are moist for prolonged periods, for example, as a result of hyperhidrosis, prolonged wearing of boots, or immersion in water. It occurs most commonly in young males from early adolescence to the late 20s. The lesions consist of 1- to 7-mm, irregularly shaped, superficial erosions of the horny layer on the soles, particularly at weight-bearing sites (Fig. 706.12). Brownish discoloration of involved areas may be apparent. A rare variant manifests as thinned, erythematous to violaceous plaques in addition to the typical pitted lesions. The condition is frequently malodorous and is painful in approximately 50% of cases. The most likely etiologic agent is *Corynebacterium (Kytococcus) sedentarius.* Treatment of hyperhidrosis is mandatory with prescription-strength aluminum chloride products or 40% formaldehyde in petrolatum ointment. Avoidance of moisture and maceration produces slow, spontaneous resolution of the infection. Topical or systemic erythromycin and topical imidazole creams are standard therapy.

ERYTHRASMA

Erythrasma is a benign chronic superficial infection caused by *Corynebacterium minutissimum.* Predisposing factors include heat, humidity, obesity, skin maceration, diabetes mellitus, and poor hygiene. Approximately 20% of affected patients have involvement of the toe webs. Other frequently affected sites are moist, intertriginous areas such as the groin and axillae. The inframammary and perianal regions are occasionally involved. Sharply demarcated, irregularly bordered, slightly scaly, brownish red patches are characteristic of the disease. Mild pruritus is the only constant symptom. *C. minutissimum* is a complex of related organisms that produce porphyrins that fluoresce brilliant coral red under ultraviolet light. The diagnosis is readily made, and erythrasma is differentiated from dermatophyte infection and from tinea versicolor on Wood lamp examination. However, bathing within 20 hours of Wood lamp examination may remove the water-soluble porphyrins. Staining of skin scrapings with methylene blue or Gram stain reveals the pleomorphic, filamentous coccobacillary forms.

Effective treatment can be achieved with topical erythromycin, clindamycin, miconazole, or a 10- to 14-day course of oral erythromycin or an oral tetracycline (in those older than 8 years of age).

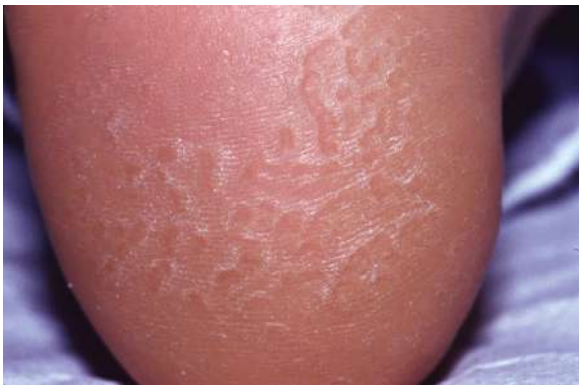

Fig. 706.12 Superficial erosions of the horny layer in pitted keratolysis.

ERYSIPELOID

A rare cutaneous infection, erysipeloid is caused by inoculation of *E. rhusiopathiae* from handling contaminated animals, birds, fish, or their products. The localized cutaneous form is most common, characterized by well-demarcated, diamond-shaped, erythematous to violaceous patches at sites of inoculation. Local symptoms are generally not severe, constitutional symptoms are rare, and the lesions resolve spontaneously after weeks but can recur at the same site or develop elsewhere weeks to months later. The diffuse cutaneous form manifests as lesions at several areas of the body in addition to the site of inoculation. It is also self-limited. The systemic form, caused by hematogenous spread, is accompanied by constitutional symptoms and may include endocarditis, septic arthritis, cerebral infarct and abscess, meningitis, and pulmonary effusion. Diagnosis is confirmed by skin biopsy, which reveals the gram-positive organisms, and culture. The treatment of choice for localized cutaneous infection is oral penicillin for 7 days; ciprofloxacin or a combination of erythromycin and rifampin may be used for penicillin-allergic patients. Severe diffuse cutaneous or systemic infection may require parenteral penicillin or ceftriaxone.

TUBERCULOSIS OF THE SKIN

See Chapters 261 and 263.

Cutaneous tuberculosis infection occurs worldwide, particularly in association with HIV infection, malnutrition, and poor sanitary conditions. Primary cutaneous tuberculosis is rare in the United States. Cutaneous disease is caused by *Mycobacterium tuberculosis, Mycobacterium bovis,* and, occasionally, by the bacillus Calmette-Guérin (BCG), an attenuated vaccine form of *M. bovis.* The manifestations caused by a given organism are indistinguishable from one another. After invasion of the skin, mycobacteria either multiply intracellularly within macrophages, leading to progressive disease, or are controlled by the host immune reaction.

Primary cutaneous tuberculosis (tuberculous chancre) results when *M. tuberculosis* or *M. bovis* gains access to the skin or mucous membranes through trauma in a previously uninfected individual without immunity to the organism. Sites of predilection are the face, lower extremities, and genitals. The initial lesion develops 2-4 weeks after introduction of the organism into the damaged tissue. A red-brown papule gradually enlarges to form a shallow, firm, sharply demarcated ulcer. Satellite abscesses may be present. Some lesions acquire a crust resembling impetigo, and others become heaped up and verrucous at the margins. The primary lesion can also manifest as a painless ulcer on the conjunctiva, gingiva, or palate and occasionally as a painless acute paronychia. Painless regional adenopathy may appear several

weeks after the development of the primary lesion and may be accompanied by lymphangitis, lymphadenitis, or perforation of the skin surface, forming **scrofuloderma**. Untreated lesions heal with scarring within 12 months but may reactivate, may form lupus vulgaris (sharply defined red-brown nodules with a gelatinous consistency that represent progressive infection), or, rarely, may progress to the acute miliary form. Therefore antituberculous therapy is indicated (see Chapter 261).

M. tuberculosis or *M. bovis* can be cultured from the skin lesion and local lymph nodes, but acid-fast staining of histologic sections, particularly of a well-controlled infection, often does not reveal the organism. The differential diagnosis is broad, including a syphilitic chancre; deep fungal or atypical mycobacterial infection; leprosy; tularemia; cat-scratch disease; sporotrichosis; nocardiosis; leishmaniasis; reaction to foreign substances such as zirconium, beryllium, silk or nylon sutures, talc, and starch; papular acne rosacea; and lupus miliaris disseminatus faciei.

Scrofuloderma results from enlargement, cold abscess formation, and breakdown of a lymph node, most frequently in a cervical chain, with extension to the overlying skin from underlying foci of tuberculous infection. Linear or serpiginous ulcers and dissecting fistulas and subcutaneous tracts studded with soft nodules may develop. Spontaneous healing may take years, eventuating in cordlike keloid scars. Lupus vulgaris may also develop. Lesions may also originate from an underlying infected joint, tendon, bone, or epididymis. The differential diagnosis includes syphilitic gumma, deep fungal infections, actinomycosis, and hidradenitis suppurativa. The course is indolent, and constitutional symptoms are typically absent. Antituberculous therapy is indicated (see Chapter 261).

Direct cutaneous inoculation of the tubercle bacillus into a previously infected individual with a moderate to high degree of immunity initially produces a small papule with surrounding inflammation. **Tuberculosis verrucosa cutis** (warty tuberculosis) forms when the papule becomes hyperkeratotic and warty, and several adjacent papules coalesce or a single papule expands peripherally to form a brownish red to violaceous, exudative, crusted verrucous plaque. Irregular extension of the margins of the plaque produces a serpiginous border. Children have the lesions most commonly on the lower extremities after trauma and contact with infected material such as sputum or soil. Regional lymph nodes are involved only rarely. Spontaneous healing with atrophic scarring takes place over months to years. Healing is also gradual with antituberculous therapy.

Lupus vulgaris is a rare, chronic, progressive form of cutaneous tuberculosis that develops in individuals with a moderate to high degree of tuberculin sensitivity induced by previous infection. The incidence is greater in cool, moist climates, particularly in females. Lupus vulgaris develops as a result of direct extension from underlying joints or lymph nodes; through lymphatic or hematogenous spread; or, rarely, by cutaneous inoculation with the BCG vaccine. It most commonly follows cervical adenitis or pulmonary tuberculosis. Approximately 33% of cases are preceded by scrofuloderma, and 90% of cases manifest on the head and neck, most commonly on the nose or cheek. Involvement of the trunk is uncommon. A typical solitary lesion consists of a soft, brownish red papule that has an apple-jelly color when examined by diascopy. Peripheral expansion of the papule or, occasionally, the coalescence of several papules forms an irregular lesion of variable size and form. One or several lesions may develop, including nodules or plaques that are flat and serpiginous, hypertrophic and verrucous, or edematous in appearance. Spontaneous healing occurs centrally, and lesions characteristically reappear within the area of atrophy. Chronicity is characteristic, and persistence and progression of plaques over many years are common. Lymphadenitis is present in 40% of those with lupus vulgaris, and 10–20% have infection of the lungs, bones, or joints. Extensive deformities may be caused by vegetative masses and ulceration involving the nasal, buccal, or conjunctival mucosa; the palate; the gingiva; or the oropharynx. Squamous cell carcinoma, with a relatively high metastatic potential, may develop, usually after several years of the disease. After a temporary impairment in immunity, particularly after measles infection (lupus exanthematicus), multiple lesions may form at distant sites as a result of hematogenous spread from a latent focus of infection. The histopathology reveals a tuberculoid granuloma without caseation; organisms are extremely difficult to demonstrate. The differential diagnosis includes sarcoidosis, atypical mycobacterial infection, blastomycosis, chromoblastomycosis, actinomycosis, leishmaniasis, tertiary syphilis, leprosy, hypertrophic lichen planus, psoriasis, lupus erythematosus, lymphocytoma, and Bowen disease. Small lesions can be excised. Antituberculous drug therapy usually halts further spread and induces involution.

Orificial tuberculosis (tuberculosis cutis orificialis) appears on the mucous membranes and periorificial skin after autoinoculation of mycobacteria from sites of progressive infection. It is a sign of advanced internal disease and carries a poor prognosis, and it occurs in a sensitized host with impaired cellular immunity. Lesions appear as painful, yellowish or red nodules that form punched-out ulcers with inflammation and edema of the surrounding mucosa. Treatment consists of identification of the source of infection and initiation of antituberculous therapy.

Miliary tuberculosis (hematogenous primary tuberculosis) rarely manifests cutaneously and occurs most commonly in infants and in individuals who are immunosuppressed after chemotherapy or infection with measles or HIV. The eruption consists of crops of symmetrically distributed, minute, erythematous to purpuric macules, papules, or vesicles. The lesions may ulcerate, drain, crust, and form sinus tracts or may form subcutaneous gummas, especially in malnourished children with impaired immunity. Constitutional signs and symptoms are common, and a leukemoid reaction or aplastic anemia may develop. Tubercle bacilli are readily identified in an active lesion. A fulminant course should be anticipated, and aggressive antituberculous therapy is indicated.

Single or multiple metastatic tuberculous abscesses **(tuberculous gummas)** may develop on the extremities and trunk by hematogenous spread from a primary focus of infection during a period of decreased immunity, particularly in malnourished and immunosuppressed children. The fluctuant, nontender, erythematous subcutaneous nodules may ulcerate and form fistulas.

Vaccination with BCG characteristically produces a papule approximately 2 weeks after vaccination. The papule expands in size, typically ulcerates within 2-4 months, and heals slowly with scarring. In 1-2 per million vaccinations, a complication caused specifically by the BCG organism occurs, including regional lymphadenitis, lupus vulgaris, scrofuloderma, and subcutaneous abscess formation. Delayed reactivation with inflammation at the site of BCG vaccination has been reported with Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C), as well as immunization with the COVID-19 and influenza vaccines.

Tuberculids are skin reactions that exhibit tuberculoid features histologically but do not contain detectable mycobacteria. The lesions appear in a host who usually has moderate to strong tuberculin reactivity, has a history of previous tuberculosis of other organs, and usually shows a therapeutic response to antituberculous therapy. The cause of tuberculids is poorly understood. Most affected patients are in good health with no clear focus of disease at the time of the eruption. The most commonly observed tuberculid is the papulonecrotic tuberculid. Recurrent crops of symmetrically distributed, asymptomatic, firm, sterile, dusky-red papules appear on the extensor aspects of the limbs, the dorsum of the hands and feet, and the buttocks. The papules may undergo central ulceration and eventually heal, leaving sharply delineated, circular, depressed scars. The duration of the eruption is variable, but it usually disappears promptly after treatment of the primary infection. Lichen scrofulosorum, another form of tuberculid, is characterized by asymptomatic, grouped, pinhead-sized, often follicular pink or red papules that form discoid plaques, mainly on the trunk. Healing occurs without scarring.

Atypical mycobacterial infection may cause cutaneous lesions in children. Interestingly, there may be some seasonable variation in incidence. It has been postulated that vitamin D may play a role. *Mycobacterium marinum* is found in saltwater, freshwater, and diseased fish. In the United States, it is most commonly acquired from tropical fish tanks and swimming pools. Traumatic abrasion of the skin serves as a portal of entry for the organism. Approximately 3 weeks after inoculation, a single reddish papule develops and enlarges slowly to form a violaceous nodule or, occasionally, a warty plaque (Fig. 706.13). The lesion occasionally breaks down to form a crusted ulcer or a suppurating

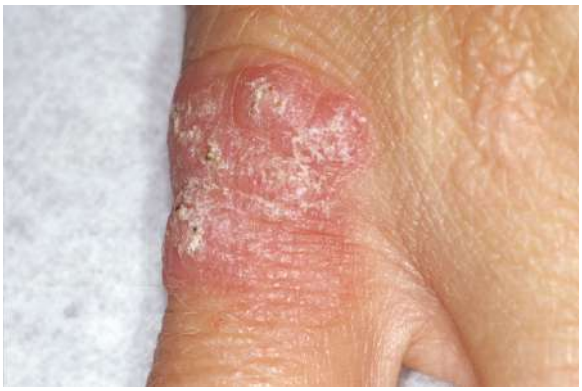

Fig. 706.13 Violaceous, warty plaque of *Mycobacterium marinum* infection.

abscess. Sporotrichoid erythematous nodules along lymphatics may also suppurate and drain. Lesions are most common on the elbows, knees, and feet of swimmers and on the hands and fingers in persons with aquarium-acquired infection. Systemic signs and symptoms are absent. Regional lymph nodes occasionally become slightly enlarged but do not break down. Rarely, the infection becomes disseminated, particularly in an immunosuppressed host. A biopsy specimen of a fully developed lesion demonstrates a granulomatous infiltrate with tuberculoid architecture. Treatment with two active agents is generally recommended, with a combination of clarithromycin and ethambutol providing a reasonable balance between effectiveness and tolerability. Rifampin should be added to clarithromycin and ethambutol for deep tissue involvement. Other agents with activity against *M. marinum* include trimethoprim-sulfamethoxazole, doxycycline, minocycline, and ciprofloxacin. Although azithromycin has been used as an alternative to clarithromycin for some mycobacterial infections, its effectiveness against *M. marinum* is not known. Treatment should continue for 1-2 months after resolution of lesions with a minimum treatment duration of 6 months. The application of heat to the affected site may be a useful adjunctive therapy (see Chapter 263).

Mycobacterium kansasii primarily causes pulmonary disease; skin disease is rare, often occurring in an immunocompromised host. Most commonly, sporotrichoid nodules develop after inoculation of traumatized skin. Lesions may develop into ulcerated, crusted, or verrucous plaques. The organism is relatively sensitive to antituberculous medications, which should be chosen on the basis of susceptibility testing.

Mycobacterium scrofulaceum causes cervical lymphadenitis (scrofuloderma) in young children, typically in the submandibular region. Nodes enlarge over several weeks, ulcerate, and drain. The local reaction is nontender and circumscribed, constitutional symptoms are absent, and there generally is no evidence of lung or other organ involvement. Other atypical mycobacteria may cause a similar presentation, including *Mycobacterium avium* complex, *M. kansasii,* and *Mycobacterium fortuitum.* Treatment is accomplished by excision and administration of antituberculous drugs (see Chapter 263).

Mycobacterium ulcerans (Buruli ulcer or Bairnsdale ulcers) causes a painless subcutaneous nodule after inoculation of abraded skin. Most infections occur in children in tropical rainforests. The nodule usually ulcerates, develops undermined edges, and may spread over large areas, most commonly on an extremity. Local necrosis of subcutaneous fat, producing a septal panniculitis, is characteristic. Ulcers persist for months to years before healing spontaneously with scarring, sometimes with contractures (if over a joint) and lymphedema. Constitutional symptoms and lymphadenopathy are absent. Diagnosis is made by culturing the organism at 32–33°C (89.6–91.4°F). **Treatment of choice** is an 8-week course of rifampin and streptomycin with surgical debridement for larger lesions. Local heat therapy and oral chemotherapy may benefit some patients.

M. avium complex, composed of more than 20 subtypes, most commonly causes chronic pulmonary infection. Cervical lymphadenitis and osteomyelitis occur occasionally, and papules or purulent leg ulcers occur rarely by primary inoculation. Skin lesions may be an early sign of disseminated infection. The lesions may take various forms, including erythematous papules, pustules, nodules, abscesses, ulcers, panniculitis, and sporotrichoid spread along lymphatics. For treatment, see Chapter 263.

M. fortuitum complex causes disease in an immunocompetent host principally by primary cutaneous inoculation after traumatic injury, injection, or surgery. A nodule, abscess, or cellulitis develops 4-6 weeks after inoculation. In an immunocompromised host, numerous subcutaneous nodules may form, break down, and drain. Treatment is based on identification and susceptibility testing of the organism. Isolates are usually susceptible to fluoroquinolones, doxycycline, minocycline, sulfonamides, cefoxitin, and imipenem; macrolides should be used with caution because many *M. fortuitum* isolates have the erythromycin methylase *(erm)* gene, which confers inducible resistance to macrolides despite "susceptible" minimum inhibitory concentrations.

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Chapter 707

Cutaneous Fungal Infections

Stephen R. Humphrey

TINEA VERSICOLOR

A common, innocuous, chronic fungal infection of the stratum corneum, tinea versicolor is most often caused by the dimorphic yeast *Malassezia globosa,* with *Malassezia furfur* and *Malassezia sympodialis* as less frequent causative agents. The synonyms *Pityrosporum ovale* and *Pityrosporum orbiculare* were used previously to identify the causal organism.

Etiology

M. globosa is part of the normal indigenous skin flora, predominantly in the yeast form, and is found particularly in areas of skin that are rich in sebum production. Proliferation of filamentous forms occurs in the disease state. Predisposing factors include a warm, humid environment, excessive sweating, occlusion, high plasma cortisol levels, immunosuppression, malnourishment, and genetically determined susceptibility. The disease is most prevalent in adolescents and young adults.

Clinical Manifestations

The lesions of tinea versicolor vary widely in color. In lighter skin, they are typically reddish brown, whereas in darker skin, they may be either hypopigmented or hyperpigmented. The characteristic macules are covered with a fine scale. They often begin in a perifollicular location, enlarge, and merge to form confluent patches, most commonly on the neck, upper chest, back, and upper arms (Fig. 707.1). Facial lesions are common in adolescents; lesions occasionally appear on the forearms, dorsum of the hands, and pubis. There may be little or no pruritus. Involved areas do not tan after sun exposure. A papulopustular perifollicular variant of the disorder may occur on the back, chest, and sometimes the extremities. These pustules tend to be monomorphic.

Differential Diagnosis

Examination with a Wood lamp discloses a yellowish gold fluorescence. A potassium hydroxide (KOH) preparation of scrapings is diagnostic, demonstrating groups of thick-walled spores and myriad short, thick,

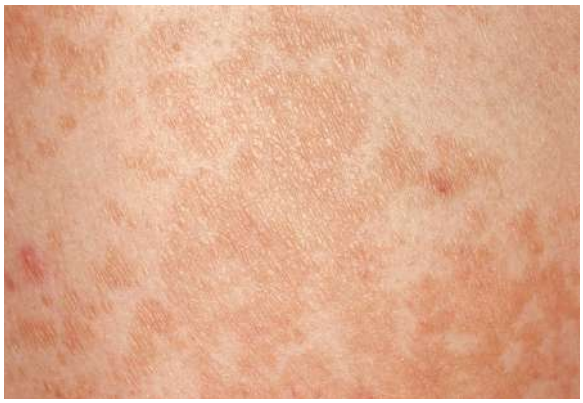

Fig. 707.1 Hyperpigmented, sharply demarcated macules of varying sizes on the upper trunk characteristic of tinea versicolor.

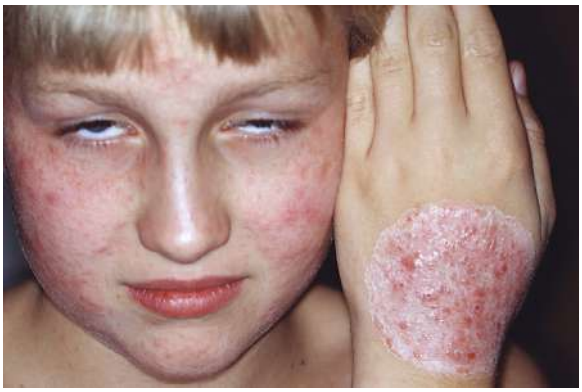

Fig. 707.2 Id reaction. Papular eruption of the face associated with severe tinea infection of the hand.

angular hyphae resembling macaroni/spaghetti and meatballs. Skin biopsy, including culture and special stains for fungi (periodic acid–Schiff), are often necessary to make the diagnosis in cases of primarily follicular involvement. Microscopically, organisms and keratinous debris can be seen within dilated follicular ostia.

Tinea versicolor must be distinguished from dermatophyte infections, seborrheic dermatitis, pityriasis alba, pityriasis rosea, and secondary syphilis. Tinea versicolor may mimic nonscaling pigmentary disorders, such as postinflammatory pigmentary change, if a patient has removed the scales by scrubbing. *M. globosa* folliculitis must be distinguished from the other forms of folliculitis.

Treatment

Many therapeutic agents can be used to treat this disease successfully. The causative agent, a normal human saprophyte, is not eradicated from the skin, however, and the disorder recurs in predisposed individuals. Appropriate topical therapy may include one of the following: selenium 2% shampoo applied for 10 minutes before rinsing for 1 week, ketoconazole 2% shampoo once daily for 3 days, and terbinafine spray once to twice daily for 1-2 weeks. Antifungal creams are available and can be used; however, these can be impractical to apply given the large surface of skin involved. Oral therapy may be more convenient and may be achieved successfully with fluconazole 300 mg/wk for 2-4 weeks or itraconazole 200 mg/24 hr for 5-7 days. Recurrent episodes continue to respond promptly to these agents. Oral therapy is particularly helpful in those with severe disease or recurrent disease or in those where topical therapies have failed. Maintenance therapy with selenium sulfide shampoo or ketoconazole 2% shampoo once a week may be used.

DERMATOPHYTOSES

Dermatophytoses are caused by a group of closely related filamentous fungi with a propensity for invading the stratum corneum, hair, and nails. The three principal genera responsible for infections are *Trichophyton, Microsporum,* and *Epidermophyton.*

Etiology

Trichophyton spp. cause lesions of all keratinized tissue, including skin, nails, and hair. *Trichophyton rubrum* is the most common dermatophyte pathogen. *Microsporum* spp. principally invade the hair, and the *Epidermophyton* spp. invade the intertriginous skin. Dermatophyte infections are designated by the word **tinea** followed by the Latin word for the anatomic site of involvement. The dermatophytes are also classified according to source and natural habitat. Fungi acquired from the soil are called *geophilic*. They infect humans sporadically, inciting an inflammatory reaction. Dermatophytes that are acquired from animals are *zoophilic*. Transmission may be through direct contact or indirectly by infected animal hair or clothing. Infected animals are frequently asymptomatic. Dermatophytes acquired from humans are referred to as *anthropophilic*. These infestations range from chronic low-grade to acute inflammatory disease. *Epidermophyton* infections are transmitted only by humans, but various species of *Trichophyton* and *Microsporum* can be acquired from both human and nonhuman sources.

Epidemiology

Host defense has an important influence on the severity of the infection. Disease tends to be more severe in individuals with diabetes mellitus, lymphoid malignancies, immunosuppression, and states with high plasma cortisol levels, such as Cushing syndrome. Some dermatophytes, most notably the zoophilic species, tend to elicit more severe, suppurative inflammation in humans. Some degree of resistance to reinfection is acquired by most infected persons and may be associated with a delayed hypersensitivity response. However, no relationship has been demonstrated between antibody levels and resistance to infection. The frequency and severity of infection are also affected by the geographic locale, the genetic susceptibility of the host, and the virulence of the strain of dermatophyte. Additional local factors that predispose to infection include trauma to the skin, hydration of the skin with maceration, occlusion, and elevated temperature.

Occasionally, a secondary skin eruption, referred to as a dermatophytid or "id" reaction, appears in sensitized individuals and has been attributed to circulating fungal antigens derived from the primary infection. The eruption is characterized by grouped papules (Fig. 707.2) and vesicles and, occasionally, by sterile pustules. Symmetric urticarial lesions and a more generalized maculopapular eruption also can occur. Id reactions are most often associated with tinea pedis, but they also occur with tinea capitis.

Tinea Capitis

Clinical Manifestations

Tinea capitis is a dermatophyte infection of the scalp most often caused by *Trichophyton tonsurans,* occasionally by *Microsporum canis*, and, much less commonly, by other *Microsporum* and *Trichophyton* spp. It is particularly common in children age 3-7 years old. In *Microsporum* and some *Trichophyton* infections, the spores are distributed in a sheathlike fashion around the hair shaft (**ectothrix** infection), whereas *T. tonsurans* produces an infection within the hair shaft (endothrix). **Endothrix** infections may continue past the anagen phase of hair growth into telogen and are more chronic than infections with ectothrix organisms that persist only during the anagen phase. *T. tonsurans* is an anthropophilic species acquired most often by contact with infected hairs and epithelial cells that are on such surfaces as theater seats, hats, and combs. Dermatophyte spores may also be airborne within the immediate environment, and high carriage rates have been demonstrated in noninfected schoolmates and household members. *M. canis* is a zoophilic species that is acquired from cats and dogs.

The clinical presentation of tinea capitis varies with the infecting organism. Endothrix infections such as those caused by *T. tonsurans* create a

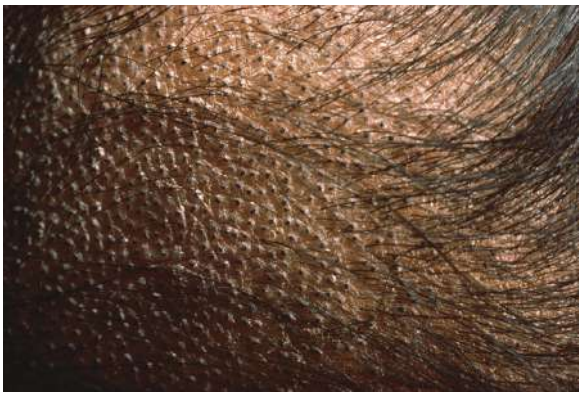

Fig. 707.3 Black-dot ringworm with hairs broken off at the scalp.

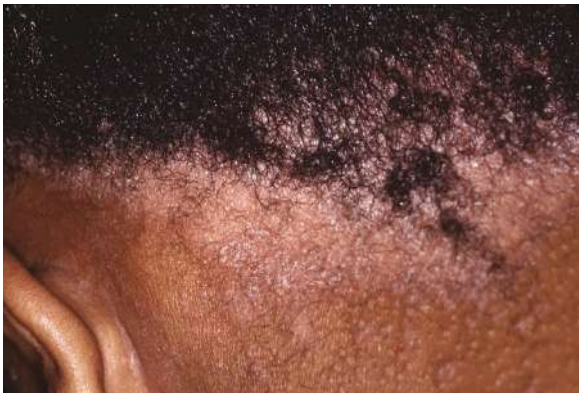

Fig. 707.4 Tinea capitis mimicking seborrheic dermatitis.

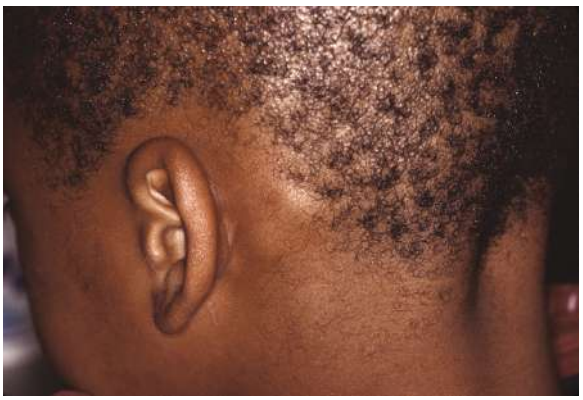

Fig. 707.5 Lymphadenopathy associated with tinea capitis.

pattern known as "black-dot ringworm," characterized initially by many small circular patches of alopecia in which hairs are broken off close to the hair follicle (Fig. 707.3). Another clinical variant manifests as diffuse scaling, with minimal hair loss secondary. It strongly resembles seborrheic dermatitis, psoriasis, or atopic dermatitis (Fig. 707.4). *T. tonsurans* may also produce a chronic and more diffuse alopecia. Lymphadenopathy is common (Fig. 707.5). A severe inflammatory response produces elevated, boggy granulomatous masses **(kerion)**, which are often studded with pustules (Fig. 707.6A). Fever, pain, and regional adenopathy are common, and permanent scarring and alopecia may result (see Fig. 707.6B). The zoophilic organism *M. canis* or the geophilic organism *Microsporum gypseum* also may cause kerion formation. The pattern produced by

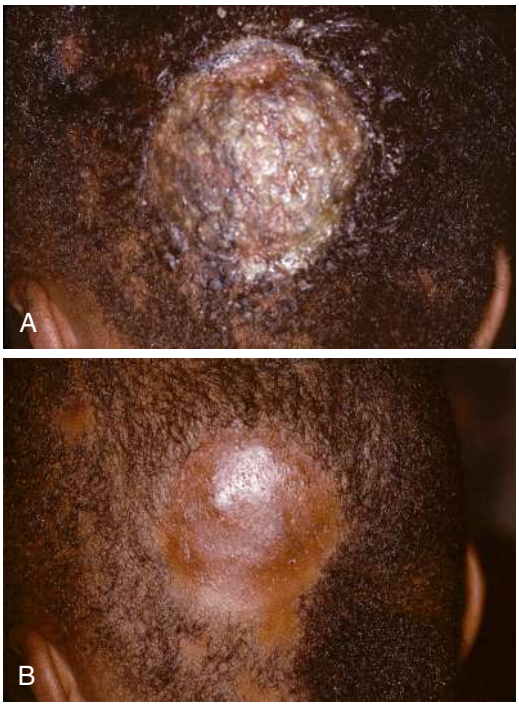

Fig. 707.6 A, Kerion. Boggy granulomatous mass of the scalp. B, Scarring after kerion.

Microsporum audouinii, the most common cause of tinea capitis in the 1940s and 1950s, is characterized initially by a small papule at the base of a hair follicle. The infection spreads peripherally, forming an erythematous and scaly circular plaque **(ringworm)** within which the infected hairs become brittle and broken. Numerous confluent patches of alopecia develop, and patients may complain of severe pruritus. *M. audouinii* infection is no longer common in the United States. **Favus** is a chronic form of tinea capitis that is rare in the United States and is caused by the fungus *Trichophyton schoenleinii*. Favus starts as yellowish red papules at the opening of hair follicles. The papules expand and coalesce to form cup-shaped, yellowish, crusted patches that fluoresce dull green under a Wood lamp. Other species, such as *Trichophyton violaceum* and *Trichophyton soudanense* are becoming more common with resettlement and emigration.

Differential Diagnosis

Tinea capitis can be confused with seborrheic dermatitis, psoriasis, alopecia areata, trichotillomania, and certain dystrophic hair disorders. When inflammation is pronounced, as in kerion, primary or secondary bacterial infection must also be considered. In adolescents, the patchy, moth-eaten type of alopecia associated with secondary syphilis may resemble tinea capitis. If scarring occurs, discoid lupus erythematosus and lichen planopilaris must also be considered in the differential diagnosis.

The important diagnostic procedures for the various dermatophyte diseases include examination of infected hairs with a Wood lamp, microscopic examination of KOH preparations of infected material, and identification of the etiologic agent by culture. Hairs infected with common *Microsporum* spp. fluoresce a bright blue-green. Most *Trichophyton*-infected hairs do not fluoresce.

Microscopic examination of a KOH preparation of infected hair from the active border of a lesion discloses tiny spores surrounding the hair shaft in *Microsporum* infections and chains of spores within the hair shaft in *T. tonsurans* infections. Fungal elements are not usually seen in scales. A specific etiologic diagnosis of tinea capitis may be obtained by planting broken-off infected hairs on Sabouraud medium with reagents to inhibit growth of other organisms. Such identification may require 2 weeks or more.

Treatment

Oral administration of griseofulvin microcrystalline (20-25 mg/kg/day with a maximum daily dose of 1000 mg, or 10-15 mg/kg/day with a maximum daily dose of 750 mg if the ultramicrosize form is used) is typically the recommended treatment for all forms of tinea capitis. Absorption of griseofulvin is enhanced by the ingestion of a fatty meal and should be recommended for the patient. A minimum of 8 weeks of treatment is usually required, though longer courses are sometimes needed. Repeat fungal cultures may help guide treatment length. Treatment for 1 month after a negative culture result minimizes the risk of recurrence. Adverse reactions to griseofulvin are rare but include nausea, vomiting, headache, blood dyscrasias, phototoxicity, and hepatotoxicity. Terbinafine dosing is weight-based. Off-label use is 125 mg daily for 6 weeks if under 25 kg. From 25 to 35 kg, the dose is 187.5 mg daily for 6 weeks. For patients greater than 35 kg, the dose is 250 mg daily for 6 weeks. It is possibly effective in pulse therapy, although it has limited activity against *M. canis*, but better activity than griseofulvin for *T. tonsurans.* The oral granule formulation of terbinafine is approved by the U.S. Food and Drug Administration (FDA) for tinea capitis in children 4 years of age and older. Oral itraconazole is useful in instances of griseofulvin resistance, intolerance, or allergy. Itraconazole is given for 4-6 weeks at a dosage of 5 mg/kg/24 hr with food. This is off-label and length of course depends on organism. Capsules are preferable to the syrup, which may cause diarrhea. Itraconazole is not approved by the FDA for treatment of dermatophyte infections in the pediatric population. Topical therapy alone is ineffective, but it may be an important adjunct because it may decrease the shedding of spores and should be recommended in all patients. Asymptomatic dermatophyte carriage in family members is common. Because one in three families have at least one member who is a carrier, treatment of both patient and potential carriers with a sporicidal shampoo may hasten clinical resolution. Vigorous shampooing with a 2.5% selenium sulfide, zinc pyrithione, or ketoconazole shampoo is helpful. It is not necessary to shave the scalp.

Tinea Corporis

Clinical Manifestations

Tinea corporis, defined as infection of the glabrous skin, excluding the palms, soles, and groin, can be caused by most of the dermatophyte species, although *T. rubrum* and *Trichophyton mentagrophytes* are the most prevalent etiologic organisms. In children, infections with *M. canis* are also common. Tinea corporis can be acquired by direct contact with infected persons or by contact with infected scales or hairs deposited on environmental surfaces. *M. canis* infections are usually acquired from infected pets.

The most typical clinical lesion begins as a dry, mildly erythematous, elevated, scaly papule or plaque that spreads centrifugally and clears centrally to form the characteristic annular lesion responsible for the designation of ringworm (Fig. 707.7). At times, plaques with advancing borders may spread over large areas. Grouped pustules are another variant. Most lesions clear spontaneously within several months, but some may become chronic. Central clearing does not always occur (Fig. 707.8), and differences in host response may result in wide variability in the clinical appearance; for example, granulomatous lesions called **Majocchi granuloma**, which are caused by the penetration of organisms along the hair follicle to the level of the dermis, produce a fungal folliculitis and perifolliculitis (Fig. 707.9) and the kerion-like lesions referred to as *tinea profunda.* Majocchi granuloma is more common after inappropriate treatment with topical corticosteroids, especially the superpotent class.

Differential Diagnosis

Many skin lesions, both infectious and noninfectious, must be differentiated from the lesions of tinea corporis. Those most frequently confused are granuloma annulare, nummular eczema, pityriasis rosea, psoriasis, seborrheic dermatitis, erythema chronicum migrans, and tinea versicolor. Microscopic examination of KOH wet mount preparations and cultures should always be performed when fungal infection is considered. Tinea corporis usually does not fluoresce with a Wood lamp.

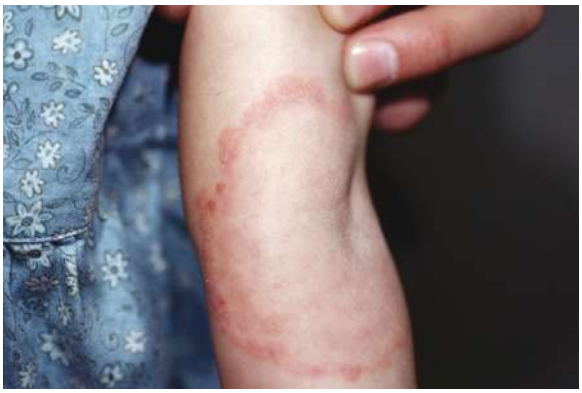

Fig. 707.7 Annular plaque of tinea corporis with central clearing.

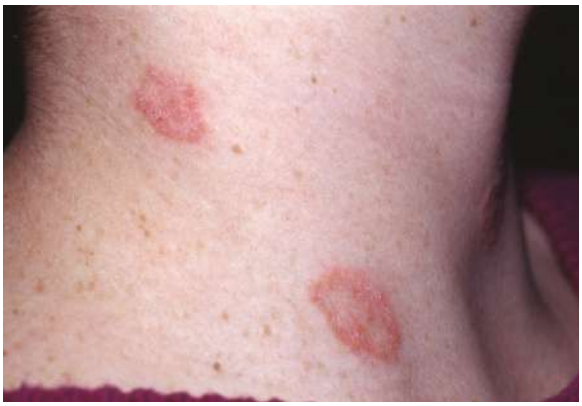

Fig. 707.8 Minimal central clearing with tinea corporis.

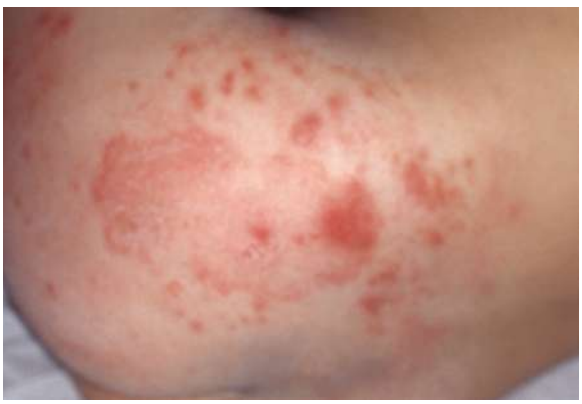

Fig. 707.9 Follicular papule and pustule in Majocchi granuloma after use of a superpotent topical steroid.

Treatment

Tinea corporis usually responds to treatment with one of the topical antifungal agents (e.g., imidazoles, terbinafine, butenafine, naftifine) twice daily for 2-4 weeks. In unusually severe or extensive disease, a course of therapy with oral griseofulvin microcrystalline may be required for 4 weeks. Terbinafine for 2 weeks can also be used. Itraconazole has produced excellent results in many cases with a 1- to 2-week course of oral therapy. Combination topical corticosteroid/antifungal preparations should not be used, as they may result in worsening or persistent infection.

Tinea Cruris

Clinical Manifestations

Tinea cruris, or infection of the groin, occurs most often in adolescent males and is usually caused by the anthropophilic species *Epidermophyton floccosum* or *T. rubrum,* but occasionally by the zoophilic species *T. mentagrophytes.*

The initial clinical lesion is a small, raised, scaly, erythematous patch on the inner aspect of the thigh. This spreads peripherally, often developing numerous tiny vesicles at the advancing margin. It eventually forms bilateral, irregular, sharply bordered patches with hyperpigmented scaly centers. In some cases, particularly in infections with *T. mentagrophytes,* the inflammatory reaction is more intense and the infection may spread beyond the crural region. The scrotum and labia are usually not involved in the infection, which is an important distinction from candidiasis. Pruritus may be severe initially but abates as the inflammatory reaction subsides. Bacterial superinfection may alter the clinical appearance, and erythrasma or candidiasis may coexist. Tinea cruris is more prevalent in obese persons and in persons who perspire excessively and wear tight-fitting clothing. It is a good idea to examine a patient's feet, which can be a source for tinea cruris.

Differential Diagnosis

The diagnosis of tinea cruris is confirmed by culture and by demonstration of septate hyphae on a KOH preparation of epidermal scrapings. The disorder must be differentiated from intertrigo, allergic contact dermatitis, candidiasis, and erythrasma. Bacterial superinfection must be precluded when there is a severe inflammatory reaction.

Treatment

Patients should be advised to wear loose cotton underwear. Topical treatment with an imidazole twice a day for 3-4 weeks is recommended for severe infection, especially because these agents are effective in mixed candidal-dermatophytic infections. Oral treatments, as mentioned earlier, may also be used.

Tinea Pedis

Clinical Manifestations

Tinea pedis (athlete's foot), infection of the toe webs and soles of the feet, is uncommon in young children but occurs with some frequency in preadolescent and adolescent males. The usual etiologic agents are *T. rubrum, T. mentagrophytes,* and *E. floccosum.*

Most commonly, the lateral toe webs (third to fourth and fourth to fifth interdigital spaces) and the subdigital crevice are fissured, with maceration and peeling of the surrounding skin (Fig. 707.10). Severe tenderness, itching, and a persistent foul odor are characteristic. These lesions may become chronic. This type of infection may involve overgrowth by bacterial flora, including *Kytococcus sedentarius, Brevibacterium epidermidis,* and gram-negative organisms. Less commonly, a chronic diffuse hyperkeratosis of the sole of the foot occurs with only mild erythema (Fig. 707.11). In some cases, two feet and one hand are involved. This type of infection is more refractory to treatment and tends to recur. An inflammatory vesicular type of reaction may occur with *T. mentagrophytes* infection. This type is most common in young children. The lesions involve any area of the foot, including the dorsal surface, and are usually circumscribed. The initial papules progress to vesicles and bullae that may become pustular (Fig. 707.12). A number of factors, such as occlusive footwear and warm, humid weather, predispose to infection. Tinea pedis may be transmitted in shower facilities and swimming pool areas.

Differential Diagnosis

Tinea pedis must be differentiated from simple maceration and peeling of the interdigital spaces, which is common in children. Infection with *Candida albicans* and various bacterial organisms (erythrasma) may cause confusion or may coexist with primary tinea pedis. Contact dermatitis, vesicular foot dermatitis, atopic dermatitis, and juvenile plantar dermatitis also simulate tinea pedis. Fungal mycelia can be seen on microscopic examination of a KOH preparation or by culture.

Treatment

Treatment for mild infections includes simple measures such as avoidance of occlusive footwear, careful drying between the toes after bathing, and the use of an absorbent antifungal powder such as zinc undecylenate. Topical therapy with an imidazole is curative in most cases. Each of these agents is also effective against candidal infection. Several weeks of therapy may be necessary, and low-grade, chronic infections, particularly those caused by *T. rubrum,* may be refractory. In refractory cases, oral griseofulvin therapy may effect a cure, but recurrences are common.

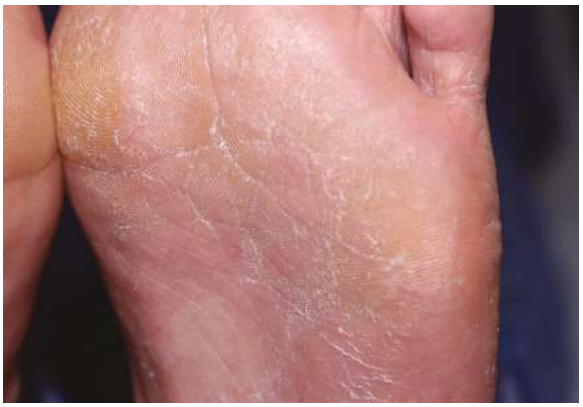

Fig. 707.11 Diffuse, minimally erythematous tinea pedis.

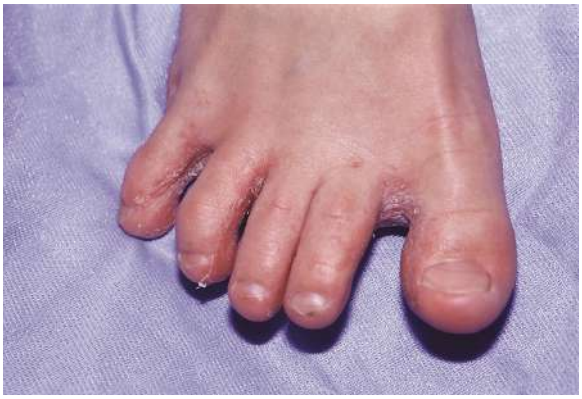

Fig. 707.10 Interdigital tinea pedis.

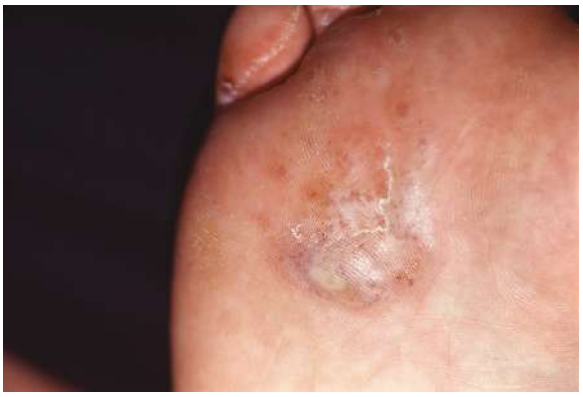

Fig. 707.12 Vesicobullous tinea pedis.

Tinea Unguium

Clinical Manifestations

Tinea unguium (onychomycosis) is a dermatophyte infection of the nail plate. It occurs most often in patients with tinea pedis, but it may occur as a primary infection. It can be caused by a number of dermatophytes, of which *T. rubrum* and *T. mentagrophytes* are the most common.

The most superficial form of tinea unguium (i.e., white superficial onychomycosis) is caused by *T. mentagrophytes.* It manifests as irregular single or numerous white patches on the surface of the nail unassociated with paronychial inflammation or deep infection. *T. rubrum* generally causes a more invasive, subungual infection that is initiated at the lateral distal margins of the nail and is often preceded by mild paronychia. The middle and ventral layers of the nail plate, and perhaps the nail bed, are the sites of infection. The nail initially develops a yellowish discoloration and slowly becomes thickened, brittle, and loosened from the nail bed (Fig. 707.13). In advanced infection, the nail may turn dark brown to black and may crack or break off.

Differential Diagnosis

Tinea unguium must be differentiated from various dystrophic nail disorders. Changes as a result of trauma, psoriasis, lichen planus, eczema, and trachyonychia can all be confused with tinea unguium. Nails infected with *C. albicans* have several distinguishing features; most prominently, a pronounced paronychial swelling. Thin shavings taken from the infected nail, preferably from the deeper areas, should be examined microscopically with KOH and cultured. Repeated attempts may be required to demonstrate the fungus. Histologic evaluation of nail clippings with special stains for dermatophytes can be diagnostic.

Treatment

Systemic antifungals are more effective at treating onychomycosis than topical antifungals. The long half-life of itraconazole in the nail has led to promising trials of intermittent short courses of therapy (double the normal dose for 1 week of each month for 3-4 months). Oral terbinafine is also used for the treatment of onychomycosis. Terbinafine once daily for 12 weeks is more effective than itraconazole pulse therapy. Pulse terbinafine treatment has also been used in adults and has been effective. Topical antifungals may be an acceptable treatment for mild disease without matrix involvement, and typically children have a better response to topical therapy than adults, likely because of faster growth of the nails. Several topical agents have been FDA approved for the treatment of onychomycosis in adults, including ciclopirox, efinaconazole, and tavaborole. Small clinical trials have demonstrated efficacy of ciclopirox in children. Efinaconazole and tavaborole can be used in children 6 and older as well.

Tinea Nigra Palmaris

Tinea nigra palmaris is a rare but distinctive superficial fungal infection that occurs principally in children and adolescents. It is caused by the dimorphic fungus *Phaeoannellomyces werneckii,* which imparts a gray-black color to the affected palm. The characteristic lesion is a well-defined hyperpigmented macule. Scaling and erythema are rare, and the lesions are asymptomatic. Tinea nigra is often mistaken for a junctional nevus, melanoma, or staining of the skin by contactants. Treatment is with an imidazole antifungal. *Keratolytic agents, such as salicylic acid, once to twice daily* can also be used.

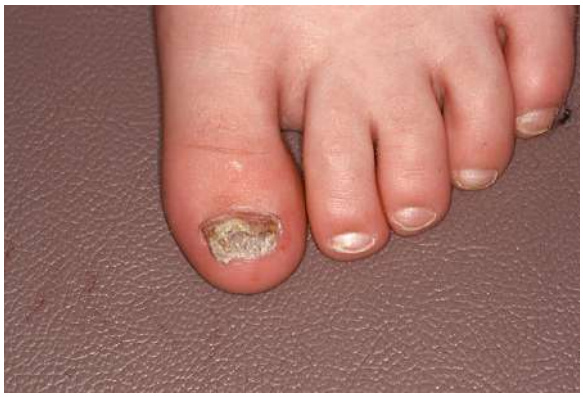

Fig. 707.13 Hyperkeratotic nail in onychomycosis.

CANDIDAL INFECTIONS (CANDIDIASIS AND MONILIASIS)

See Chapter 280.

The dimorphic yeasts of the genus *Candida* are ubiquitous in the environment, but *C. albicans* usually causes candidiasis in children. This yeast is not part of the indigenous skin flora, but it is a frequent transient on skin and may colonize the human alimentary tract and the vagina as a saprophytic organism. Certain environmental conditions, notably elevated temperature and humidity, are associated with an increased frequency of isolation of *C. albicans* from the skin. Many bacterial species inhibit the growth of *C. albicans,* and alteration of normal flora by the use of antibiotics may promote overgrowth of the yeast.

Chronic mucocutaneous candidiasis is associated with a diverse group of primary immunodeficiency diseases (Table 707.1). Chronic mucocutaneous candidiasis is characterized by chronic or recurrent *Candida* infections of the oral cavity, esophagus, genitals, nails, and skin. Chronic mucocutaneous candidiasis may also be seen as an acquired infection in patients with HIV infection and during immunosuppressive treatments.

Oral Candidiasis (Thrush)

See Chapter 280.

Vaginal Candidiasis

See Chapters 163 and 280.

C. albicans is an inhabitant of the vagina in 5–10% of women, and vaginal candidiasis is not uncommon in adolescent girls. A number of factors can predispose to this infection, including antibiotic therapy, corticosteroid therapy, diabetes mellitus, pregnancy, and the use of oral contraceptives. The infection manifests as cheesy white plaques on an erythematous vaginal mucosa and a thick white-yellow discharge. The disease may be relatively mild or may produce pronounced inflammation and scaling of the external genitals and surrounding skin with progression to vesiculation and ulceration. Patients often complain of severe itching and burning in the vaginal area. Before treatment is initiated, the diagnosis should be confirmed by microscopic examination and/or culture. The infection may be eradicated by insertion of nystatin or imidazole vaginal tablets, suppositories, creams, or foam. If these products are ineffective, the addition of one dose of fluconazole (150 mg) is effective for adolescents.

Congenital Cutaneous Candidiasis

See Chapter 280.

Candidal Diaper Dermatitis

Candidal diaper dermatitis is a ubiquitous problem in infants and, although relatively benign, is often frustrating because of its tendency to recur. Predisposed infants usually carry *C. albicans* in their intestinal tracts, and the warm, moist, occluded skin of the diaper area provides an optimal environment for its growth. A seborrheic, atopic, or primary irritant contact dermatitis usually provides a portal of entry for the yeast.

The primary clinical manifestation consists of an intensely erythematous, confluent plaque with a scalloped border and a sharply demarcated edge. It is formed by the confluence of numerous papules and vesicular pustules. Satellite pustules, those that stud the contiguous skin, are a hallmark of localized candidal infections. The perianal skin, inguinal folds, perineum, and lower abdomen are usually involved (Fig. 707.14). In males, the entire scrotum and penis may be involved, with an erosive balanitis of the perimeatal skin. In females, the lesions may be found on the vaginal mucosa and labia. In some infants, the process is generalized, with erythematous lesions distant from the diaper

Table 707.1 Primary Immunodeficiencies Underlying Candida and Other Fungal Infections

DISEASE	ASSOCIATED INFECTIONS	IMMUNOLOGIC PHENOTYPE	GENE, TRANSMISSION
CMC			
SCID	Bacteria, viruses, fungi, mycobacteria	No T cells, with or without B and/or NK cell lymphopenia	>30 genes: *IL2RG*, X-linked; *JAK3*, autosomal recessive; *RAG1*, autosomal recessive; *RAG2*, autosomal recessive; *ARTEMIS*, autosomal recessive; *ADA*, autosomal recessive; *CD3*, autosomal recessive, etc.
CID			
CD25 deficiency	Viruses and bacteria	T-cell defect	*IL2RA*, autosomal recessive
NEMO or iκBγ deficiency	Pyogenic bacteria, mycobacteria, viruses		*NEMO* or *IKBG* X-linked
IκBα GOF pathogenic variant			*IKBA*, autosomal dominant
DOCK8 deficiency	Viruses, bacteria and fungi		*DOCK8*, autosomal recessive
TCR-α deficiency	Viruses and bacteria		*TCRA*, autosomal recessive
CRACM1 deficiency	Viruses, mycobacteria, bacteria and fungi		*CRACM1*, autosomal recessive
MST1/STK4 deficiency	Viruses and bacteria		*MST1/STK4*, autosomal recessive
MHC class II deficiency	Viruses, bacteria and fungi		*CIITA, RFXANK, RFXC, RFXAP*, all autosomal recessive
Idiopathic CD4 lymphopenia	*Pneumocystis, Cryptococcus*, virus	CD4 T cells <300 cells/mm^3	*UNC119*, autosomal dominant, *MAGT1* X-linked, *RAG1*, autosomal recessive
SYNDROMIC CMC			
Interleukin-12Rβ1 and interleukin-12p40 deficiencies	*Mycobacteria, Salmonella*	Deficit of interleukin-17–producing T cells	*IL12RB1*, autosomal recessive, *IL12B*, autosomal recessive
STAT3 deficiency (autosomal dominant-HIES)	*Staphylococcus aureus, Aspergillus*	Hyperimmunoglobulin E, deficit of interleukin-17–producing T cells	*STAT3*, autosomal dominant
APECED/APS-1	No	Neutralizing antiinterleukin-17A, antiinterleukin-17F, and/or antiinterleukin-22 autoantibodies	*AIRE*, autosomal recessive
CARD9 deficiency	Dermatophytes, *Candida*, brain abscess	Deficit of interleukin-17–producing T cells	*CARD9*, autosomal recessive
CMCD			
Complete interleukin-17RA deficiency	*S. aureus*	No interleukin-17 response	*IL17RA*, autosomal recessive
Partial interleukin-17F deficiency	*S. aureus*	Impaired interleukin-17F, interleukin-17A/F function	*IL17F*, autosomal dominant
STAT1 GOF pathogenic variants	Bacteria, viruses, fungi, mycobacteria	Low interleukin-17–producing T cells	*STAT1*, autosomal dominant

CMC, Chronic mucocutaneous candidiasis; SCID, severe combined immunodeficiency; NK, natural killer; CID, combined immunodeficiency; NEMO, nuclear factor κβ essential modulator; iκBγ, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B cells, gamma; IκBα, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B cells, alpha; GOF, gain-of-function; DOCK8, dedicator of cytokinesis 8; TCR, T-cell receptor; CRACM1, calcium release-activated calcium modulator 1; MST1, macrophage stimulating 1; STK4, serine/threonine protein kinase 4; MHC, major histocompatibility complex; STAT, signal transducer and activator of transcription; HIES, hyperimmunoglobulin E syndrome; APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; APS-1, autoimmune polyendocrinopathy syndrome type 1; AIRE, autoimmune regulator; CARD9, caspase recruitment domain-containing protein 9; CMCD, chronic mucocutaneous candidiasis disease.

From Lanternier F, Cypowyj S, Picard, C, et al. Primary immunodeficiencies underlying fungal infections. *Curr Opin Pediatr.* 2013;25:736–747.

area. In some cases, the generalized process may represent a fungal id (hypersensitivity) reaction.

The differential diagnosis of candidal diaper dermatitis includes other eruptions of the diaper area that may coexist with candidal infection. For this reason, it is important to establish a diagnosis by means of KOH preparation or culture.

Treatment consists of applications of an imidazole cream 2 times daily. The combination of a corticosteroid and an antifungal agent may be justified if inflammation is severe but may confuse the situation if the diagnosis is not firmly established. Corticosteroids should not be continued for more than a few days. Protection of the diaper area by an application of thick zinc oxide paste overlying the anticandidal preparation may be helpful. The paste is more easily removed with mineral oil than with soap and water. Fungal id reactions gradually abate with successful treatment of the diaper dermatitis or may be treated with a mild corticosteroid preparation. When

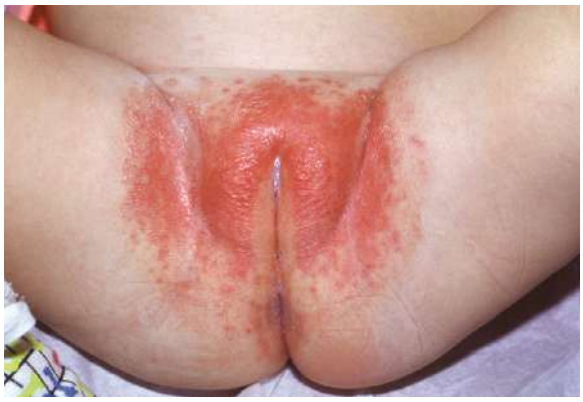

Fig. 707.14 Erythematous confluent plaque caused by candidal infection.

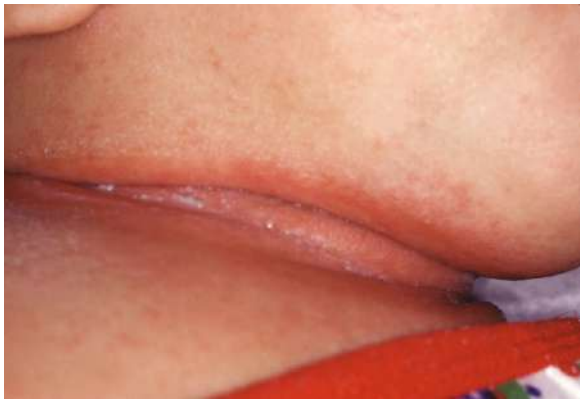

Fig. 707.15 Intertriginous candidiasis of the neck.

recurrences of diaper candidiasis are frequent, it may be helpful to prescribe a course of oral anticandidal therapy to decrease the yeast population in the gastrointestinal tract. Some infants seem to be receptive hosts for *C. albicans* and may reacquire the organism from a colonized adult.

Intertriginous Candidiasis

Intertriginous candidiasis occurs most often in the axillae and groin, on the neck (Fig. 707.15), under the breasts, under pendulous abdominal fat folds, in the umbilicus, and in the gluteal cleft. Typical lesions are large, confluent areas of moist, denuded, erythematous skin with an irregular, macerated, scaly border. Satellite lesions are characteristic and consist of small vesicles or pustules on an erythematous base. With time, intertriginous candidal lesions may become lichenified, dry, scaly plaques. The lesions develop on skin subjected to irritation and maceration. Candidal superinfection is more likely to occur under conditions that lead to excessive perspiration, especially in obese children and in children with underlying disorders, such as diabetes mellitus. A similar condition, interdigital candidiasis, commonly occurs in individuals whose hands are constantly immersed in water. Fissures occur between the fingers and have red denuded centers, with an overhanging white epithelial fringe. Similar lesions between the toes may be secondary to occlusive footwear. Treatment is the same as for other candidal infections.

Perianal Candidiasis

Perianal dermatitis develops at sites of skin irritation as a result of occlusion, constant moisture, poor hygiene, anal fissures, and pruritus from pinworm infestation. It may become superinfected with *C. albicans,* especially in children who are receiving oral antibiotic or corticosteroid medication. The involved skin becomes erythematous, macerated, and excoriated, and the lesions are identical to those of candidal intertrigo or candidal diaper rash. Application of a topical antifungal agent in conjunction with improved hygiene is usually effective. Underlying disorders such as pinworm infection must also be treated (see Chapter 339).

Candidal Paronychia and Onychia

See Chapter 704.

Candidal Granuloma

Candidal granuloma is a rare response to an invasive candidal infection of skin. The lesions appear as crusted, verrucous plaques and hornlike projections on the scalp, face, and distal limbs. Affected patients may have single or numerous defects in immune mechanisms, and the granulomas are often refractory to topical therapy. A systemic anticandidal agent may be required for palliation or eradication of the infection.

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Chapter 708

Cutaneous Viral Infections

Lamiaa Hamie and Stephen R. Humphrey

WART (VERRUCA)

Etiology

Human papillomaviruses (HPVs) cause a spectrum of diseases from warts (verrucae vulgaris) to squamous cell carcinoma of the skin and mucous membranes, including the larynx (see Chapter 438.2). The HPVs are classified by genus, species, and type. More than 200 types are known, and the entire genomes of approximately 100 are completely sequenced. The incidence of all types of warts is highest in children and adolescents. HPV is spread by direct contact and autoinoculation; transmission within families and by fomites also occurs. The clinical manifestations of infection develop 1 month or longer after inoculation and depend on the HPV type, the size of the inoculum, the immune status of the host, and the anatomic site.

Clinical Manifestations

Cutaneous warts develop in 5–10% of children. **Common warts** (verruca vulgaris), caused most commonly by HPV types 2 and 4, occur most frequently on the fingers, dorsum of the hands (Fig. 708.1), paronychial areas, face, knees, and elbows. They are well-circumscribed papules with an irregular, roughened, keratotic surface. When the surface is pared away, many black dots representing thrombosed dermal capillary loops are often visible. **Periungual warts** are often painful and may spread beneath the nail plate, separating it from the nail bed (Fig. 708.2). **Plantar warts (verruca plantaris)**, although similar to the common wart, are caused by HPV type 1 and are usually flush with the surface of the sole because of the constant pressure from weight bearing. When plantar warts become hyperkeratotic (Fig. 708.3), they may be painful. Similar lesions (palmar-verruca palmaris) can also occur on the palms. They are sharply demarcated, often with a ring of thick callus. The surface keratotic material must sometimes be removed before the boundaries of the wart can be appreciated. Several

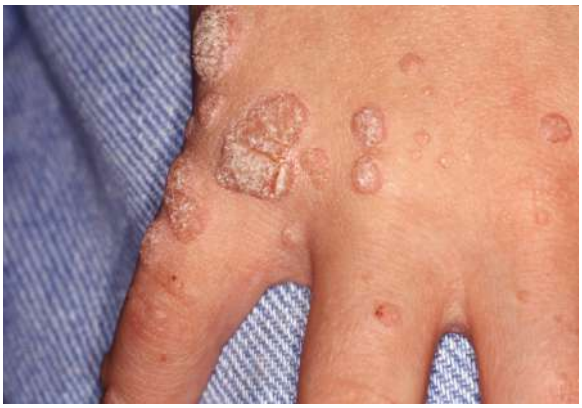

Fig. 708.1 Verrucous papules on the back of the hand.

Fig. 708.2 Periungual wart with disruption of nail growth.

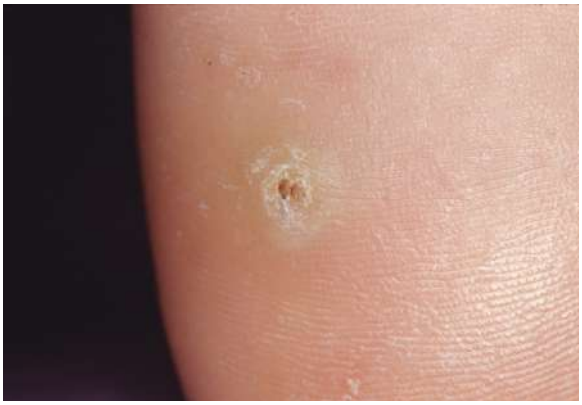

Fig. 708.3 Hyperkeratotic plantar wart.

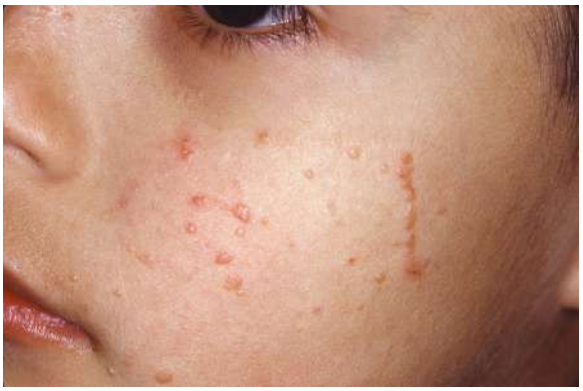

Fig. 708.4 Multiple flat warts on the face with lesions in line of trauma.

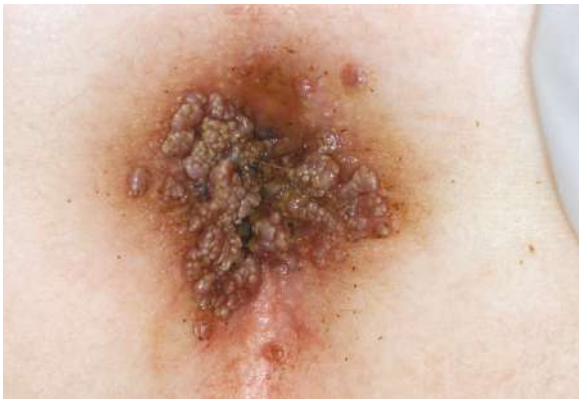

Fig. 708.5 Condylomata acuminata in the perianal area of a toddler.

contiguous warts (HPV type 4) may fuse to form a large plaque, known as the *mosaic wart*. **Flat warts (verruca plana)**, caused by HPV types 3 and 10, are slightly elevated, minimally hyperkeratotic papules that usually remain <3 mm in diameter and vary in color from pink to brown. They may occur in profusion on the face, arms, dorsum of the hands, and knees. The distribution of several lesions along a line of cutaneous trauma (koebnerization) is a helpful diagnostic feature (Fig. 708.4). Lesions may be disseminated in the beard area and on the legs by shaving and from the hairline onto the scalp by combing the hair. **Epidermodysplasia verruciformis** (*EVER1, EVER2* genes), caused primarily by HPV types 5 and 8 (β-papillomaviruses, species 1), manifests as many diffuse verrucous papules. Wart types 9, 12, 14, 15, 17, 25, 36, 38, 47, and 50 may also be involved. Inheritance is thought to be primarily autosomal recessive, but an X-linked recessive form has also been postulated. Warts progress to **squamous cell carcinoma** in 10% of patients with epidermodysplasia verruciformis.

Genital HPV infection occurs in sexually active adolescents, most commonly as a result of infection with HPV types 6 and 11. **Condylomata acuminata** (mucous membrane warts) are moist, fleshy, papillomatous lesions that occur on the perianal mucosa (Fig. 708.5), labia, vaginal introitus, and perineal raphe and on the shaft, corona, and glans penis. Occasionally, they can obstruct the urethral meatus or the vaginal introitus. Because they are located in intertriginous areas, they may become moist and friable. When left untreated, condylomata proliferate and become confluent, at times forming large cauliflower-like masses. Lesions can also occur on the lips, gingivae, tongue, and conjunctivae. Genital warts in children may occur after inoculation during birth through an infected birth canal, as a consequence of sexual abuse, or from incidental spread from cutaneous warts. A significant proportion of genital warts in children contain HPV types that are usually isolated from cutaneous warts. HPV infection of the cervix is a major risk factor for the development of carcinoma, particularly if the infection is caused by HPV type 16, 18, 31, 33, 35, 39, 45, 52, 59, 67, 68, or 70. Immunization against types 6, 11, 16, 18, 31, 33, 45, 52, and 58 is available (see Chapter 438.2). Laryngeal (respiratory) papillomas contain the same HPV types as in anogenital papillomas. Transmission is believed to occur from mothers with a genital HPV infection to

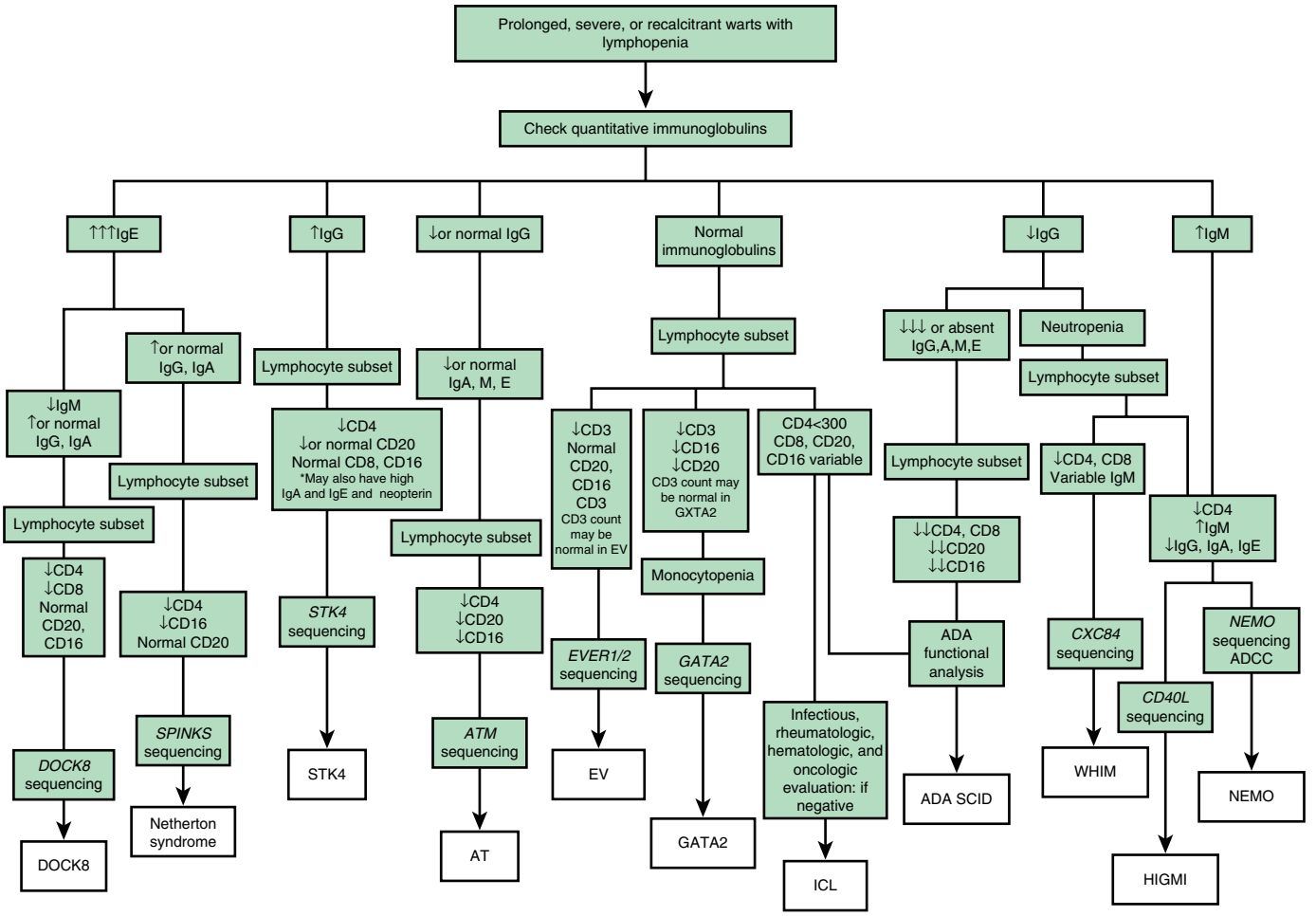

Fig. 708.6 Algorithm for diagnosis of primary immune deficiency with warts and lymphopenia. ADA SCID, adenosine deaminase severe combined immunodeficiency; AT, ataxia-telangiectasia; DOCK8, Dedicator of cytokinesis 8; EV, epidermodysplasia verruciformis; ICL, idiopathic CD4 lymphopenia; NEMO, nuclear factor κB essential modulator deficiency; STK4, serine/threonine kinase 4 deficiency; WHIM, warts, hypogammaglobulinemia, recurrent bacterial infections, and myelokathexis; XHIGM1, x-linked hyper IgM syndrome type 1/CD40L deficiency. *(From Lieding JW, Holland SM. Warts and all: HPV in primary immunodeficiencies. J Allergy Clin Immunol. 2012;130[5]:1030–1048, Fig. 3, p. 1043.)*

neonates who aspirate infectious virus during birth and may subsequently develop laryngeal papillomatosis.

Differential Diagnosis

Common warts are most often confused with molluscum contagiosum. Plantar and palmar warts may be difficult to distinguish from punctate keratoses, corns, and calluses. In contrast to calluses, warts obliterate normal skin markings. Juvenile flat warts mimic lichen planus, lichen nitidus, angiofibromas, syringomas, milia, and acne. Condylomata acuminata may resemble condylomata lata of secondary syphilis. Patients with recurrent, multiple, difficult-to-treat or disseminated warts may have a primary immune deficiency disorder (Fig. 708.6).

Treatment

Various therapeutic measures are effective in the treatment of warts. More than 65% of warts disappear spontaneously within 2 years. Warts are epidermal lesions and do not produce scarring unless subjected to surgical procedures or overly aggressive treatments. Hyperkeratotic lesions (common, plantar, and palmar warts) are more responsive to therapy if the excess keratotic debris is gently pared with a scalpel until thrombosed capillaries are apparent; further paring may induce bleeding. Treatment is most successful when performed regularly and frequently (every 2-4 weeks).

Common warts can be eradicated by applications of liquid nitrogen or by laser therapy, such as carbon dioxide or pulsed dye laser. Daily application of salicylic acid in flexible collodion or as a stick is a slow but painless method of removal that is effective in some patients. Plantar and palmar warts may be treated with 40% salicylic acid plasters. These should be applied for 5 days at a time with a 2-day rest period between applications. After removal of the plaster and prolonged soaking in hot water, keratotic debris can be removed with an emery board or pumice stone. Condylomata respond best to weekly applications of 25% podophyllin in tincture of benzoin. The medication should be left on the warts for 4-6 hours and then removed by bathing. Keratinized warts near the genitals (buttocks) do not respond to podophyllin. Imiquimod (5% cream) applied 3 times weekly is also beneficial. Imiquimod is not only indicated for genital warts but also has been used successfully to treat warts in other locations; however, it can cause inflammation and irritation, particularly in occluded areas. For nongenital warts, imiquimod should be applied daily. Cimetidine 30-40 mg/kg/day by mouth has been used in children with multiple warts unresponsive to other treatment, though its efficacy remains unclear. Immunotherapy with intralesional candida, MMR (measles, mumps, and rubella)

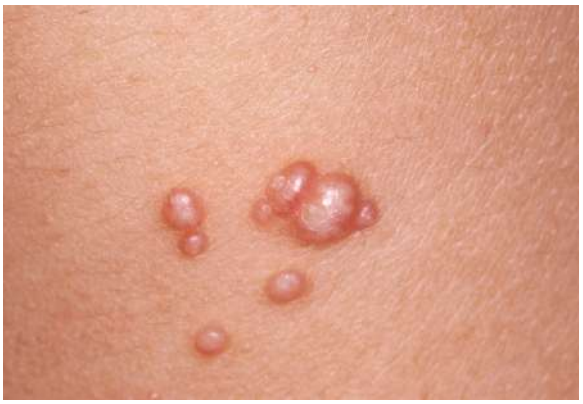

Fig. 708.7 Grouped molluscum.

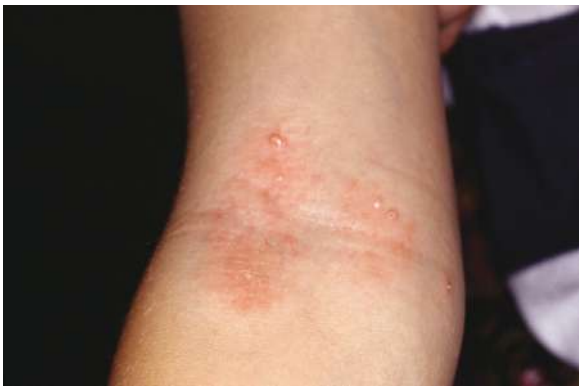

Fig. 708.8 Molluscum with surrounding dermatitis.

vaccine or *Trichophyton* antigen may also be employed, especially when lesions are numerous or resistant to other therapies. Immunotherapy is performed in clinic, and multiple treatments at 1-month intervals (at least three to four) are usually required. With all types of therapy, care should be taken to protect the surrounding normal skin from irritation. Other treatments include 5-fluorouracil, a chemotherapy agent, which can be helpful, particularly when used with occlusion and sometimes in combination with salicylic acid. Topical cidofovir, an antiviral agent, and intralesional bleomycin, have also been used in refractory cases.

MOLLUSCUM CONTAGIOSUM

Etiology

The poxvirus that causes molluscum contagiosum is a large double-stranded DNA virus that replicates in the cytoplasm of host epithelial cells. Type 1 virus causes most infections. The disease is acquired by direct contact with an infected person or from fomites and is spread by autoinoculation. Children age 2-6 years who are otherwise well and individuals who are immunosuppressed are most commonly affected. The incubation period is estimated to be 2 weeks or longer.

Clinical Manifestations

Discrete, pearly, skin-colored, smooth, dome-shaped papules vary in size from 1 to 5 mm. They typically have a central umbilication from which a plug of cheesy material can be expressed. Although these papules can emerge anywhere on the body, they have a predilection for sites such as the face, eyelids, neck, axillae, and thighs (Fig. 708.7). They may be found in clusters on the genitals or in the groin of adolescents and may be associated with other venereal diseases in sexually active individuals. Lesions commonly involve the genital area in children but are not acquired by sexual transmission in most cases. Mild surrounding erythema or an eczematous dermatitis may accompany the papules (Fig. 708.8). Lesions on patients with AIDS tend to be large and numerous, particularly on the face. Exuberant lesions may also be found in children with leukemia and other immunodeficiencies. Children with atopic dermatitis are susceptible to widespread involvement in areas of dermatitis. A pustular eruption can develop at the site of individual molluscum lesions (Fig. 708.9). It is not a secondary bacterial infection, but rather an immunologic reaction to the molluscum virus; hence treatment with antibiotics is unnecessary. Atrophic scars may often follow this type of reaction.

Differential Diagnosis

The differential diagnosis of molluscum contagiosum includes trichoepithelioma, basal cell carcinoma, ectopic sebaceous glands, syringoma, hidrocystoma, keratoacanthoma, juvenile xanthogranulomas, and warty dyskeratoma. In individuals with AIDS, cryptococcosis may be indistinguishable clinically from molluscum contagiosum. Rarely, coccidioidomycosis, histoplasmosis, or *Penicillium marneffei* infection masquerades as molluscum-like lesions in an immunocompromised host.

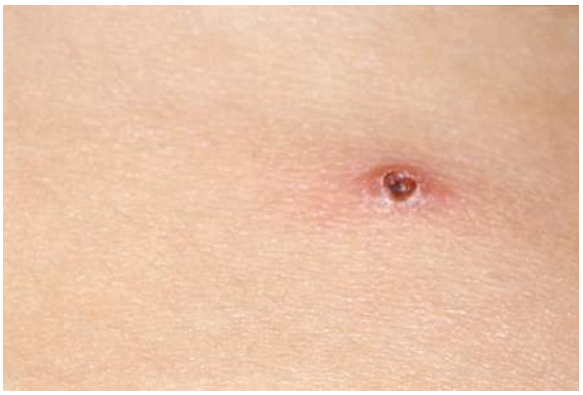

Fig. 708.9 Inflamed molluscum. Crusted papule at the site of a previous molluscum.

Treatment

Molluscum contagiosum is a self-limited disease, with an average duration of 6-9 months. However, lesions can persist for years, spreading to distant sites and potentially transmitting to others. Affected patients should be advised to avoid shared baths and towels until the infection is clear. In cases of atopic dermatitis or immunodeficiency, infection may rapidly spread, leading to the development of hundreds of lesions in children. *Immunotherapy with either* Candida *or* Trichophyton *antigen is the most commonly used treatment*. This is repeated every 4 weeks until resolution. If lesions are limited in number, then depending on the age of the patient, individual lesions can be treated with liquid nitrogen cryotherapy. For younger children, cantharidin may be applied to the lesions and covered with adhesive bandages to prevent unwanted spread of the blistering agent. A blister forms at the application site, facilitating the removal of the molluscum. However, it's important to note that cantharidin should not be applied to the face. Cantharidin availability is either very limited or completely unavailable in the United States. Imiquimod has not been proven more effective than placebo in randomized trials. Considering that molluscum is an epidermal disease, caution should be exercised to avoid excessive treatment that may result in scarring.

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Chapter 709

Arthropod Bites and Infestations

709.1 Arthropod Bites

Lamiaa Hamie and Stephen R. Humphrey

Arthropod bites are a common affliction of children and occasionally pose a problem in diagnosis. A patient may be unaware of the source of the lesions or may deny being bitten, making interpretation of the eruption difficult. In these cases, knowledge of the habits, life cycle, and clinical signs of the more common arthropod pests of humans may help lead to a correct diagnosis (Table 709.1).

CLINICAL MANIFESTATIONS

The type of reaction that occurs after an arthropod bite depends on the insect species and the age-group and reactivity of the human host. Arthropods may cause injury to a host by various mechanisms, including mechanical trauma, such as the lacerating bite of a tsetse fly; invasion of host tissues, as in myiasis; contact dermatitis, as seen with repeated exposure to cockroach antigens; granulomatous reaction to retained mouthparts; transmission of systemic disease; injection of irritant cytotoxic or pharmacologically active substances, such as hyaluronidase, proteases, peptidases, and phospholipases in sting venom; and induction of anaphylaxis. Most reactions to arthropod bites depend on antibody formation to antigenic substances in saliva or venom. The type of reaction is determined primarily by the degree of previous exposure to the same or a related species of arthropod. When someone is bitten for the first time, no reaction develops. An immediate petechial reaction is occasionally seen. After repeated bites, sensitivity develops, producing a pruritic papule (Fig. 709.1) approximately 24 hours after the bite. This is the most common reaction seen in young children. With prolonged, repeated exposure, a wheal develops within minutes after a bite, followed 24 hours later by papule, vesicle, or bullae formation. By adolescence or adulthood, only a wheal may form, unaccompanied by the delayed papular reaction. Thus adults in the same household as affected children may be unaffected. Ultimately, as a person becomes insensitive to the bite, no reaction occurs at all. This stage of nonreactivity is maintained only as long as the individual continues to be bitten regularly. Individuals in whom papular urticaria develops are in the transitional phase between development of a primarily delayed papular reaction and development of an immediate urticarial reaction.

Arthropod bites may occur as solitary, numerous, or profuse lesions, depending on the feeding habits of the perpetrator. Fleas tend to sample their host several times within a small localized area, whereas mosquitoes tend to attack a host at more randomly scattered sites. Delayed

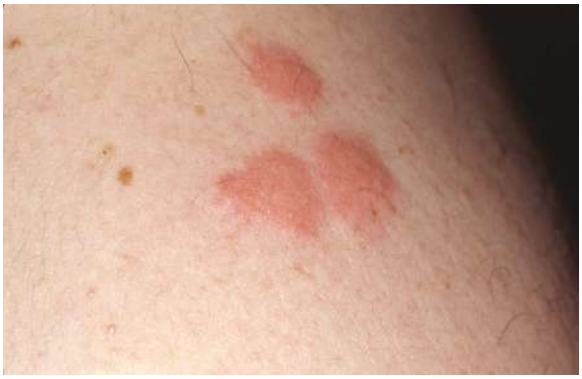

Fig. 709.1 Pruritic papules after bed bug bites.

Table 709.1 Bed Bugs Versus Other Arthropod Bites: Main Clinical and Epidemiologic Features*

ARTHROPOD	CLINICAL FEATURES ON EXAMINATION	LOCATION	TIMING OF PRURITUS	CONTEXT
Bed bugs	3-4 bites in a line or curve	Uncovered areas	Morning	Traveling
Fleas	3-4 bites in a line or curve	Legs and buttocks	Daytime	Pet owners or rural living
Mosquitoes	Nonspecific urticarial papules	Potentially anywhere	*Anopheles* spp. night; *Culex* spp. night; *Aedes* spp. day	Worldwide distribution
Head lice	Live lice on the head associated with itchy, scratched lesions	Scalp, ears, and neck	Any	Children, parents, or contact with children
Body lice	Excoriated papules and hyperpigmentation; live lice inside clothes	Back	Any	Unhoused people
Sarcoptes scabiei mites (scabies)	Vesicles, burrows, nodules, and nonspecific secondary lesions	Interdigital spaces, forearms, breasts, genitals	Night	Sexually transmitted, households or institutions
Ticks	Erythema migrans or ulcer	Potentially anywhere	Asymptomatic	Pet owners or hikers
Pyemotes ventricosus	Comet sign, a linear, erythematous, macular tract	Under clothes	Any time when inside habitat	People exposed to woodworm-contaminated furniture (*Pediculoides ventricosus* is a woodworm parasite)
Spiders	Necrosis (uncommon)	Face and arms	Immediate pain, no itching	Rural living

*It is difficult to diagnose a bite. Diagnosis relies on an array of arguments, none of which is specific by itself; it is the association of elements that is suggestive. Any arthropod bite can be totally asymptomatic.

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O. Bed bug infestation [published correction appears in *BMJ*. 2013;346:F1044]. *BMJ*. 2013;346:f138.

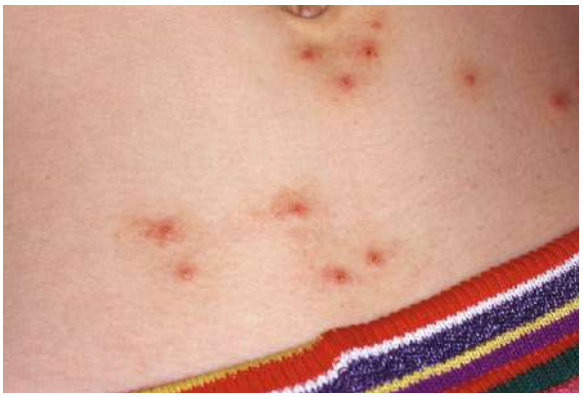

Fig. 709.2 Red-brown papules in papular urticaria.

hypersensitivity reactions to insect bites—the predominant lesions in the young and uninitiated—are characterized by firm, persistent papules that may become hyperpigmented and are often excoriated and crusted. Pruritus may be mild or severe, transient or persistent. A central punctum is usually visible but may disappear as the lesion ages or is scratched. The immediate hypersensitivity reaction is characterized by an evanescent, erythematous wheal. If edema is marked, a tiny vesicle may surmount the wheal. Certain beetles produce bullous lesions through the action of cantharidin, and various insects, including beetles and spiders, may cause hemorrhagic nodules and ulcers. Bites on the lower extremities are more likely to be severe or persistent or become bullous than those located elsewhere. Complications of arthropod bites include development of impetigo, folliculitis, cellulitis, lymphangitis, and severe anaphylactic hypersensitivity reactions, particularly after the bite of certain hymenopterans. The histopathologic changes are variable, depending on the arthropod, the age of the lesion, and the reactivity of the host. Acute urticarial lesions tend to show central vesiculation in which eosinophils are numerous. Papules most commonly show dermal edema and a mixed superficial and deep perivascular inflammatory infiltrate, often including a number of eosinophils. At times, however, the dermal cellular infiltrate is so dense that a lymphoma is suspected. Many young children demonstrate extensive dermal but nonerythematous, nontender edema in response to mosquito bites **(Skeeter syndrome)**, which responds to oral antihistamines; this must be distinguished from cellulitis, which tends to be painful, tender, and red. Retained mouthparts may stimulate a foreign body type of granulomatous reaction.

Papular urticaria occurs principally in the first decade of life. It may occur at any time of the year. The most common culprits are species of fleas, mites, bed bugs, gnats, mosquitoes, chiggers, and animal lice. Individuals with papular urticaria have predominantly transitional lesions in various stages of evolution between delayed-onset papules and immediate-onset wheals. The most characteristic lesion is an edematous, red-brown papule (Fig. 709.2). An individual lesion frequently starts as a wheal that, in turn, is replaced by a papule. A given bite may incite an id reaction at distant sites of quiescent bites in the form of erythematous macules, papules, or urticarial plaques. After a season or two, the reaction progresses from a transitional to a primarily immediate hypersensitivity urticarial reaction.

One of the most commonly encountered arthropod bites is that resulting from human, cat, or dog fleas (family Pulicidae). Eggs, which are generally laid in dusty areas and cracks between floorboards, give rise to larvae that then form cocoons. The cocoon stage can persist for up to 1 year, and the flea emerges in response to vibrations from footsteps, accounting for the assaults that frequently befall the new owners of a recently reopened dwelling. Adult dog fleas can live without a blood meal for approximately 60 days. Attacks from fleas are more likely to occur when the fleas do not have access to their usual host; cat or dog fleas are more voracious and problematic when one visits an area frequented by the pet than when the pet is encountered directly. Flea bites tend to be grouped in lines or irregular clusters on the lower extremities. Fleas are often not seen on the body of a pet. Diagnosis of flea bites is aided by examination of debris from the animal's bedding material. The debris is collected by shaking the bedding into a plastic bag and examining the contents for fleas or their eggs, larvae, or feces.

Table 709.2 Patient Education to Eliminate Bed Bugs

DETECTION
• Look for brown insects no bigger than apple seeds on the mattress, sofa, and curtains and in darker places in the room (especially cracks in the walls, crevices in box springs, and furniture)
• Look for black spots on the mattress or blood traces on the sheets
ELIMINATION
• Contact a pest management company
• Wash clothes at 60°C (140°F) or freeze delicate clothing, vacuum, and clean your home before the pest manager visits
• Collaborate with professionals who are used to dealing with bed bug infestation to increase eradication efficacy
PREVENTION
• Carefully examine secondhand furniture to assure the absence of bed bugs before purchase so as not to contaminate your home
• When sleeping in a hotel, even an upmarket establishment, lift mattresses to look for bed bugs or black spots
• Do not leave luggage in dark places, near furniture, or close to your bed. Before going to bed, close suitcases and put them in the bathroom—in the bathtub or shower stall

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O. Bed bug infestation [published correction appears in *BMJ*. 2013;346:F1044]. *BMJ*. 2013;346:f138.

TREATMENT

Treatment is directed at alleviation of pruritus by oral antihistamines and cool compresses. Potent topical corticosteroids are helpful. Topical antihistamines are potent immunologic sensitizers and have no role in the treatment of insect bite reactions. A short course of systemic steroids may be helpful if many severe reactions occur, particularly around the eyes. Insect repellents containing *N,N*-diethyl-3-methylbenzamide (DEET) may afford moderate protection against mosquitoes, fleas, flies, chiggers, and ticks, but are relatively ineffective against wasps, bees, and hornets. DEET must be applied to exposed skin and clothing to be effective. The most effective protection against mosquitoes, the human body louse, and other blood-feeding arthropods is the use of DEET and permethrin-impregnated clothing. However, these measures are not effective against the phlebotomine sand fly, which transmits leishmaniasis. Because of the potential for toxicity, the lowest effective DEET dose should be selected. Additional insect repellents include picaridin (flies, mosquitoes, chiggers, ticks), IR3535 (mosquitoes), oil of lemon, eucalyptus (mosquitoes), and citronella (mosquitoes). Table 709.2 lists methods to eliminate bed bugs.

An effort should be made to identify and eradicate the etiologic agent. Pets should be carefully inspected. Crawl spaces, eaves, and other sites of the house or outbuildings frequented by animals and birds should be decontaminated, and baseboard crevices, mattresses, rugs, furniture, and animal sleeping quarters should be decontaminated. Agents that are effective for ridding the home of fleas include lindane, pyrethroids, and organic thiocyanates. Flea-infested pets may be treated with powders containing rotenone, pyrethroids, malathion, or methoxychlor. Lufenuron, an agent that prevents fleas from reproducing, is effective for animals in oral and injectable formulations. Fipronil is effective as a topical agent for the prevention of flea infestation.

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709.2 Scabies

Lamiaa Hamie and Stephen R. Humphrey

Scabies is caused by burrowing and release of toxic or antigenic substances by the female mite *Sarcoptes scabiei* var. *hominis*. The most

Table 709.3 Different Presenting Forms of Scabies

PRESENTING FORMS OF SCABIES	SPECIFIC HIGH-RISK POPULATIONS	CLINICAL MANIFESTATIONS	LIMITED DIFFERENTIAL DIAGNOSES
Classic scabies (scabies vulgaris)	Infants and children; sexually active adults; men who have sex with men	Intense generalized pruritus, worse at night; inflammatory pruritic papules localized to finger webs, flexor aspects of wrists, elbows, axillae, buttocks, genitalia, female breasts; lesions and pruritus spare the face, head, and neck; secondary lesions include eczematization, excoriation, impetigo	Dermatitis herpetiformis, drug reactions, eczema, pediculosis corporis, lichen planus, pityriasis rosea
Scalp scabies	Infants and children; institutionalized older adults; AIDS patients; patients with preexisting crusted scabies	Atypical crusted papular lesions of the scalp, face, palms, and soles	Dermatomyositis, ringworm, seborrheic dermatitis
Crusted scabies (Norwegian scabies, scabies norvegica, scabies crustosa)	Institutionalized older adults; institutionalized developmentally disabled (Down syndrome); unhoused persons, especially HIV-positive; all immunocompromised patients, particularly those with AIDS or positive for HIV or HTLV-1; transplant recipients; patients on prolonged systemic corticosteroids and chemotherapy	Psoriasiform hyperkeratotic papular lesions of the scalp, face, neck, hands, feet, with extensive nail involvement; eczematization and impetigo common	Contact dermatitis, drug reactions, eczema, erythroderma, ichthyosis, psoriasis
Nodular scabies	Sexually active adults; men who have sex with men; HIV-positive men > HIV-positive women	Violaceous pruritic nodules localized to male genitalia, groin, axillae, representing hypersensitivity reaction to mite antigens	Acropustulosis, atopic dermatitis, Darier disease, lupus erythematosus, lymphomatoid papulosis, papular urticaria, necrotizing vasculitis, secondary syphilis

HTLV-1, Human T-cell lymphotropic virus type 1.
From Bennett JE, Blaser MJ, Dolin R, et al., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases,* 8th ed. Philadelphia: Saunders; 2015: Table 295.1, p. 3252.

important factor that determines spread of scabies is the extent and duration of physical contact with an affected individual. Children and sexual partners of affected individuals are most at risk. Scabies is transmitted only rarely by fomites because the isolated mite dies within 2-3 days.

ETIOLOGY AND PATHOGENESIS

An adult female mite measures approximately 0.4 mm in length; has four sets of legs; and has a hemispheric body marked by transverse corrugations, brown spines, and bristles on the dorsal surface. A male mite is approximately half her size and is similar in configuration. After impregnation on the skin surface, a gravid female exudes a keratolytic substance and burrows into the stratum corneum, often forming a shallow well within 30 minutes. She gradually extends this tract by 0.5-5.0 mm/24 hours along the boundary with the stratum granulosum. She deposits 10-25 oval eggs and numerous brown fecal pellets (scybala) daily. When egg laying is completed, in 4-5 weeks, she dies within the burrow. The eggs hatch in 3-5 days, releasing larvae that move to the skin surface to molt into nymphs. Maturity is achieved in approximately 2-3 weeks. Mating occurs, and the gravid female invades the skin to complete the life cycle.

CLINICAL MANIFESTATIONS

In an immunocompetent host, scabies is frequently heralded by intense pruritus, particularly at night (Table 709.3). The first sign of the infestation often consists of 1- to 2-mm red papules, some of which are excoriated, crusted, or scaling. Threadlike burrows are the classic lesion of scabies (Figs. 709.3 and 709.4) but may not be seen in infants. In infants, bullae and pustules are relatively common. The eruption may also include wheals, papules, vesicles, and a superimposed eczematous dermatitis (Fig. 709.5). The palms, soles, and scalp are often affected. In older

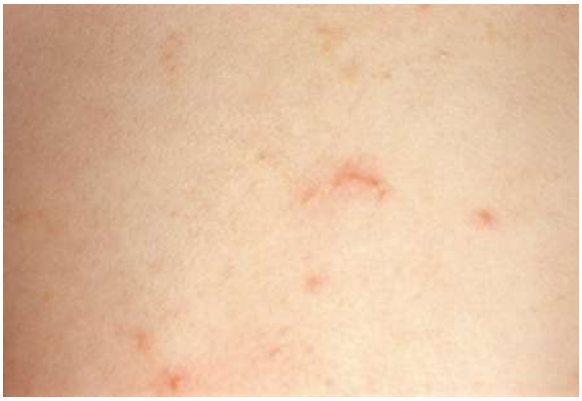

Fig. 709.3 Classic scabies burrow.

children and adolescents, the clinical pattern is similar to that in adults, in whom preferred sites are the interdigital spaces; wrist flexors; anterior axillary folds; ankles, buttocks, umbilicus and belt line; groin; genitals in men; and areolas in women. The head, neck, palms, and soles are generally spared. Infants will often have a diffuse eczematous eruption that will involve the scalp, neck, and face. Red-brown nodules, most often located in covered areas such as the axillae, groin, and genitals, predominate in the less common variant called *nodular scabies.* Additional clues include facial sparing, affected family members, poor response to topical antibiotics, and transient response to topical steroids. Untreated, scabies may lead to eczematous dermatitis, impetigo, ecthyma, folliculitis, furunculosis,

cellulitis, lymphangitis, and id reaction. Glomerulonephritis has developed in children from streptococcal impetiginization of scabies lesions. In some tropical areas, scabies is the predominant underlying cause of pyoderma. A latent period of approximately 1 month follows an initial infestation. Thus itching may be absent and lesions may be relatively inapparent in contacts who are asymptomatic carriers. However, on reinfestation, reactions to mite antigens are noted within hours.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of scabies can often be made clinically but is confirmed by microscopic identification of mites (Fig. 709.6A), ova, and scybala (see Fig. 709.6B) in epithelial debris. Scrapings most often test positive when obtained from burrows or fresh papules. A reliable method is application of a drop of mineral oil on the selected lesion, scraping of it with a No. 15 blade, and transferring the oil and scrapings to a glass slide.

The differential diagnosis depends on the types of lesions present. **Burrows** are virtually pathognomonic for human scabies. **Papulovesicular lesions** are confused with papular urticaria, canine scabies, chickenpox, viral exanthems, drug eruptions, dermatitis herpetiformis, and folliculitis. **Eczematous lesions** may mimic atopic dermatitis and seborrheic dermatitis, and the less common bullous disorders of childhood may be suspected in infants with predominantly bullous lesions. **Nodular scabies** is frequently misdiagnosed as urticaria pigmentosa and Langerhans cell histiocytosis. The histopathologic appearance of nodular scabies, consisting of a deep, dense, perivascular infiltrate of lymphocytes, histiocytes, plasma cells, and atypical mononuclear cells, may mimic malignant lymphoid neoplasms.

TREATMENT

The treatment of choice for scabies is permethrin 5% cream (Elimite) applied to the entire body from the neck down, with particular attention to intensely involved areas, which is also standard therapy (Table 709.4). Scabies is frequently found above the neck in infants (younger than 2

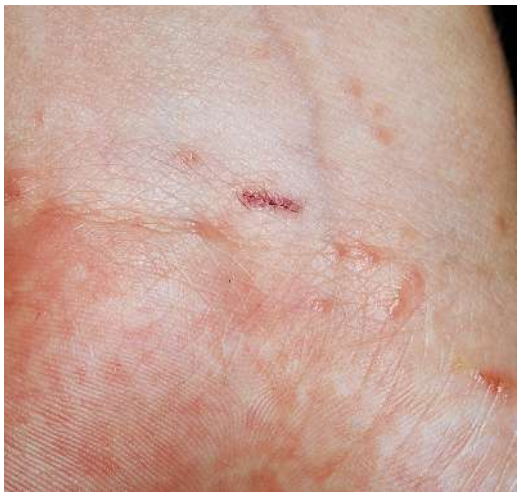

Fig. 709.4 Scabies. Felt-tipped ink pen has penetrated and highlighted a burrow. The ink is retained after the surface is wiped clean with an alcohol swab. *(From Habif TP, ed. Clinical Dermatology, 6th ed. Philadelphia: Mosby; 2016: Fig 15-16.)*

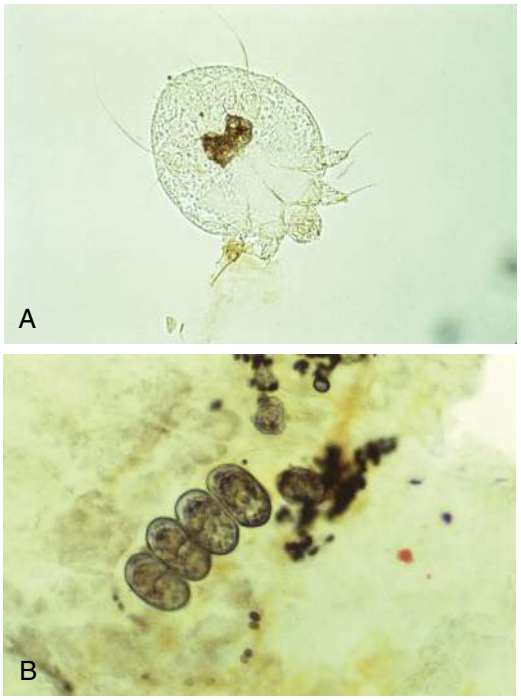

Fig. 709.6 A, Human scabies mite obtained from scraping. B, Scabies ova and scybala.

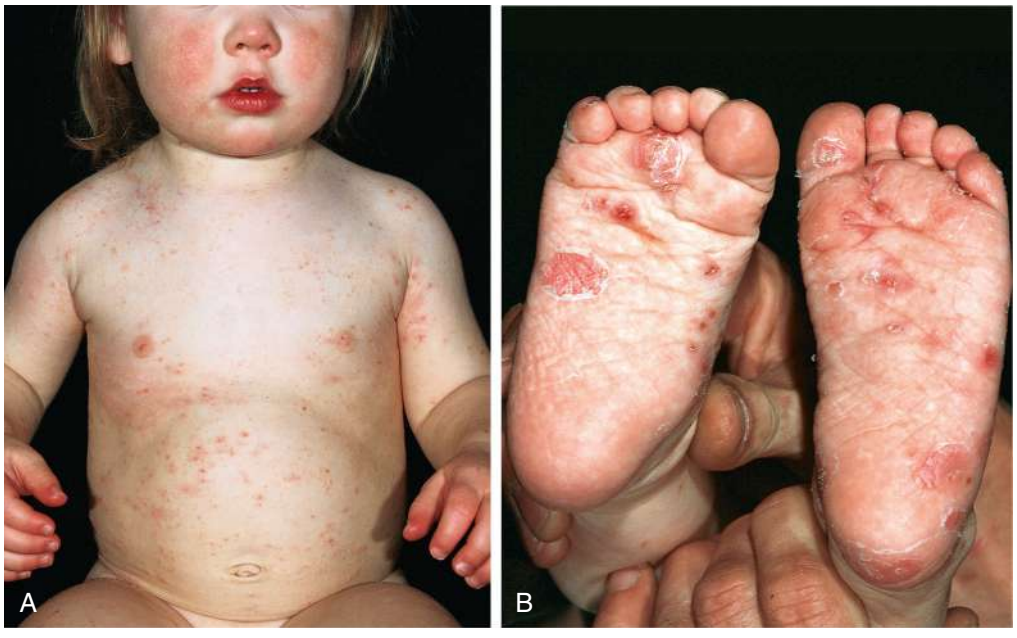

Fig. 709.5 A, Diffuse scabies on an infant. The face is clear. The lesions are most numerous around the axillae, chest, and abdomen. B, Scabies. Infestation of the palms and soles is common in infants. The vesicular lesions have all ruptured. *(From Habif TP, ed. Clinical Dermatology, 4th ed. Philadelphia: Mosby; 2004: Figs. 15.8 and 15.9.)*

Table 709.4 Currently Recommended Treatment for Scabies

SCABICIDES	FDA APPROVED?	PREGNANCY CATEGORY*	DOSING SCHEDULE	SAFETY PROFILE	CONTRAINDICATIONS
5% Permethrin cream (Actin, Nix, Elimite)	Yes	B	Apply from neck down; wash off after 8-14 hr; good residual activity, but second application recommended after 1 wk	Excellent; itching and stinging on application	Prior allergic reactions; infants <2 mo of age; breastfeeding
1% Lindane lotion or cream	Yes	B	Apply 30-60 mL from neck down; wash off after 8-12 hr; no residual activity; increasing drug resistance	Potential for central nervous system toxicity from organochloride poisoning, usually manifesting as seizures, with overapplication and ingestions	Preexisting seizure disorder; infants and children <6 mo of age; pregnancy; breastfeeding
10% Crotamiton cream or lotion (Eurax)	Yes	C	Apply from neck down on 2 consecutive nights; wash off 24 hr after second application	Excellent; not very effective; exacerbates pruritus	None
2–10% Sulfur in petrolatum ointments	No	C	Apply for 2-3 days, then wash	Excellent; not very effective	Preexisting sulfur allergy
10–25% Benzoyl benzoate lotion	No	None	Two applications for 24 hr with 1-day to 1-wk interval	Irritant; exacerbates pruritus; can induce contact irritant dermatitis and pruritic cutaneous xerosis	Preexisting eczema
0.5% Malathion lotion (Ovide), 1% malathion shampoo (unavailable in the United States)	No	B	95% ovicidal; rapid (5 min) killing; good residual activity; increasing drug resistance	Flammable 78% isopropyl alcohol vehicle stings eyes, skin, mucosa; increasing drug resistance; organophosphate poisoning risk with overapplication and ingestions	Infants and children <6 mo of age; pregnancy; breastfeeding
Ivermectin (Stromectol)	Yes	C	200-μg/kg single PO dose, may be repeated in 14-15 days; not ovicidal, second dose on day 14 or 15 highly recommended; recommended for endemic or epidemic scabies in institutions and refugee camps	Excellent; may cause nausea and vomiting; take on empty stomach with water	Safety in pregnancy uncertain; probably safe during breastfeeding; not recommended for children younger than 5 yr of age or weighing <15 kg

*U.S. Food and Drug Administration safety in pregnancy categories: A, safety established; B, presumed safe; C, uncertain safety; D, unsafe; X, highly unsafe.
From Bennett JE, Blaser MJ, Dolin R, et al., eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Saunders; 2015: Table 295.2, p. 3253.

years old), necessitating treatment of the scalp. The medication is left on the skin for 8-12 hours and should be reapplied in 1 week for another 8- to 12-hour period. Additional therapies include sulfur ointment 5–10%, and crotamiton 10% lotion or cream. Lindane 1% lotion or cream should only be used as an alternative therapy, given the risk of systemic toxicity. For severe infestations or in immunocompromised patients, ivermectin 200 μg/kg per dose given orally for two doses 2 weeks apart can be used (off-label use). Single-dose ivermectin (200 μg/kg) has also been effective in immunocompetent patients, with improvement (cure) noted in 60% at 2 weeks and 89% at 4 weeks after treatment (see Table 709.4).

Transmission of mites is unlikely more than 24 hours after treatment. Pruritus, which is a result of hypersensitivity to mite antigens, may persist for a number of days to weeks, and may be alleviated by a topical corticosteroid preparation. If pruritus persists for >2 weeks after treatment and new lesions are occurring, the patient should be reexamined for mites. Nodules are extremely resistant to treatment and may take several months to resolve. The entire family should be treated, as should caretakers of the infested child. Clothing, bed linens, and towels should be washed in hot water and dried using high heat. Clothing or other items (e.g., stuffed animals) that cannot be washed may be dry cleaned or stored in bags for 3 days to 1 week, as the mite will die when separated from the human host.

CRUSTED SCABIES

The Norwegian variant of human scabies is highly contagious and occurs mainly in individuals who are cognitively and physically debilitated, particularly those who are institutionalized and those with Down syndrome; in patients with poor cutaneous sensation (leprosy, spina bifida); in patients who have severe systemic illness (leukemia, diabetes); and in immunosuppressed patients (HIV infection). Affected individuals are infested by a myriad of mites that inhabit the crusts and exfoliating scales of the skin and scalp (Fig. 709.7). The nails may become thickened and dystrophic. The subungual debris is densely populated by mites. The infestation is often accompanied by generalized lymphadenopathy and eosinophilia. There is massive orthokeratosis and parakeratosis with numerous interspersed mites, psoriasiform epidermal hyperplasia, foci of spongiosis, and neutrophilic abscesses. Norwegian scabies is thought to represent a deficient host immune response to the organism. Management is difficult, requiring scrupulous isolation measures, removal of the thick scales, and repeated but careful applications of permethrin 5% cream. Ivermectin (200-250 μg/kg) has been used successfully as single-dose therapy in refractory cases, particularly in HIV-infected patients. A second dose may be needed a week later. The U.S. Food and Drug Administration has not approved this agent for the treatment of scabies.

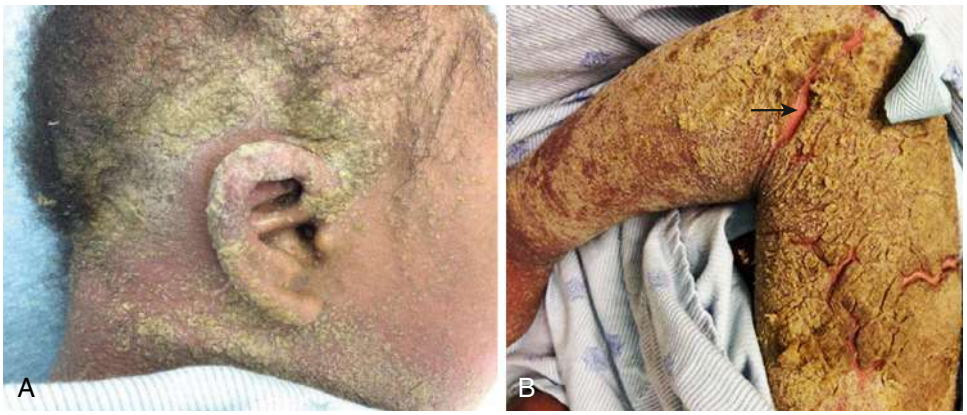

Fig. 709.7 Norwegian scabies. A and B, Right side of the head and neck and right leg before treatment showing diffuse, scaly hyperkeratotic rash, crusts, and fissures with areas of skin erythema *(arrow)* caused by hyperinfestation after infection with *Sarcoptes scabiei* in a patient with Down syndrome. *(Modified from Lee K, Heresi G, Hammond RA. Norwegian scabies in a patient with Down syndrome. J Pediatr. 2019;209:253.)*

CANINE SCABIES

Canine scabies is caused by *S. scabiei* var. *canis,* the dog mite that is associated with mange. The eruption in humans, which is most frequently acquired by cuddling an infested puppy, consists of tiny papules, vesicles, wheals, and excoriated eczematous plaques. Burrows are not present because the mite infrequently inhabits human stratum corneum. The rash is pruritic and has a predilection for the arms, chest, and abdomen, the usual sites of contact with dogs. Onset is sudden and usually follows exposure by 1-10 days, possibly resulting from development of a hypersensitivity reaction to mite antigens. Recovery of mites or ova from scrapings of human skin is rare. The disease is self-limited because humans are not a suitable host. Bathing and changing clothes are generally sufficient. Removal or treatment of the infested animal is necessary. Symptomatic therapy for itching is helpful. In rare cases in which mites are demonstrated in scrapings from an affected child, they can be eradicated by the same measures applicable to human scabies.

OTHER TYPES OF SCABIES

Other mites that occasionally bite humans include the chigger or harvest mite *(Eutrombicula alfreddugesi),* which prefers to live on grass, shrubs, vines, and stems of grain. Larvae have hooked mouthparts, which allow the chigger to attach to the skin, but not to burrow, to obtain a blood meal, most commonly on the lower legs. Avian mites may affect those who come into close contact with chickens or pet gerbils. Humans may occasionally be assaulted by avian mites that have infested a nest outside a window, an attic, heating vents, or an air conditioner. The dermatitis is variable, including grouped papules, wheals, and vesicular lesions on the wrists, neck, breasts, umbilicus, and anterior axillary folds. A prolonged investigation is often undertaken before the cause and source of the dermatitis are discovered.

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709.3 Pediculosis

Lamiaa Hamie and Stephen R. Humphrey

Three types of lice are obligate parasites of the human host: body or clothing lice *(Pediculus humanus corporis),* head lice *(Pediculus humanus capitis),* and pubic or crab lice *(Phthirus pubis).* Only the body louse serves as a vector of human disease (typhus, trench fever, relapsing fever). Body and head lice have similar physical characteristics. They are approximately 2-4 mm in length. Pubic lice are only 1-2 mm in length and are greater in width than in length, giving them a crablike appearance. Female lice live for approximately 1 month and deposit 3-10 eggs daily on the human host. However, body lice generally lay eggs in or near the seams of clothing. The ova or nits are glued to hairs or fibers of clothing but not directly on the body. Ova hatch in 1-2 weeks and require another week to mature. Once the eggs hatch, the nits remain attached to the hair as empty sacs of chitin. Freshly hatched larvae die unless a meal is obtained within 24 hours and every few days thereafter. Both nymphs and adult lice feed on human blood, injecting their salivary juices into the host and depositing their fecal matter on the skin. Symptoms of infestation do not appear immediately but develop as an individual becomes sensitized. The hallmark of all types of pediculosis is pruritus.

Pediculosis corporis is rare in children except under conditions of poor hygiene, especially in colder climates when the opportunity to change clothes on a regular basis is lacking. The parasite is transmitted mainly on contaminated clothing or bedding. The primary lesion is a small, intensely pruritic, red macule or papule with a central hemorrhagic punctum, located on the shoulders, trunk, or buttocks. Additional lesions include excoriations, wheals, and eczematous, secondarily infected plaques. Massive infestation may be associated with constitutional symptoms of fever, malaise, and headache. Chronic infestation may lead to "vagabond's skin," which manifests as lichenified, scaling, hyperpigmented plaques, most commonly on the trunk. Lice are found on the skin only transiently when they are feeding. At other times, they inhabit the seams of clothing. Nits are attached firmly to fibers in the cloth and may remain viable for up to 1 month. Nits hatch when they encounter warmth from the host's body when the clothes are worn again. Therapy consists of improved hygiene and hot water laundering of all infested clothing and bedding. A uniform temperature of 65°C (149°F), wet or dry, for 15-30 minutes kills all eggs and lice. Alternatively, eggs hatch and nymphs starve if clothing is stored for 2 weeks at 23.9–29.4°C (75–85°F).

Pediculosis capitis is an intensely pruritic infestation of lice in the scalp hair. It is the most common form of lice to affect children, in particular those between the ages of 3 and 12 years. Fomites and head-to-head contact are important modes of transmission. In summer months in many areas of the United States and in the tropics at all times of the year, shared combs, brushes, or towels have a more important role in louse transmission. Translucent 0.5-mm eggs are laid near the proximal portion of the hair shaft and become adherent to one side of the shaft (Fig. 709.8). A nit cannot be moved along or knocked off the hair shaft with the fingers. Secondary pyoderma, after trauma from scratching, may result in matting together of the hair and cervical and occipital lymphadenopathy. Hair loss does not result from pediculosis but may accompany the secondary pyoderma. Head lice are a major cause of numerous pyodermas of the scalp, particularly in tropical environments. Lice are not always visible, but nits are detectable on the hairs, most commonly in the occipital region and above the ears, rarely on beard or pubic hair. Dermatitis may also be noted on the neck and pinnae. An **id reaction**, consisting of erythematous patches and plaques, may develop, particularly on the trunk.

In cases of resistance (which is common) of head lice to pyrethroids, malathion 0.5% in isopropanol is the treatment of choice and should be applied to dry hair until hair and scalp are wet and left on for 12 hours. A second application 7-9 days after the initial treatment may be necessary. This product is flammable, so care should be taken to avoid open flames. Malathion, like lindane shampoo, is not indicated for use in neonates and infants; however, additional approved therapies include spinosad (if >6 months), benzyl alcohol lotion (if >6 months), and ivermectin for difficult-to-treat head lice (Table 709.5). All household members should be treated at the same time. Nits can be removed

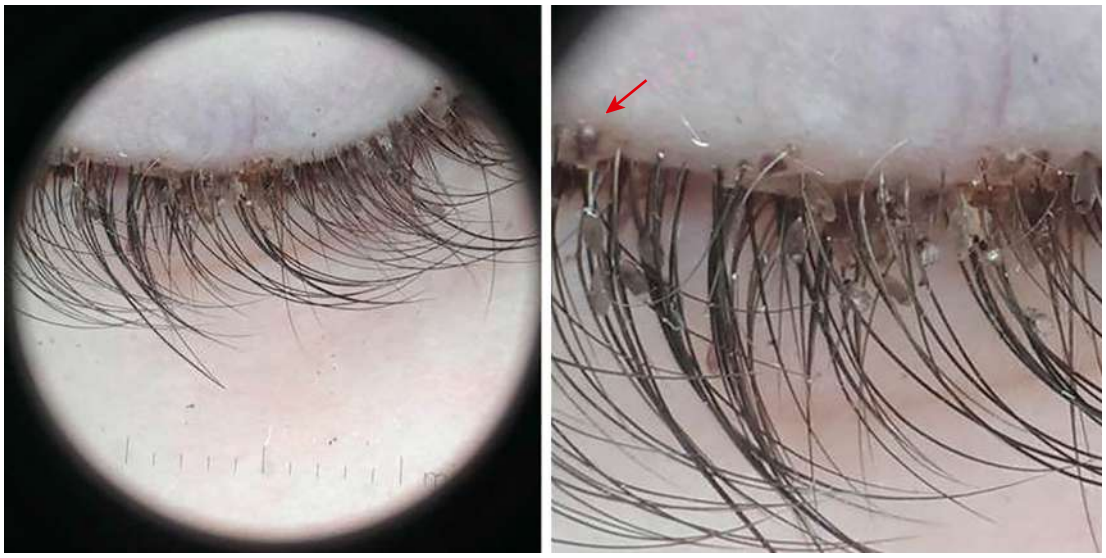

Fig. 709.8 Phthiriasis palpebrarum. Dermoscopy examination of eyelashes in a 27-mo-old boy, showing nits and parasites *(arrow)*. *(From Ouedraogo M, Ventejou S, Leducq S, et al. Crusts on the eyelashes. J Pediatr. 2019;209:254.)*

Table 709.5 Drugs for Head Lice

DRUG	RESISTANCE	FDA-APPROVED LOWER AGE OR WEIGHT LIMIT	DOSAGE AND ADMINISTRATION	COST*/SIZE
Ivermectin 0.5% lotion—Sklice (Arbor)	No	6 mo	Apply to dry hair and scalp for 10 min, then rinse†	$297.60/4 oz
Ivermectin tablets‡—Stromectol (MSD)	No	15 kg§	200-400 µg/kg PO once; repeat 7-10 days later	$9.30#
Spinosad 0.9% suspension—Natroba (ParaPro)	No	6 mo	Apply to dry hair for 10 min, then rinse; repeat 7 days later if necessary¶	$246.10/4 oz
Benzyl alcohol 5% lotion—Ulesfia (Lachlan)	No	6 mo	Apply to dry hair for 10 min, then rinse; repeat 7 days later**	$181.30/8 oz
Pyrethrins with piperonyl butoxide shampoo‡—Generic Rid (Bayer)	Yes	2 yr	Apply to dry hair for 10 min, then shampoo; repeat 7-10 days later	$15.00/8 oz‡‡ $20.00/8 oz‡‡
Permethrin 1% creme rinse‡—Generic Nix (Insight)	Yes	2 mo	Apply to shampooed, towel-dried hair for 10 min, then rinse; repeat 7 days later	$18.00/4 oz‡‡ $21.00/4 oz‡‡
Malathion 0.5% lotion—Generic Ovide (Taro)	Not in the United States	6 yr§§	Apply to dry hair for 8-12 hr, then shampoo; repeat 7-9 days later if necessary##,¶¶	$221.70/2 oz $246.40/2 oz
Abametapir lotion 0.74% (Xeglyze)	No	6 mo	Apply to dry hair for 10 min on day 0 and then rinse with water	Not available yet

*Approximate WAC for the indicated size. WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource Monthly. November 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. Copyright 2016. www.fdbhealth.com/policies/drug-pricing-policy. Total cost of treatment may vary based on hair length and number of applications required to completely eradicate lice.

†The manufacturer recommends using up to one single-use, 4-oz tube of topical ivermectin lotion per application.

‡Not FDA approved for treatment of head lice.

§The safety and effectiveness of oral ivermectin have not been established in children weighing <15 kg.

#Cost of two 3-mg tablets (one dose for a 30-kg child at the lowest dosage).

¶The manufacturer recommends using up to one 4-oz (120-mL) bottle of spinosad 0.9% suspension per application.

**The amount of benzoyl alcohol 5% lotion recommended per application depends on hair length.

‡‡Approximate cost according to Walgreens.com. Accessed November 10, 2016.

§§The safety and effectiveness of malathion lotion have not been established in children <6 yr old; it is contraindicated in children <24 mo old.

##In clinical trials, patients used a maximum of 2 fl oz of malathion lotion per application.

¶¶One or two 20-min applications have also been effective (Meinking TL, Vicaria M, Eyerdam DH, et al: Efficacy of a reduced application time of Ovide lotion [0.5% malathion] compared to Nix creme rinse [1% permethrin] for the treatment of head lice. *Pediatr Dermatol* 21:670–674, 2004.)

††Available without a prescription.

FDA, U.S. Food and Drug Administration; MSD, Merck Sharp Dohme; WAC, wholesaler acquisition cost or manufacturer's published price to wholesalers.

From The Medical Letter. Drugs for head lice. *Med Lett Drugs Ther.* 2016;58:150–152.

Fig. 709.9 Intact nits on human hairs.

with a fine-toothed comb after application of a damp towel to the scalp for 30 minutes. Clothing and bed linens should be laundered in very hot (54.4°C [>130°F]) water and then dried for at least 10 minutes at the highest setting or dry-cleaned; brushes and combs should be discarded or coated with a pediculicide for 15 minutes and then thoroughly cleaned in boiling water. If the object cannot be washed, it can be sealed in a plastic bag for 48 hours. Children may return to school after the initial treatment.

Pediculosis pubis is transmitted by skin-to-skin or sexual contact with an infested individual; the chance of acquiring the lice with one sexual exposure is 95%. The infestation is usually encountered in adolescents, although small children may occasionally acquire pubic lice on the eyelashes (see Fig. 709.8). Patients experience moderate to severe pruritus and may develop a secondary pyoderma from scratching. Excoriations tend to be shallow, and the incidence of secondary infection is lower than in pediculosis corporis. Maculae ceruleae are steel-gray spots, usually <1 cm in diameter, which may appear in the pubic area and on the chest, abdomen, and thighs. Oval translucent nits, which are firmly attached to the hair shafts, may be visible to the naked eye or may be readily identified by a hand lens or by microscopic examination (Fig. 709.9). Grittiness, as a result of adherent nits, may sometimes be detected when the fingers are run through infested hair. Adult lice are more difficult to detect than head or body lice because of their lower level of activity and smaller, translucent bodies. Because pubic lice occasionally may wander or may be transferred to other sites on fomites, terminal hair on the trunk, thighs, axillary region, beard area, and eyelashes should be examined for nits. The coexistence of other venereal diseases should be considered. Treatment with a 10-minute application of a pyrethrin preparation is usually effective. Retreatment may be required in 7-10 days. Infestation of eyelashes is eradicated by petrolatum applied 3-5 times per 24 hours for 8-10 days. Clothing, towels, and bed linens may be contaminated with nit-bearing hairs and should be thoroughly laundered or dry-cleaned.

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709.4 Seabather's Eruption

Lamiaa Hamie and Stephen R. Humphrey

Seabather's eruption is a severely pruritic dermatosis of inflammatory papules that develops within about 12 hours of bathing in saltwater, primarily on body sites that were covered by a bathing suit. The eruption has been described primarily in connection with bathing in the waters of Florida and the Caribbean. Lesions, which may include pustules, vesicles, and urticarial plaques, are more numerous in individuals who keep their bathing suits on for an extended period after leaving the water. The eruption may be accompanied by systemic symptoms of fatigue, malaise, fever, chills, nausea, and headache; in one large series, ~40% of children younger than 16 years of age had fever. Duration of the pruritus and skin eruption is 1-2 weeks. Lesions consist of a superficial and deep perivascular and interstitial infiltrate of lymphocytes, eosinophils, and neutrophils. The eruption appears to be caused by an allergic hypersensitivity reaction to venom from larvae of the thimble jellyfish *(Linuche unguiculata)*. Treatment is largely symptomatic. Potent topical corticosteroids have been shown to provide relief to some patients.

Chapter 710
Acne

Leah Lalor

ACNE VULGARIS

Acne is a chronic inflammatory disorder of the pilosebaceous unit with a multifactorial pathogenesis that affects at least 85% of adolescents but can occur in any age-group.

Pathogenesis

There are four main pathogenic factors leading to the development of acne: (1) increased sebum production; (2) abnormal keratinization of the follicular infundibulum; (3) *Cutibacterium acnes* (formerly *Propionibacterium acnes*)–mediated responses; and (4) inflammation.

The initial lesion of acne is a microcomedone, which progresses to a comedone. A comedone is a dilated, epithelium-lined follicular sac filled with lamellated keratinaceous material, lipid, and bacteria. An open comedone, known as a **blackhead**, has a patulous pilosebaceous orifice that permits visualization of the plug. An open comedone becomes inflammatory less commonly than does a closed comedone, or **whitehead**, which has only a pinpoint opening. An inflammatory papule or nodule develops from a comedone that has ruptured and extruded its follicular contents into the subadjacent dermis, inducing a neutrophilic inflammatory response. If the inflammatory reaction is close to the surface, a **papule or pustule** develops. If the inflammatory infiltrate develops deeper in the dermis, a **nodule** forms. Suppuration and an occasional giant cell reaction to keratin and hair are the cause of **nodulocystic** lesions. These are not true cysts but liquefied masses of inflammatory debris.

Comedonal acne (Fig. 710.1), particularly of the forehead and central face, is frequently the first sign of pubertal maturation. Most patients with acne do not have endocrine abnormalities. Many women with acne (25–50%) note acne flares about 1 week before menstruation.

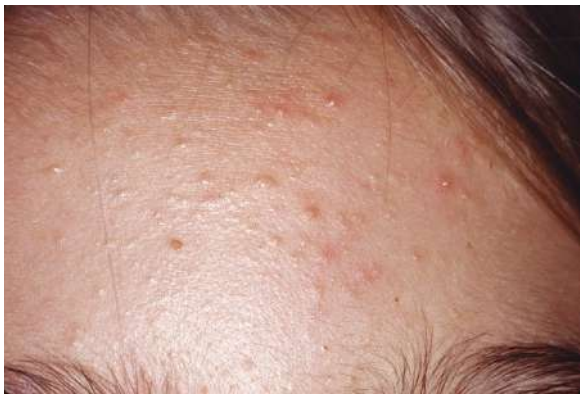


Fig. 710.1 Primarily comedonal acne in a 7-yr-old female.

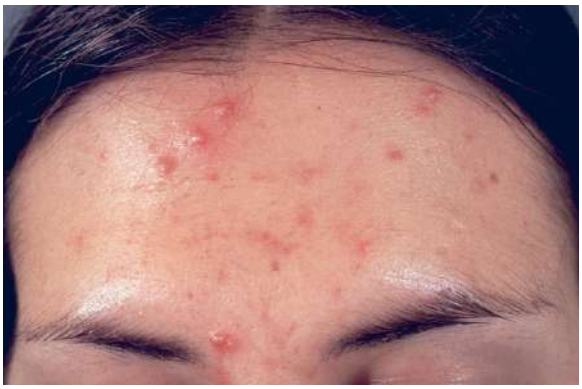


Fig. 710.2 Inflammatory papules and pustules.

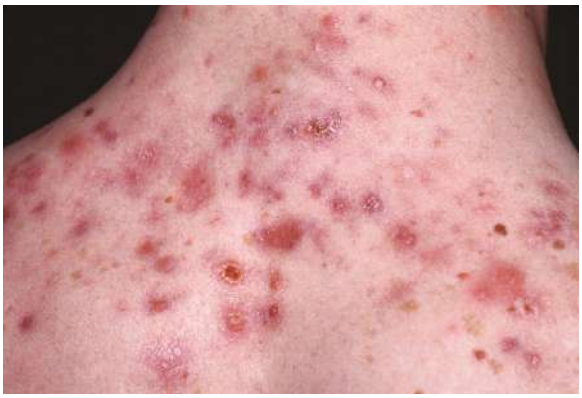


Fig. 710.3 Severe nodulocystic acne.

Clinical Manifestations

Acne vulgaris is characterized by four basic types of lesions: open and closed comedones, papules, pustules (Fig. 710.2), and nodulocystic lesions (Fig. 710.3 and Table 710.1). One or more types of lesions may predominate. In its mildest form, which is often seen early in adolescence, lesions are limited to comedones on the central area of the face. Lesions may also involve the chest, upper back, and deltoid areas. A predominance of lesions on the forehead, particularly closed comedones, is common in early acne but can also be seen with prolonged use of greasy hair preparations (pomade acne) (Fig. 710.4). Marked involvement on the trunk is most often seen in males. Lesions often heal with temporary postinflammatory erythema and hyperpigmentation. Pitted, atrophic, or hypertrophic scars may be interspersed, depending on the severity, depth, and chronicity of the process.

Diagnosis of acne is rarely difficult, although flat warts, folliculitis, and other types of acne (drug-induced or exacerbated: glucocorticoid agents, anabolic steroids, gold, dactinomycin, isoniazid, iodides, bromides, cyclosporin, interferon beta, epidermal growth factor inhibitors, lithium, phenobarbital, phenytoin, progestins/Depo-Provera) may be confused with acne vulgaris. Definable autoinflammatory syndromes and androgen excess disorders are often associated with difficult-to-treat acne or when acne is noted with other cutaneous or systemic symptoms (Fig. 710.5). The differential diagnosis includes sarcoidosis, angiofibromas, keratosis pilaris, chloracne, rosacea, and fibrofolliculomas.

Treatment

An effective treatment strategy targets multiple pathogenic factors. There is no single treatment that addresses all four pathogenic factors other than the systemic retinoid isotretinoin; thus a **combination approach is typically preferred**. Therapy must be individualized based on acne lesion assessment and severity and aimed at preventing comedone formation. Inflammatory acne is frequently underdiagnosed in people of color, as the characteristic erythema may be masked by darker skin pigment. Careful evaluation of acne type is warranted to ensure appropriate treatment is selected.

Initial control requires 10-12 weeks of regular daily use of medications. Acne can be controlled and severe scarring prevented by judicious maintenance therapy that is continued until the disease process has abated spontaneously (Table 710.2 and Fig. 710.6).

It is also important to address the potentially severe emotional impact of acne on adolescents. The pediatrician must be aware of the frequently poor correlation between acne severity and psychosocial impact, particularly in adolescents. As adolescents become preoccupied with their appearance, offering treatment even to the youngster whose acne is mild may enhance self-image.

Table 710.1 One Approach to the Classification of Acne

SEVERITY	DESCRIPTION
Mild	Comedones (noninflammatory lesions) are the main lesions. Papules and pustules may be present but are small and few in number (generally <10).
Moderate	Moderate numbers of papules and pustules (10-40) and comedones (10-40) are present. Mild disease of the back and trunk may also be present.
Moderately severe	Numerous papules and pustules are present (40-100), usually with many comedones (40-100) and occasional larger, deeper nodular inflammatory lesions (up to 5). Widespread affected areas usually involve the face, chest, and back.
Severe	Nodulocystic acne and conglobate acne, including many large inflammatory, painful nodular or pustular lesions along with many smaller papules, pustules, and comedones.

The American Academy of Dermatology acknowledges that there is no universally agreed upon grading/severity classification for acne.
Modified from James WD. Clinical practice: Acne. *N Engl J Med.* 2005;352:1463–1472.

Diet

Little evidence shows that the ingestion of particular foods can trigger acne flares, though high nonfat milk ingestion and high-glycemic-load diets may be contributory. When a patient is convinced that certain

dietary items exacerbate acne, it is prudent for the patient to omit those foods, provided that such omissions do not lead to excessive dietary restrictions.

Climate

Climate appears to influence acne in that improvement frequently occurs in summer and flares are more common in winter. Remission in summer may relate partly to the relative absence of stress. Emotional tension and fatigue seem to exacerbate acne in many individuals; the mechanism is unclear but has been proposed to relate to an increased adrenocortical response.

Cleansing

Cleansing with soap and water removes surface lipid and renders the skin less oily in appearance. It is generally recommended to wash with a gentle cleanser twice daily, followed by moisturizing with a noncomedogenic emollient, for all acne patients. Repetitive cleansing can be harmful because it irritates the skin, and use of harsh scrubs is not recommended. Greasy cosmetic and hair preparations must be discontinued because they exacerbate preexisting acne and cause further plugging of follicular pores. Manipulation and squeezing of facial lesions can lead to scarring and should be avoided.

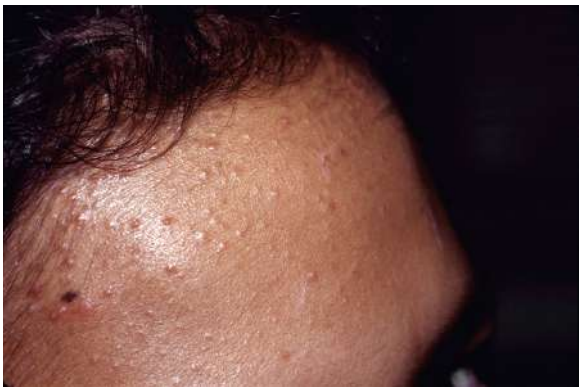


Fig. 710.4 Pomade acne along the hairline.

Topical Therapy

All topical preparations must be used for 10-12 weeks before their effectiveness can be assessed (Table 710.3). Retinoids are first-line therapy and may be used alone for mild acne, but combination therapy is frequently more effective. A popular and effective combination is use of a benzoyl peroxide preparation in the morning and a retinoid at night. Recommendations for specific acne presentations are presented in Tables 710.2 and 710.3.

Retinoids. A topical retinoid should be the primary treatment for acne vulgaris. Topical retinoids have multiple actions, including inhibition of the formation and number of microcomedones, reduction of mature comedones, reduction of inflammatory lesions, and production of normal desquamation of the follicular epithelium. Retinoids should be applied nightly to all affected areas. The main side effects of retinoids are irritation and dryness. Not all patients initially tolerate daily use of a retinoid. It may be prudent to begin therapy every other or every third day and slowly increase the frequency of application as tolerated. Tretinoin, adapalene, tazarotene, and trifarotene (Table 710.4) are the available retinoids. They vary in strength and efficacy, although adapalene tends to be less irritating and tazarotene is more irritating but may be more effective.

Benzoyl Peroxide. Benzoyl peroxide is primarily an antimicrobial agent and does have mild comedolytic activity. It has an advantage over topical antibiotics in that it does not enhance antimicrobial resistance. It is available in multiple formulations and concentrations. The gel formulations are preferred, owing to better stability and more consistent release of the active ingredient. Washes and cleansers are useful for covering large surface areas such as the chest and back. As with retinoids, the main side effects are irritation and drying. Benzoyl peroxide can also bleach clothing, which sometimes limits the use of leave-on preparations like gels.

Topical Antibiotics. Topical antibiotics are indicated for the treatment of inflammatory acne. Clindamycin is the most commonly used. It is not as effective as oral antibiotics. It should never be used as monotherapy because it does not inhibit microcomedone formation and has the potential to induce antimicrobial resistance. Irritation and dryness are generally less than with retinoids or benzoyl peroxide. Topical antibiotics should not be used as monotherapy and can be prescribed as a combination product or separately. The most common combination product is benzoyl peroxide/clindamycin. A combination tretinoin/clindamycin product may also be used.

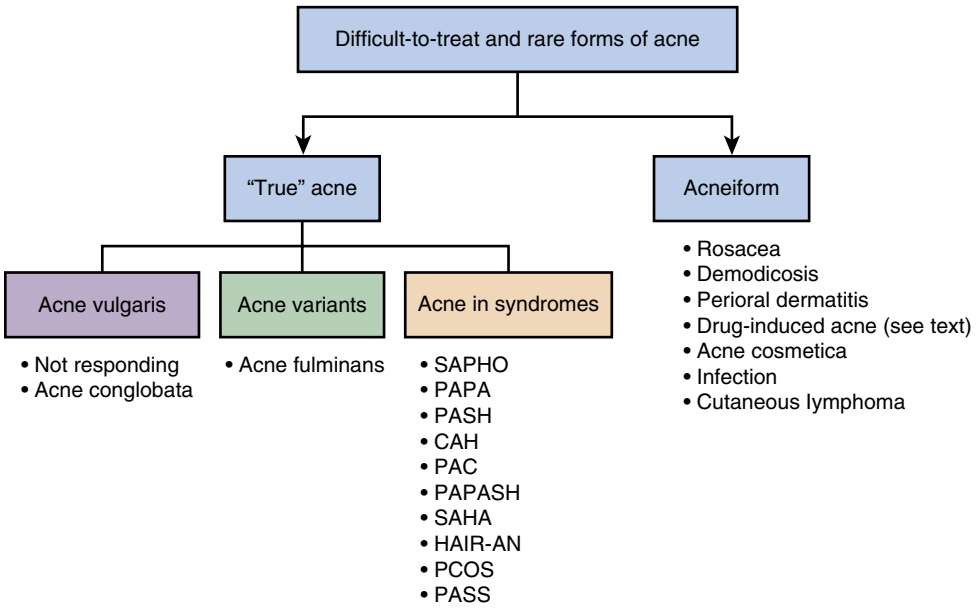


Fig. 710.5 Rare and difficult forms of acne. CAH, Congenital adrenal hyperplasia; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PASH, pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome; PAC, pyoderma gangrenosum, acne, ulcerative colitis; PAPASH, pyogenic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis; SAHA, seborrhea, acne, hirsutism, androgenic alopecia; HAIR-AN, hyperandrogenism, insulin resistance, acanthosis nigricans; PCOS, polycystic ovarian syndrome; PASS, pyoderma gangrenosum acne, spondyloarthritis. *(Modified from Dessinioti C, Katsambas A. Difficult and rare forms of acne. Clin Dermatol. 2017;35[2]:138–146.)*

Table 710.2 Acne Treatment Algorithm

THERAPY	SEVERITY (LESION TYPE)				
	MILD (COMEDONAL)	MILD (INFLAMMATORY/ MIXED)	MODERATE (INFLAMMATORY/ MIXED)	SEVERE (INFLAMMATORY/ MIXED)	SEVERE (NODULAR/ SCARRING)
Initial therapy options*,†	Topical retinoid BP Salicylic acid cleanser	BP/retinoid combo BP/antibiotic combo Antibiotic/retinoid combo + BP	BP/retinoid combo BP/antibiotic combo ± topical retinoid Antibiotic/retinoid combo + BP ± oral antibiotic	BP/retinoid combo + oral antibiotic BP/antibiotic combo + topical retinoid + oral antibiotic Antibiotic/retinoid combo + BP + oral antibiotic	Isotretinoin
Alternative therapy options*,†,‡	Add BP or retinoid if not already prescribed BP/antibiotic combo BP/retinoid combo Antibiotic/retinoid combo	Substitute another combo product Add missing component (e.g., topical retinoid, BP, topical antibiotic) Change type, strength, or formulation of topical retinoid	Substitute another combo product Add missing component (i.e., topical retinoid, BP, topical antibiotic, oral antibiotic) Change type, strength, or formulation of topical retinoid Consider hormonal therapy§ for female patients Consider oral isotretinoin	Consider changing oral antibiotic Consider isotretinoin Consider hormonal therapy§ for female patients	Consider hormonal therapy§ for female patients
Maintenance therapy	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/ retinoid combo

*If combination products not available to patient, consider substitution of individual components as separate prescriptions.
†Topical dapsone may be considered in place of topical antibiotic.
‡If needed as determined by physician assessment and patient satisfaction.
§Combined oral contraceptive or oral spironolactone.
BP, Benzoyl peroxide.
Adapted from Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics* 2006;118(3):1188–1199; Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. *J Am Acad Dermatol.* 2009;60:S1–50; Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131(3):S163–S186; Thiboutot DM, Gollnick HP. Treatment considerations for inflammatory acne: Clinical evidence for adapalene 0.1% in combination therapies. *J Drugs Dermatol.* 2006;5(8):785–794; Gollnick H, Cunliffe W, Berson D, et al. Management of acne: A report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(Suppl 1):S1–S37; and Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74:945–973. From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology,* 6th ed. Philadelphia: Elsevier; 2022, Table 8.1, p. 210.

Azelaic Acid. Azelaic acid (20% cream) has mild antimicrobial and keratolytic properties. It can also help expedite resolution of postinflammatory hyperpigmentation and is less irritating than many other topical acne treatments.

Clascoterone. Clascoterone 1% cream is a topical androgen antagonist, a first in its class, and is approved for use in males and females 12 years and older. It has shown efficacy in improving both inflammatory and noninflammatory acne in trials, but how this medication will be used under real-world circumstances is yet to be determined.

Systemic Therapy

Antibiotics, especially tetracycline and its derivatives (see Table 710.4), are indicated for the treatment of patients whose acne has not responded to topical medications, who have moderate to severe inflammatory papulopustular and nodulocystic acne, and who have a propensity for scarring (Table 710.5). Tetracycline and its derivatives act by reducing the growth and metabolism of *C. acnes*. They also have antiinflammatory properties. For most adolescent patients, therapy may be initiated twice daily, for at least 6-8 weeks, in combination with a judicious topical regimen, and should not be used for longer than 3-6 months. The drugs should always be administered in combination with a topical retinoid and topical benzoyl peroxide but not with topical antibiotics. Doxycycline is the preferred oral antibiotic in acne because of its high efficacy and lower risk of long-term side effects compared with similar medications. Minocycline and doxycycline should be taken with food. Side effects of tetracycline and derivatives are rare and include vaginal candidiasis, particularly in those who take tetracycline concurrently with oral contraceptives; gastrointestinal irritation; phototoxic reactions, including onycholysis and brown discoloration of nails; esophageal ulceration; inhibition of fetal skeletal growth; and staining of growing teeth, precluding its use during pregnancy and in those younger than 8 years of age. Doxycycline is the most photosensitizing of the tetracycline derivatives and is also more likely to cause pill esophagitis. Rarely, minocycline causes dizziness, intracranial hypertension, bluish discoloration of the skin and mucous membranes, hepatitis, a lupus-like syndrome, and drug hypersensitivity. A possible complication of prolonged systemic antibiotic use is proliferation of gram-negative organisms—particularly *Enterobacter, Klebsiella, Escherichia coli,* and *Pseudomonas aeruginosa*—producing severe refractory folliculitis.

Females who have acne and hormonal abnormalities, whose acne is unresponsive to antibiotic therapy, or who are not candidates for isotretinoin therapy should be considered for a trial of hormonal therapy. Combined oral contraceptive pills are the primary form of hormonal therapy. Spironolactone has also shown effectiveness. Young women with acne that is refractory to conventional therapy and have other signs of hyperandrogenism should be evaluated for polycystic ovarian syndrome.

Isotretinoin (13-*cis*-retinoic acid) is indicated for *severe nodulocystic acne and moderate to severe acne that has not responded to conventional*

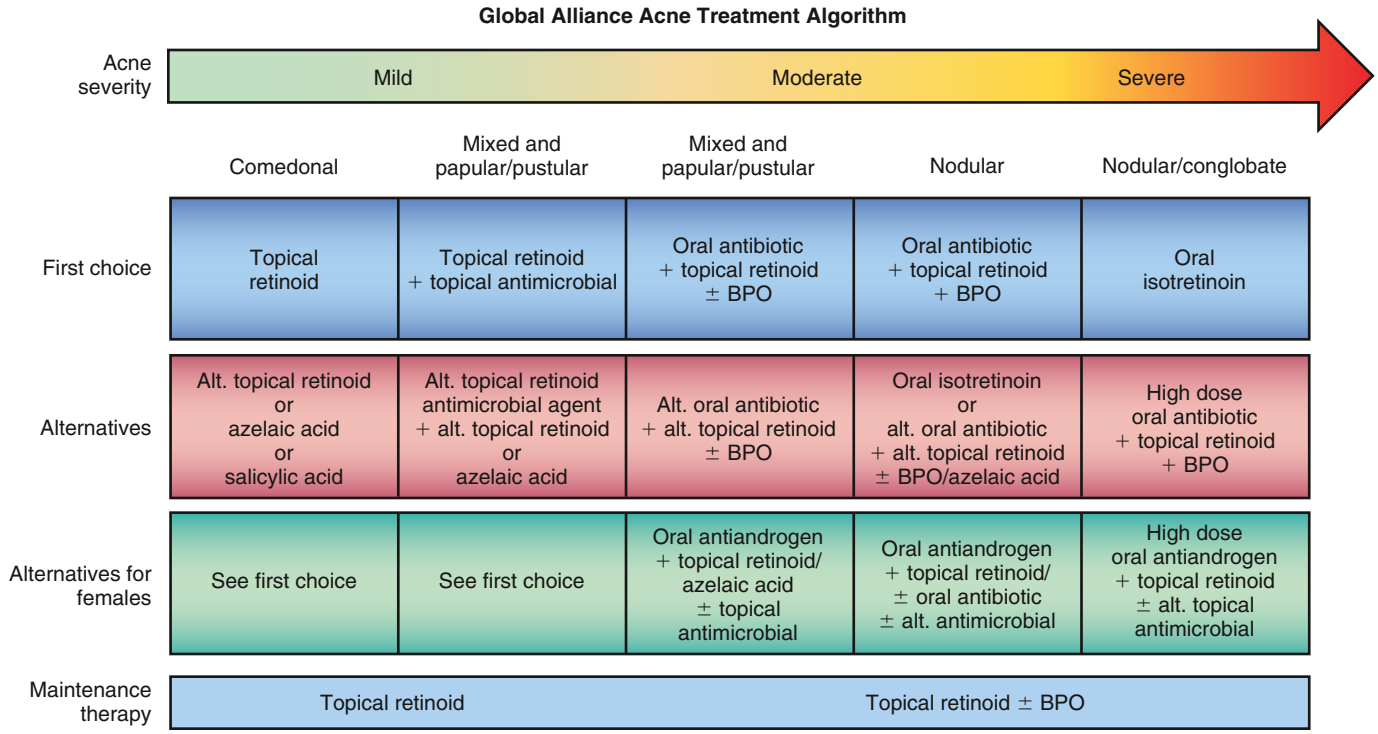


Fig. 710.6 Acne treatment algorithm. BPO, Benzoyl peroxide. *(From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al. New insights into the management of acne: an update from the Global Allegiance to Improve Outcomes in Acne. J Am Acad Dermatol. 2009;60:S1–S50.)*

Table 710.3 Recommendations for Topical Therapies

- Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne.
- Benzoyl peroxide is effective in the prevention of bacterial resistance and is recommended for patients on topical or systemic antibiotic therapy.
- Topical antibiotics (e.g., erythromycin and clindamycin) are effective acne treatments but are not recommended as monotherapy because of the risk of bacterial resistance.
- Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions.
- Treatment with multiple topical agents that affect different aspects of acne pathogenesis can be useful. Combination therapy should be used in the majority of patients with acne.
- Topical adapalene, tretinoin, and benzoyl peroxide can be safely used in the management of preadolescent acne in children.
- Azelaic acid is a useful adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation.
- Topical dapsone 5% gel is recommended for inflammatory acne, particularly in adult females with acne.
- There is limited evidence to support recommendations for sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc in the treatment of acne.

From Zaenglein AL, Pathy AL, Scholsser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945–973, Table V, p. 951.

therapy. The recommended dosage is 0.5-1.0 mg/kg/day. A standard course in the United States lasts 16-20 weeks or until acne is clear. At the end of one course of isotretinoin, 70–80% of patients are cured, 10–20% need conventional topical and/or oral medications to maintain adequate control, and 10–20% have relapses and need an additional course of isotretinoin. Isotretinoin addresses all four pathogenic mechanisms of acne, is highly effective, and only has very rare treatment failures.

Isotretinoin use has many side effects. It is highly **teratogenic** and is **absolutely contraindicated** in pregnancy. Pregnancy should be avoided for 4 weeks after discontinuation of therapy. Two forms of birth control are required, or a confirmation of total abstinence, as are monthly pregnancy tests. *Concerns over cases of pregnancy despite warnings have prompted a manufacturer registration program, iPLEDGE (www.ipledgeprogram.com), which requires physician enrollment and careful patient pregnancy screening to prescribe isotretinoin.* Many patients also experience cheilitis, xerosis, periodic epistaxis, and blepharoconjunctivitis. Increased serum triglyceride and cholesterol levels are also common. It is important to rule out preexisting liver disease and hyperlipidemia before initiating therapy and to recheck laboratory values when the dosage is established. Less common but significant side effects include arthralgias, myalgias, temporary thinning of the hair, paronychia, increased susceptibility to sunburn, formation of pyogenic granulomas, and colonization of the skin with *Staphylococcus aureus,* leading to impetigo, secondarily infected dermatitis, and scalp folliculitis. Rarely, hyperostotic lesions of the spine develop after more than one course of isotretinoin. Concomitant use of an oral tetracycline and isotretinoin is contraindicated because either drug, but particularly when they are used together, can cause benign intracranial hypertension. Although no cause-and-effect relationship has been established, drug-induced mood changes and depression and/or suicide have mandated close attention to psychiatric well-being before and during isotretinoin prescription. An increased risk of inflammatory bowel disease with the use of isotretinoin is debated.

Surgical Therapy

Intralesional injection of low-dose (3-5 mg/mL) midpotency glucocorticoids (e.g., triamcinolone) with a 30-gauge needle on a tuberculin syringe may hasten the healing of individual painful nodulocystic lesions. Dermabrasion or laser peel to minimize scarring should be considered only after the active process is quiescent. Figure 710.7 describes the management of scarring.

The role of pulsed dye laser in the treatment of inflammatory acne is controversial and inconclusive.

Table 710.4 Medications for the Treatment of Acne

DRUG	DOSE	SIDE EFFECTS	OTHER CONSIDERATIONS
TOPICAL AGENTS			
Retinoids			
Tretinoin	Applied once nightly; strengths of 0.025–0.1% available*	Irritation (redness and scaling)	Generics available.
Adapalene	Applied once daily, at night or in the morning; 0.1% and 0.3%*	Minimal irritation	0.1% generic available.
Tazarotene†	Applied once nightly; 0.05% and 0.1%*	Irritation	Limited data suggest tazarotene is more effective than alternatives.
Trifarotene	Applied once nightly; 0.005% cream	Mild irritation	Labeled for trunk use.
Antimicrobials			
Benzoyl peroxide, 2.5–10%	Applied once or twice daily	Benzoyl peroxide can bleach clothing and bedding	Available over the counter; 2.5–5% concentrations as effective as and less drying than 10% concentration.
Clindamycin, erythromycin‡	Applied once or twice daily	Propensity to resistance	Most effective for inflammatory lesions (rather than comedones); resistance a concern when used alone.
Minocycline	Applied once or twice daily; 4% foam	None	Brand name, expensive.
Combination benzoyl peroxide and clindamycin or erythromycin; combination tretinoin and clindamycin	Applied once or twice daily	Side effects from benzoyl peroxide (bleach clothing or bedding) and from topical antibiotics (propensity to resistance)	Combination more effective than topical antibiotics alone; limits development of resistance; use of individual products in combination less expensive and appears similarly effective.
Other Topical Agents			
Azelaic acid‡	Applied twice daily; 20% cream	Well tolerated	Helpful for postinflammatory dyspigmentation; 10% cream available over the counter
Salicylic acid	Applied once or twice daily	Peeling, irritation	Low efficacy
Dapsone	Applied once daily; 5% and 7.5% gel	Mild irritation	Evidence of particular efficacy in skin of color
Clascoterone	Applied twice daily; 1% cream	Mild irritation	Brand name, expensive.
ORAL ANTIBIOTICS§			
Tetracycline#	250-500 mg once or twice daily	Gastrointestinal upset, intracranial hypertension	Inexpensive; dosing limited by need to take on empty stomach.
Doxycycline#	50-100 mg once or twice daily	Phototoxicity, intracranial hypertension, pill esophagitis, gastrointestinal upset	20-mg dose antiinflammatory only; limited data on efficacy.
Minocycline#	50-100 mg once or twice daily	Hyperpigmentation of teeth, oral mucosa, and skin; lupus-like reactions with long-term treatment, intracranial hypertension, drug hypersensitivity	
Sarecycline	Daily for 12 wk based on weight; 60-mg, 100-mg, 150-mg tablets	Intracranial hypertension, lightheadedness, candidiasis, nausea	Newest antimicrobial agent
Trimethoprim-sulfamethoxazole	One dose (160 mg trimethoprim, 800 mg sulfamethoxazole) twice daily	Toxic epidermal necrolysis and allergic eruptions	Trimethoprim may be used alone in a 300-mg dose twice daily; limited data available; not generally recommended.
Erythromycin‡	250-500 mg twice daily	Gastrointestinal upset	Resistance problematic; efficacy is limited.

Table 710.4 Medications for the Treatment of Acne—cont'd

DRUG	DOSE	SIDE EFFECTS	OTHER CONSIDERATIONS
HORMONAL AGENTS[¶]			
Spironolactone[#]	50-200 mg in 1-2 divided doses	Temporary menstrual irregularities and breast tenderness; possible potassium elevations in those with renal or cardiac disease	Higher doses more effective but cause more side effects; best given in combination with oral contraceptives.
Estrogen-containing oral contraceptives	Daily	Potential side effects include thromboembolism	Several approved specifically for acne, but all COCs have efficacy in acne treatment
ORAL RETINOID			
Isotretinoin[**]	0.5-1.0 mg/kg/day in 2 divided doses	Birth defects; adherence to pregnancy prevention program outlined by drug manufacturer, including two initial negative pregnancy tests, is essential; hypertriglyceridemia, elevated results on liver function tests, abnormal night vision, benign intracranial hypertension, dryness of the lips, ocular, nasal, and oral mucosa and skin, secondary staphylococcal infections, arthralgias, and mood disturbances are possible common or important side effects; laboratory testing of lipid profiles and liver function tests when dosage established	Relapse rate higher if patient is younger than age 16 yr at initial treatment, if acne is of high severity and involves the trunk, or if drug is used in adult women

*As cream or gel.
[†]Tazarotene is in pregnancy category X: contraindicated in pregnancy.
[‡]Clindamycin, erythromycin, and azelaic acid are in pregnancy category B: no evidence of risk in humans.
[§]Oral antibiotics are indicated for moderate to severe disease; for the treatment of acne on the chest, back, or shoulders; and in patients with inflammatory disease in whom topical combinations have failed or are not tolerated.
[#]This drug is in pregnancy category D: positive evidence of risk in humans.
[¶]Hormonal agents are for use in women only.
**Isotretinoin is in pregnancy category X: contraindicated in pregnancy. It should be used only in patients with severe acne that does not clear with combined oral and topical therapy.
Modified from James WD. Clinical practice: Acne. *N Engl J Med.* 2005;352:1463–1472.

Table 710.5 Recommendations for Systemic Antibiotics

- Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments.
- Doxycycline and minocycline are more effective than tetracycline.
- Although oral erythromycin or azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (i.e., pregnant women or children <8 years of age). Erythromycin use should be restricted because of its increased risk of bacterial resistance.
- Use of systemic antibiotics other than the tetracyclines and macrolides is discouraged because there are limited data for their use in acne. Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients who are unable to tolerate tetracyclines or to treatment-resistant patients.
- The use of systemic antibiotics should be limited to the shortest possible duration. Reevaluate at 3-4 mo to minimize the development of bacterial resistance. Monotherapy with systemic antibiotics is not recommended.
- Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy.

From Zaenglein AL, Pathy AL, Scholsser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945–973, Table VI, p. 952.

DRUG-INDUCED ACNE

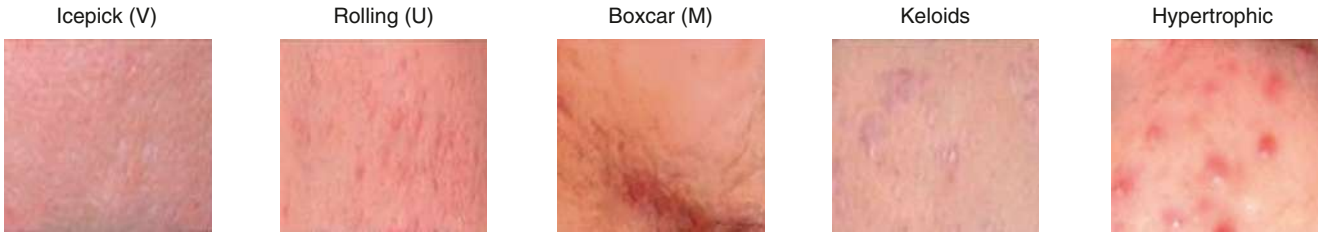
Pubertal and postpubertal patients who are receiving systemic corticosteroid therapy are predisposed to steroid-induced acne. This monomorphous folliculitis occurs primarily on the face, neck, chest (Fig. 710.8), shoulders, upper back, arms, and, rarely, on the scalp. Onset follows the initiation of steroid therapy by approximately 2 weeks. The lesions are small, erythematous papules or pustules that may erupt in profusion and are all in the same stage of development. Comedones may occur subsequently, but nodulocystic lesions and scarring are rare. Pruritus is occasional. Although steroid acne is relatively refractory if the medication is continued, the eruption may respond to the use of tretinoin and a benzoyl peroxide gel.

Other drugs that can induce acneiform lesions in susceptible individuals include isoniazid, phenytoin, phenobarbital, trimethadione, lithium carbonate, androgens (anabolic steroids), and vitamin B_{12}.

Other causes of acne, including halogens and chloracne, are rare and typically obvious with judicious history-taking.

NEONATAL CEPHALIC PUSTULOSIS (FORMERLY NEONATAL ACNE)

Approximately 20% of normal neonates demonstrate pustules and red papules on the face in the first 6 weeks of life. Small inflammatory papules and pustules predominate on the cheeks and forehead (Fig. 710.9); comedones are absent. The cause of neonatal acne is unknown, but it has been theorized that it may be an inflammatory reaction to *Pityrosporum* species rather than true acne. Other theories include placental transfer of maternal androgens, hyperactive neonatal adrenal glands, and a hypersensitive neonatal end-organ response to androgenic hormones. The eruption involutes spontaneously over a few months. Treatment is usually unnecessary. If desired, the lesions can be treated effectively with topical antifungals and/or benzoyl peroxide.



Icepick (V)	Rolling (U)	Boxcar (M)	Keloids	Hypertrophic
Punch excision (deep bases) Elevation and grafting Laser resurfacing/ dermabrasion (many scars close together) Spot TCA peel	**Combined therapy** Micrograft and subcision + ± Filler Resurfacing microdermabrasion Deep-spot TCA peel	**Shallow** ≤3 mm diameter-laser skin resurfacing >3 mm diameter-laser skin resurfacing ± punch elevation **Deep** ≤3 mm diameter-punch excision >3 mm diameter-punch excision or punch elevation Fractional thermolysis (deep or shallow) Dermabrasion CO_2 laser resurfacing	Intralesional corticosteroids Intralesional 5-FU Intralesional bleomycin Compression Imiquimod after intralesional excision Cryotherapy Pulsed-dye laser Excision + electrotherapy	Intralesional steroids Intralesional 5-FU Vascular laser Intralesional bleomycin Compression Imiquimod after intralesional excision
Adjunctive treatment: Topical retinoids 2 wk before and after treatment, sunscreens, moisturizers				
Nonablative lasers for mild disease; ablative and fractional lasers for moderate scarring				

Fig. 710.7 Treatment options for acne scars. CO_2, Carbon dioxide; FU, fluorouracil; TCA, trichloroacetic acid. *(From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al. New insights into the management of acne: an update from the Global Allegiance to Improve Outcomes in Acne. J Am Acad Dermatol. 2009;60:S1–S50.)*

INFANTILE ACNE

Infantile acne usually manifests between 6 weeks and 2 years of age, more commonly in males than in females (Fig. 710.10). Open and closed comedones predominate on the face. Papules and pustules occur frequently, but only occasionally do nodulocystic lesions develop. Pitted scarring is seen in 10–15%. The course may be relatively brief, or the lesions may persist for many months or years, although the eruption generally resolves by 4 years of age. Use of topical benzoyl peroxide gel and topical retinoid, as would be recommended for typical acne, is effective but off-label. Some acne medications are approved down to age 9 years but none for infants. Oral erythromycin is occasionally necessary, and isotretinoin can be used in severe cases. A child with refractory acne or other signs of pubertal development warrants a search for an abnormal source of androgens, such as a virilizing tumor or congenital adrenal hyperplasia.

MID-CHILDHOOD ACNE

Acne that begins between 1 and 7 years of age is not considered normal. Although the neonatal adrenal gland secretes high levels of androgens through the first year of life, it becomes quiescent until adrenarche, which occurs around age 7. Underlying endocrine abnormality should be investigated in those presenting with acne in middle childhood. Precocious puberty, late-onset congenital adrenal hyperplasia, or an androgen-secreting tumor may underlie acne in this age-group. Workup for androgen excess is indicated.

ACNE FULMINANS (ACUTE FEBRILE ULCERATIVE ACNE)

Acne fulminans is characterized by abrupt onset of extensive inflammatory, tender, ulcerative acneiform lesions in typically male teenagers and may be related to recent initiation of isotretinoin. The distinctive feature is the tendency for large nodules to form exudative, necrotic, ulcerated, crusted plaques. Lesions heal with extensive scarring. A preceding history of mild papulopustular or nodular acne is noted in most patients. Constitutional symptoms and signs are common, including fever, debilitation, arthralgias, myalgias, weight loss, and leukocytosis. Blood cultures are sterile. Lesions of erythema nodosum sometimes develop on the shins. Osteolytic bone lesions may develop in the clavicle, sternum, and epiphyseal growth plates; affected bones appear normal or have slight sclerosis or thickening on healing. Salicylates may be helpful for the myalgias, arthralgias, and fever. Treatment should be directed by a dermatologist and includes systemic corticosteroids and isotretinoin. Antibiotics are not indicated unless there is evidence of secondary infection.

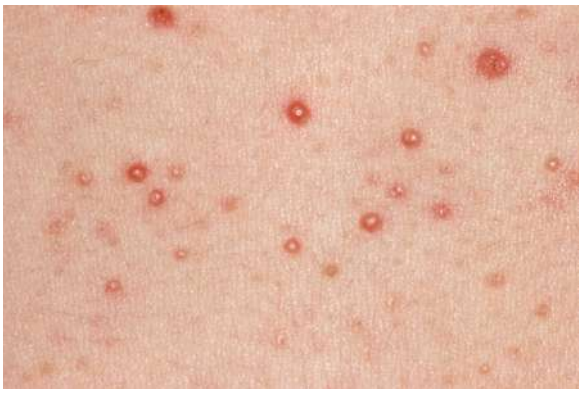


Fig. 710.8 Monomorphous papular eruption of steroid acne.

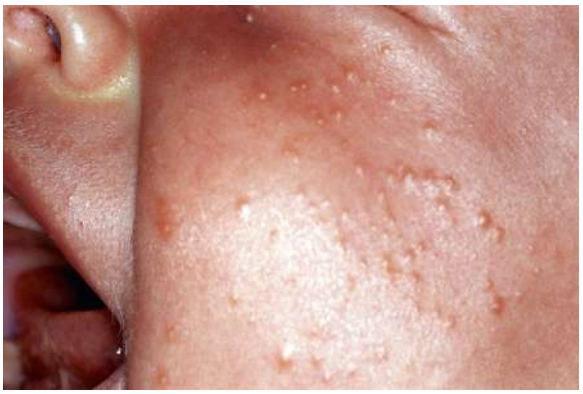


Fig. 710.9 Comedonal acne in a neonate.

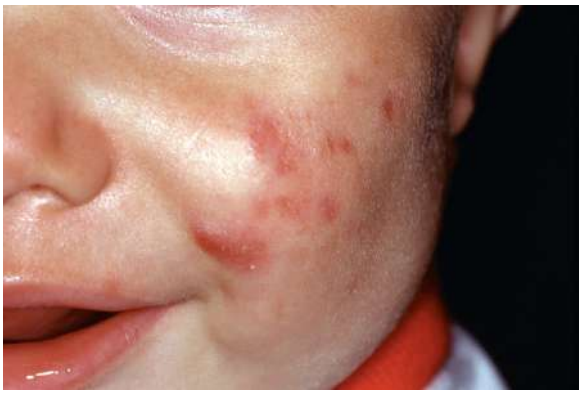


Fig. 710.10 Inflammatory infantile acne.

Pyogenic Arthritis with Pyoderma Gangrenosum and Acne (PAPA Syndrome) (see Fig. 710.5, Chapter 204, and Chapter 702).

Chronic Recurrent Multifocal Osteomyelitis/Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome (see Chapter 204).

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Chapter 711

Tumors of the Skin

Kari L. Martin

See also Chapter 636.

INFUNDIBULAR FOLLICULAR CYST

Infundibular follicular cysts (more commonly referred to as *epidermoid cysts* or *sebaceous cysts*) are the nodules most commonly seen in children. Such a cyst is a sharply circumscribed, dome-shaped, firm, freely movable, skin-colored nodule (Fig. 711.1), often with a central dimple or punctum that is a plugged, dilated pore of a pilosebaceous follicle. Follicular cysts form most frequently on the face, neck, chest, or upper back and may periodically become inflamed and infected secondarily, particularly in association with acne vulgaris. The cyst wall may also rupture and induce an inflammatory reaction in the dermis. The wall of the cyst is derived from the follicular infundibulum. A mass of layered keratinized material that may have a cheesy consistency fills the cavity. Cysts may arise from occlusion of pilosebaceous follicles (acneiform cysts), implantation of epidermal cells into the dermis as a result of an injury that penetrates the epidermis (epidermal inclusion cysts), and rests of epidermal cells (epidermoid cysts). Multiple epidermoid cysts may be present in Gardner syndrome and nevoid basal cell carcinoma syndrome. Excision of the cyst with removal of the entire sac and its contents is indicated, particularly if the cyst becomes recurrently inflamed. A fluctuant cyst should be incised and drained and, if there is surrounding erythema, treated with antibiotics or intralesional corticosteroids. After the inflammation subsides, the cyst may be removed.

MILIUM

A milium is a 1- to 2-mm, firm, pearly white or yellowish subepidermal keratin cyst. Milia in newborns are discussed in Chapter 688. Secondary milia occur in association with subepidermal blistering diseases and after dermabrasion or other injury to the skin. They are retention cysts caused by hyperproliferation of injured epithelium and are indistinguishable histopathologically from primary milia. Those that develop after blistering usually arise from the eccrine sweat duct, but they may develop from the hair follicle, sebaceous duct, or epidermis. A milium body differs from an infundibular follicular cyst only in its small size and superficial location.

FIBROFOLLICULOMAS

These lesions usually appear in late adolescence or in young adults and are characterized by multiple dome-shaped, clear-white papules appearing on the nose, cheeks, and neck, and at times the trunk or ears (Fig. 711.2). They are associated with the familial cancer syndrome of **Birt-Hogg-Dubé**, an autosomal dominant disorder that results from a pathogenic variant in the folliculin *(FLCN)* tumor suppressor gene. Associated features include pulmonary cysts, pneumothorax, renal cell carcinoma, and other benign or malignant tumors.

PILAR CYST (TRICHILEMMAL CYST)

A pilar cyst may be clinically indistinguishable from an infundibular follicular cyst. It manifests as a smooth, firm, mobile nodule, predominantly on the scalp (Fig. 711.3). Pilar cysts occasionally develop on the face, neck, or trunk. A cyst may become inflamed and may occasionally suppurate and ulcerate. The cyst wall is composed of stratified squamous epithelium with indistinct intercellular bridges. The peripheral cell layer of the wall shows a palisade arrangement, which is not seen in an epidermoid cyst. No granular layer is present. The cyst cavity contains dense homogeneous eosinophilic keratinous material, and foci of calcification are seen in 25% of cases. The propensity for development of pilar cysts may be inherited in an autosomal dominant manner. More than one cyst generally develops in a patient. Numerous pilar and epidermoid cysts, desmoid tumors, fibromas, lipomas, or osteomas may be associated with colonic polyposis or adenocarcinoma in Gardner syndrome. Pilar cysts shell out easily from the dermis.

PILOMATRICOMA (PILOMATRIXOMA)

The second most common nodule seen in children, pilomatricoma is a benign tumor that manifests as a 3- to 30-mm, firm, solitary, deep dermal or subcutaneous tumor on the head, neck, or upper extremities. The overlying epidermis is usually normal. The tumor may occasionally be located more superficially, however, tinting the overlying skin blue-red (Fig. 711.4). Multiple pilomatricomas are seen in myotonic dystrophy, Gardner syndrome, Rubinstein-Taybi syndrome, and Turner syndrome. In general, however, pilomatricomas are not hereditary. Histopathologically, irregularly shaped islands of epithelial cells with eosinophilic, anucleate "ghost cells" are embedded in a cellular stroma. Calcium deposits are found in 75% of tumors. Pilomatricomas are caused by pathogenic variants in β-catenin.

TRICHOEPITHELIOMA

A 2- to 8-mm, smooth, round, firm, skin-colored papule, trichoepithelioma is derived from an immature hair follicle.

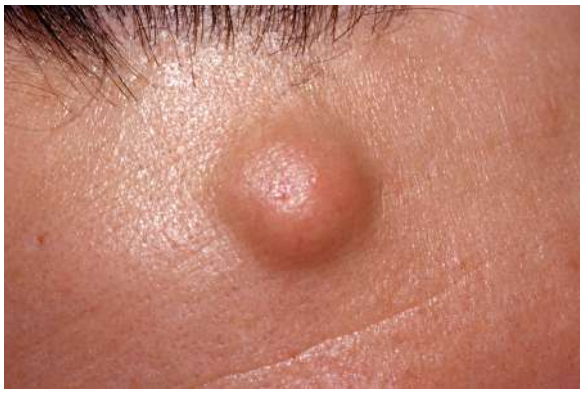


Fig. 711.1 Flesh-colored cyst on the forehead.

Fig. 711.2 Multiple dome-shaped, whitish papules on the nose and cheeks in a 31-yr-old carrier of an *FLCN* pathogenic variant. *(From Menko FH, van Steensel MAM, Giraud S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet. 2009;10:1199–1206, Fig. 1.)*

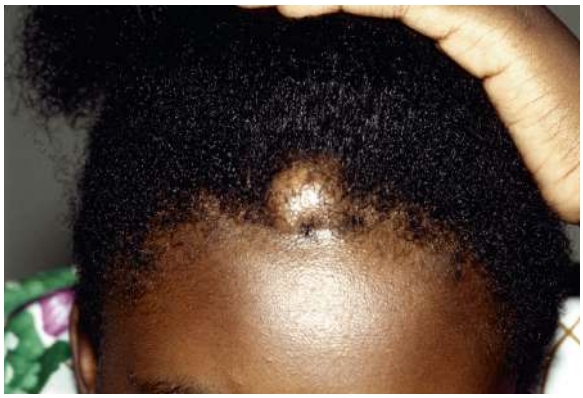


Fig. 711.3 Pilar cyst of the anterior scalp.

Trichoepitheliomas generally occur singly on the face in childhood or early adulthood. Multiple trichoepitheliomas are inherited autosomal dominantly (type 1: *CYLD* gene; type 2: 9p21 gene currently unidentified), appear in childhood or at puberty, and gradually increase in number on the nasofacial folds, nose, forehead, and upper lip; occasionally they occur on the scalp, neck, and upper trunk. Microscopically, these benign tumors are characterized by horn cysts composed of a fully keratinized center surrounded by basophilic cells in an adenoid network. Topical imiquimod therapy may be beneficial. Surgical excision has been used for therapy, as have cryotherapy, electrosurgery, and laser vaporization.

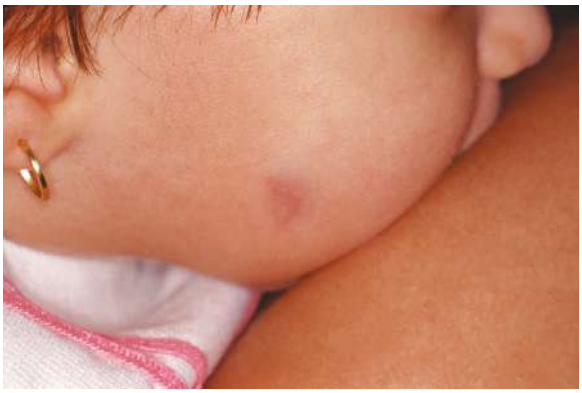


Fig. 711.4 Pilomatricoma. Firm tumor with overlying bluish discoloration of the skin.

ERUPTIVE VELLUS HAIR CYSTS

Eruptive vellus hair cysts are 1- to 3-mm, asymptomatic, soft, skin-colored follicular papules on the central chest (Fig. 711.5). They may become crusted or umbilicated. Abnormal vellus hair follicles become occluded at the level of the infundibulum, resulting in retention of hairs within an epithelium-lined cystic dilation of the proximal part of the follicle. Most cases are chronic, but spontaneous regression has been reported.

STEATOCYSTOMA MULTIPLEX

An autosomal dominant (*KRT17* gene) condition, steatocystoma multiplex usually manifests in adolescence or early adulthood as numerous soft to firm cystic nodules that are adherent to the underlying skin and are 3 mm to 3 cm in diameter. When punctured, the cysts may drain oily or cheesy material. Sites of predilection include the sternal region, axillae, arms, and scrotal skin. The multiply folded cyst wall is lined on the luminal side with a thick, homogeneous, eosinophilic horny layer; there is no granular layer. Flattened sebaceous gland lobules are often visible in the cyst wall, and lanugo hairs may be present in a cystic cavity that appears otherwise empty (a processing artifact).

SYRINGOMA

The benign tumors known as syringomas are soft, small, skin-colored or yellowish-brown papules that develop on the face, particularly in the periorbital regions (Fig. 711.6). Other sites of predilection include the axillae and umbilical and pubic areas. They often develop during puberty and are more frequent in females. Eruptive syringomas develop in crops over the anterior trunk during childhood or adolescence. A syringoma is derived from an intraepidermal sweat gland duct. Syringomas are of cosmetic significance only. Sparse lesions may be excised, but they are often too numerous to remove.

INFANTILE DIGITAL FIBROMA

Infantile digital fibroma is a smooth, firm, erythematous or skin-colored nodule on the dorsal or lateral surface of a distal phalanx of a finger or toe. More than 80% of tumors occur in infancy or may be present at birth. Lesions may be solitary or multiple and may manifest as "kissing" tumors on opposing digits. They are usually asymptomatic, but flexion deformity of the digits may occur. Clinically the lesion resembles a fibroma, leiomyoma, angiofibroma, acquired digital fibrokeratoma, accessory digit, or mucous cyst. The diagnosis is confirmed by the finding of numerous spindle-shaped fibroblasts that contain small, round, dense eosinophilic cytoplasmic inclusion bodies composed of collections of actin microfilaments. Local recurrence after simple excision of this tumor has been reported in 75% of patients. Because the tumor does not metastasize and may regress spontaneously in 2-3 years, a course of expectant observation is advised. If functional impairment or flexion deformity of the digit becomes apparent, prompt full excision of the tumor is indicated.

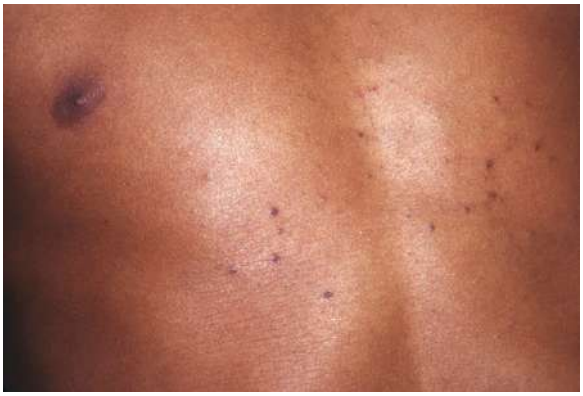


Fig. 711.5 Eruptive vellus hair cysts. Multiple papules on the chest.

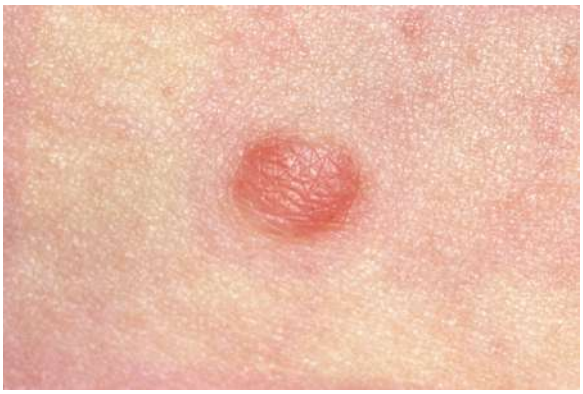


Fig. 711.7 Dermatofibroma. Red-brown nodular variant.

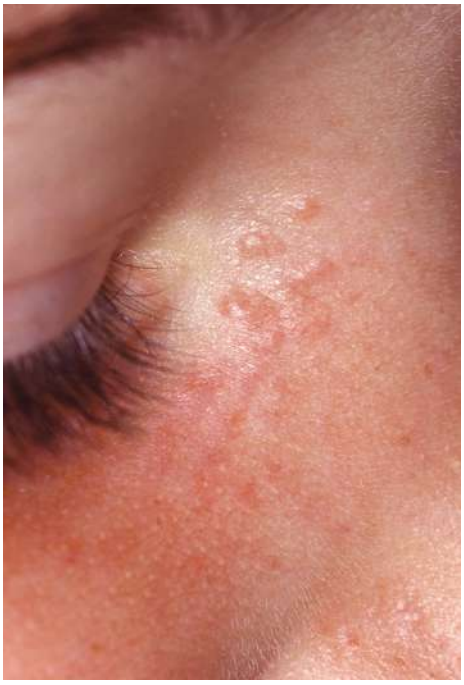
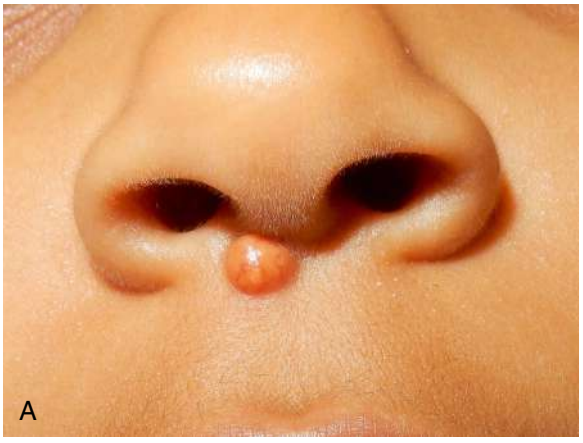


Fig. 711.6 Syringomas. Multiple yellow papules near the eye.



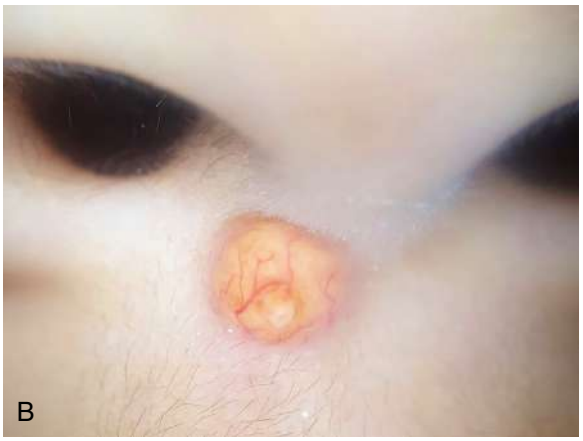


Fig. 711.8 A, Juvenile xanthogranuloma. A 4-mm, apricot-colored, dome-shaped, firm papule with overlying telangiectasias below the nasal columella. B, Pink-red rim in a "setting-sun" pattern seen by dermoscopy. *(From Bell KA, Marathe K, Burke KT, Cardis MA. A persistent pimple in a 5-year-old girl. J Pediatr. 2020;224:172–173, Figs. 1 and 2, p. 172).*

DERMATOFIBROMA

A benign dermal tumor, dermatofibroma may be pedunculated, nodular (Fig. 711.7), or flat and is usually well circumscribed and firm but occasionally feels soft on palpation. The overlying skin is usually hyperpigmented; it may be shiny or keratotic and dimples when the tumor is pinched. Dermatofibromas range in size from 0.5 to 10.0 mm, arise most frequently on the limbs, and are usually asymptomatic but may occasionally be pruritic. They are composed of fibroblasts, young and mature collagen, capillaries, and histiocytes in varying proportions, forming a nodule in the dermis that has poorly defined edges. The cause of these tumors is unknown, but trauma such as an insect bite or folliculitis appears to induce reactive fibroplasia. The differential diagnosis includes epidermal inclusion cyst, juvenile xanthogranuloma, hypertrophic scar, and neurofibroma. Dermatofibromas may be excised or left intact, according to the patient's preference. They usually persist indefinitely.

JUVENILE XANTHOGRANULOMA

A firm, dome-shaped, yellow, pink, or orange papule or nodule (Fig. 711.8), juvenile xanthogranuloma varies from 5 mm to approximately 4 cm in diameter. The average age at onset is 2 years. These nodules are 10 times more common in White than in Black individuals. Sites of predilection are the scalp, face, and upper trunk, where they may erupt in profusion or remain as solitary lesions. Nodular lesions may appear on the oral mucosa. The diagnosis is usually made clinically. Mature lesions are characterized histopathologically by a dermal infiltrate of lipid-laden histiocytes, admixed inflammatory cells, and Touton giant cells. Clinically the lesions may resemble papulonodular urticaria pigmentosa, dermatofibromas, or xanthomas of hyperlipoproteinemia, but they can be distinguished from these entities histopathologically.

Affected infants are nearly always otherwise normal, and blood lipid values are not elevated. Café-au-lait macules are found on 20% of

patients with juvenile xanthogranuloma. Xanthogranulomatous infiltrates occur occasionally in the iris or other ocular tissues. This process may result in glaucoma, hyphema, uveitis, heterochromia iridis, iritis, or sudden proptosis. When seen in patients <2 years of age, multiple lesions and periocular location may heighten concerns for intraocular involvement. There appears to be an association among juvenile xanthogranuloma, neurofibromatosis, and childhood leukemia, most frequently juvenile chronic myelogenous leukemia. There is no need to remove the benign lesions of juvenile xanthogranuloma because most of them regress spontaneously in the first few years. Residual dyspigmentation and atrophy may result.

LIPOMA

A benign collection of fatty tissue, lipoma appears on the trunk, neck, or proximal portions of the limbs. Lipomas are soft, compressible, lobulated subcutaneous masses. Multiple lesions may occur occasionally, as in Gardner syndrome. Atrophy, calcification, liquefaction, or xanthomatous change may sometimes complicate their course. A lipoma is composed of normal fat cells surrounded by a thin connective tissue capsule. Lipomas represent a cosmetic defect and may be surgically excised. Multiple lipomas, identical to those that occur singly, are inherited in an autosomal dominant fashion and often appear by the third decade in patients with familial multiple lipomatosis. Lipomas may appear intraabdominally, intramuscularly, and subcutaneously. Congenital lipomatosis manifests in the first few months of life as large subcutaneous fatty masses on the chest with extension into skeletal muscle. Congenital lipomatosis can also be a manifestation of **Proteus syndrome** (overgrowth/hyperplasia skin, connective tissue, pathogenic variant in *AKT1*). Angiolipomas usually manifest as numerous painful subcutaneous nodules on the arms and trunk.

CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies) is usually a sporadic disorder caused by a pathogenic variant in the ***PIK3CA*** gene with an asymmetric truncal lipomatous mass present at birth. Additional features include macrodactyly, vascular malformations (low flow), linear epidermal nevus, and renal anomalies. The differential diagnosis includes Proteus, Klippel-Trenaunay, and Bannayan-Riley-Ruvalcaba syndromes.

PIK3CA somatic pathogenic variants and those in the related AKT-mTOR pathway (*PIK3CA*-related overgrowth spectrum [PROS]) are associated with segmental overgrowth syndromes (Fig. 711.9; see also Fig. 691.6). In addition to regional/localized tissue overgrowth, there is a spectrum of malformations (hemimegaloencephaly, macrodactyly, lymphatic, muscle hemihypertrophy, epidermal nevi, capillary, polydactyly, syndactyly).

BASAL CELL CARCINOMA

Basal cell carcinoma is very rare in children in the absence of a predisposing condition, such as nevoid basal cell carcinoma syndrome, xeroderma pigmentosum, nevus sebaceus of Jadassohn, arsenic intake, or exposure to irradiation. The lesions are smooth, pearly, pink telangiectatic papules that enlarge slowly and may bleed or ulcerate. Sites of predilection are the face, scalp, and upper back. The differential diagnosis includes pyogenic granuloma, nevocellular nevus, epidermal inclusion cyst, closed comedo, dermatofibroma, and adnexal tumor. Depending on the site of occurrence and associated disease of the host, electrodesiccation and curettage or simple excision of basal cell carcinoma is usually curative. When the tumor is recurrent, >2 cm in diameter, located on problematic anatomic areas such as the midface or ears, or is an aggressive histopathologic type, Mohs microscopically controlled surgery may be the most appropriate treatment.

NEVOID BASAL CELL CARCINOMA SYNDROME (BASAL CELL NEVUS SYNDROME, GORLIN SYNDROME)

The autosomal dominant entity known as nevoid basal cell carcinoma syndrome is caused by pathogenic variants in the *PTCH1*, *PTCH2* ("patched"), and *SUFU* genes. These tumor-suppressor genes, part of the hedgehog signaling pathway, are important in determining embryonic patterning and cell fate in a number of structures in the developing embryo. Pathogenic variants in these genes produce dysregulation of several genes involved in organogenesis and

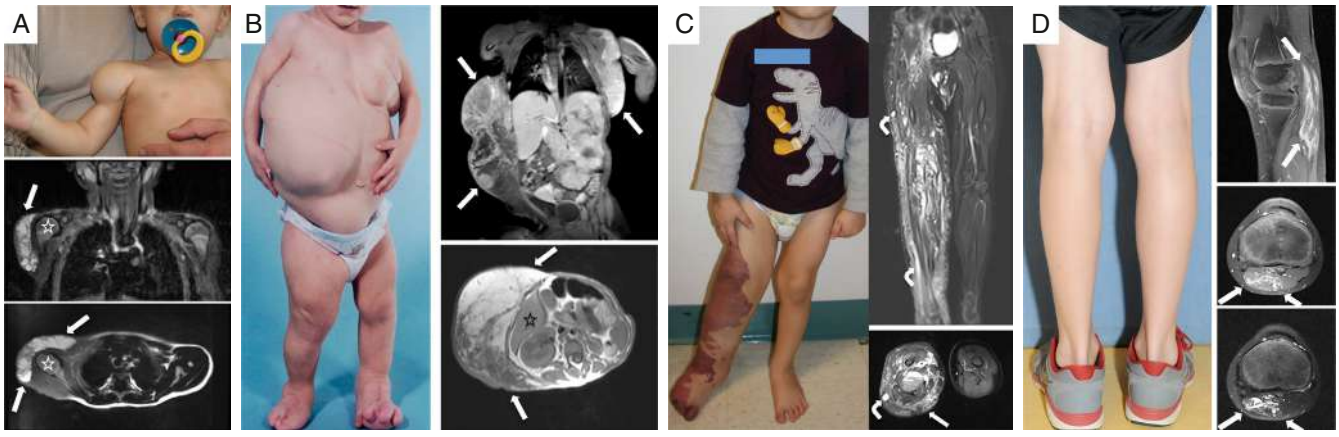


Fig. 711.9 Photographs and MRIs of participants with isolated LM, CLOVES, KTS, and FAVA. **A,** An 8-mo-old boy (LM1) with isolated LM. Note swelling in deltoid region without cutaneous vascular signs. Coronal and sagittal fat-saturated T2-weighted MRI demonstrates macrocystic LM (a multilocular cystic mass) involving the anterolateral aspects of the right shoulder without muscular infiltration *(arrows)*; humeral head *(asterisk)*. **B,** A 19-mo-old female (CL12) with CLOVES syndrome. Note asymmetric distribution of truncal lipomatous masses and bilateral lower extremity involvement. Coronal fat-saturated T1-weighted MRI after contrast administration demonstrates moderate heterogeneous enhancement of the bilateral truncal masses *(arrows)*. Axial T1-weighted MRI without contrast depicts truncal lipomatous overgrowth *(arrows)*; segment VI of the liver *(asterisk)*. **C,** A 3-yr-old boy (KT4) with KTS. Note capillary LM and overgrowth involving the right lower extremity. Coronal and axial fat-saturated T2-weighted MRI shows the persistent marginal vein system *(bent arrows)* and marked enlargement of the subcutaneous tissues due to a combination of lymphatic fluid and fat *(straight arrow)*. There are also intramuscular venous malformations. **D,** A 9-yr-old boy (F8) with FAVA of the left gastrocnemius muscle; note absence of overgrowth and cutaneous vascular anomalies. Sagittal fat-saturated T1-weighted MRI after contrast administration demonstrates the longitudinal distribution of the diffuse FAVA *(arrows)*. Axial fat-saturated T2-weighted MRI with *(upper)* and without *(lower)* contrast. Note that the right head of the gastrocnemius muscle is diffusely replaced by a contrast-enhancing heterogeneous soft tissue lesion *(arrows)*. CLOVES, Congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies; FAVA, fibroadipose vascular anomaly; KTS, Klippel-Trenaunay syndrome; LM, lymphatic malformation. *(From Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic pathogenic variants in PIK3CA. J Pediatr. 2015;166:1048–1054, Fig. 1, p. 1051.)*

carcinogenesis. Consequently, the syndrome includes a wide spectrum of defects involving the skin, eyes, central nervous and endocrine systems, and bones. The predominant features are early-onset basal cell carcinomas and mandibular cysts. Approximately 20% of those in whom a basal cell carcinoma develops before age 19 years have this syndrome. Basal cell carcinomas appear between puberty and age 35 years, erupting in crops of tumors that vary in size, color, and number; they may be difficult to distinguish from other types of skin lesions. Sites of predilection are the periorbital skin, nose, malar areas, and upper lip, but the lesions can also develop on the trunk and limbs and are not restricted to sun-exposed areas. Ulceration, bleeding, crusting, and local invasion can occur. Small milia, epidermal cysts, pigmented lesions, hirsutism, and palmar and plantar pits are additional cutaneous findings.

The facies of patients with this syndrome are characterized by temporoparietal bossing, prominent supraorbital ridges, a broad nasal root, ocular hypertelorism or dystopia canthorum, and prognathism. Keratinized cysts (odontogenic keratocysts) in the maxilla and mandible occur in most patients. These cysts range in size from a few millimeters to several centimeters; may result in maldevelopment of the teeth; and cause pain, swelling of the jaw, facial deformity, bone erosion, pathologic fractures, and suppurating sinus tracts. Osseous defects such as anomalous rib development, spina bifida, kyphoscoliosis, and brachymetacarpalism occur in 60% of patients, and ocular abnormalities—including cataracts, glaucoma, coloboma, strabismus, and blindness—occur in approximately 25%. Some males have hypogonadism, and the testes are absent or undescended. Kidney malformations have also been reported. Neurologic manifestations include calcification of the falx, seizures, mental retardation, partial agenesis of the corpus callosum, hydrocephalus, and nerve deafness. The incidence of medulloblastoma, ameloblastoma of the oral cavity, fibrosarcoma of the jaw, teratoma, cystadenoma, cardiac fibroma, ovarian fibroma, and fetal-onset rhabdomyoma is higher in patients with nevoid basal cell carcinoma syndrome.

Treatment of these patients requires the participation of various specialists according to individual clinical problems. Basal cell carcinomas should not be treated with irradiation. Most of the basal cell carcinomas have a clinically benign course, and it is often impossible to remove them all. Those with an aggressive growth pattern and those on the central areas of the face, however, should be removed promptly. Treatment options include surgery, Mohs micrographic surgery, laser ablation, cryotherapy, photodynamic therapy, topical 5% imiquimod and oral retinoids (0.5-1.0 mg/kg/day). Vismodegib, which inhibits smoothened protein in the hedgehog pathway, is a targeted therapy available for unresectable basal cell carcinomas. Genetic counseling is also indicated.

MELANOMA

See Chapter 692.

MUCOSAL NEUROMA SYNDROME (MULTIPLE ENDOCRINE NEOPLASIA TYPE IIB)

Mucosal neuroma syndrome, an autosomal dominant trait, is characterized by an asthenic or marfanoid habitus with scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The syndrome is caused by pathogenic variants in the tyrosine kinase domain of the *RET* gene. Patients have thick, patulous lips and soft tissue prognathism simulating acromegaly. Multiple mucosal neuromas or neurofibromas appear as pink, pedunculated, or sessile nodules on the anterior third of the tongue, at the commissures of the lips, and on the buccal mucosa and palpebral conjunctiva. Various ophthalmologic defects and intestinal ganglioneuromatosis with recurrent diarrhea are additional common findings. There is a high incidence of medullary thyroid carcinoma in association with high calcitonin levels, pheochromocytoma, and hyperparathyroidism in patients with this syndrome. Periodic screening tests for the associated malignant tumors are mandatory.

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Chapter 712 Nutritional Dermatoses

Joel C. Joyce

OVERVIEW

There are many cutaneous manifestations of nutritional deficiencies (Table 712.1). For more details see Chapters 64-72.

ACRODERMATITIS ENTEROPATHICA

Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by an inability to absorb sufficient zinc from the diet. The genetic variant is in the intestinal zinc-specific transporter gene *SLC39A4*. Initial signs and symptoms usually occur in the first few months of life, often after weaning from breast milk to cow's milk. The cutaneous eruption consists of vesiculobullous, eczematous, dry, scaly, or psoriasiform skin lesions symmetrically distributed in the perioral, acral, and perineal areas (Fig. 712.1) and on the cheeks, knees, and elbows (Fig. 712.2). The hair often has a peculiar, reddish tint, and alopecia of some degree is characteristic. Ocular manifestations include photophobia, conjunctivitis, blepharitis, and corneal dystrophy detectable by slit-lamp examination. Associated manifestations include chronic diarrhea, stomatitis, glossitis, paronychia, nail dystrophy, growth retardation, irritability, delayed wound healing, intercurrent bacterial infections, and superinfection with *Candida albicans*. Lymphocyte function and free radical scavenging are impaired. Without treatment the course is chronic and intermittent but often relentlessly progressive. When the disease is less severe, only growth retardation and delayed development may be apparent.

The diagnosis is established by the constellation of clinical findings and detection of a low plasma zinc concentration. A serum zinc level less than 50 μg/dL is suggestive, but not diagnostic, of **acrodermatitis enteropathica**. Levels of alkaline phosphatase, a zinc-dependent enzyme, may also be decreased. Histopathologic changes in the skin are nonspecific and include parakeratosis and pallor of the upper epidermis. The variety of manifestations of the syndrome may stem from the fact that zinc has a role in numerous metabolic pathways—including those of copper, protein, essential fatty acids, and prostaglandins—and that zinc is incorporated into many zinc metalloenzymes. Other nutritional deficiencies may produce similar findings (see Table 712.1), although the classic findings are highly suggestive of acrodermatitis enteropathica.

Oral therapy with zinc compounds is the treatment of choice. Replacement for individuals with inherited acrodermatitis enteropathica is with elemental zinc 3 mg/kg/24 hr in the form of zinc sulfate, gluconate, or acetate (i.e., 220 mg of zinc sulfate contains 50 mg of elemental zinc). Zinc gluconate carries less risk of gastrointestinal distress. However, plasma zinc levels should be monitored every 3-6 months so as to individualize the dosage. Zinc therapy rapidly abolishes the manifestations of the disease. Supplementation is for life. A syndrome resembling acrodermatitis enteropathica has been observed in patients with secondary zinc deficiency resulting from long-term total parenteral nutrition without supplemental zinc or to chronic malabsorption syndromes. A rash similar to acrodermatitis enteropathica has also been reported in infants fed breast milk that is low in zinc and in those with maple syrup urine disease, organic aciduria, methylmalonic acidemia, biotinidase deficiency, essential fatty acid deficiency, severe protein malnutrition (kwashiorkor), and cystic fibrosis. Cutaneous manifestations tend to appear in more severe forms. For those individuals with acquired zinc deficiency, oral replacement with elemental zinc, 0.5-1.0 mg/kg/24 hr, should be undertaken and the cause of underlying malnutrition should be addressed.

Table 712.1 Distinctive Skin Changes of Nutritional Disorders and Selected Differential Diagnosis

SKIN CHANGE	NUTRITIONAL DISORDER	SELECTED DIFFERENTIAL DIAGNOSIS
Exfoliative erythroderma	Kwashiorkor	Atopic dermatitis, psoriasis, staphylococcal scalded skin syndrome
Phrynoderma	Vitamin A deficiency, vitamin B–complex deficiencies, vitamin C deficiency, essential fatty acid deficiency	Keratosis pilaris, pityriasis rubra pilaris
Petechiae, purpura	Vitamin K deficiency, vitamin C deficiency (perifollicular petechiae)	Consumptive coagulopathy, coagulation disorder, thrombocytopenia, vascular fragility syndrome (Ehlers-Danlos), cutaneous vasculitis (e.g., Henoch-Schoenlein purpura)
Yellow-orange discoloration	Carotenemia	Jaundice, quinacrine-induced
Hyperpigmentation	Vitamin B12 deficiency, folate deficiency	Addison disease
Photodistributed dermatitis	Vitamin B3 deficiency (pellagra), vitamin B6 deficiency	Connective tissue disease (systemic lupus erythematosus, dermatomyositis), polymorphous light eruption
Seborrheic dermatitis–like changes	Vitamin B–complex deficiencies	Seborrheic dermatitis, psoriasis
Angular stomatitis	Vitamin B–complex deficiencies, iron deficiency	Angular cheilitis with candidal overgrowth
Glossitis	Vitamin B–complex deficiencies, zinc deficiency, iron deficiency	Sjogren syndrome, oral lichen planus, syphilis
Diaper dermatitis	Zinc deficiency, vitamin B–complex deficiencies	Irritant or allergic contact dermatitis, seborrheic dermatitis, inverse psoriasis, Langerhans cell histiocytosis
Lightening of hair	Kwashiorkor, marasmus, vitamin B–complex deficiencies, copper deficiency	Poliosis, vitiligo
Corkscrew hairs	Vitamin C deficiency	
Nail changes	Koilonychia: iron deficiency Longitudinal hyperpigmented streaks: vitamin B3 deficiency (pellagra)	Koilonychia: chronic irritant, lichen planus, psoriasis, Plummer–Vinson syndrome, transient in young children Longitudinal hyperpigmented streaks: physiologic, drug-induced, trauma

From Wong CY, Chu DH. Cutaneous signs of nutritional disorders. *Inter J Women Dermatol*. 2021;7:647–652: Table 1, p. 649.

ESSENTIAL FATTY ACID DEFICIENCY

Essential fatty acid deficiency causes a generalized scaly dermatitis composed of thickened, erythematous, desquamating plaques. Individuals may also show failure to thrive, growth retardation, alopecia, thrombocytopenia, and poor wound healing. The eruption has been induced experimentally in animals fed a fat-free diet and has been observed in patients with chronic severe malabsorption, as in short-gut syndrome, and in those sustained on a fat-free diet or fat-free parenteral alimentation. Linoleic acid (18:2 n-6) and arachidonic acid (20:4 n-6) are deficient, and an abnormal metabolite, 5,8,11-eicosatrienoic acid (20:3 n-9), is present in the plasma. Alterations in the triene/tetraene ratio are diagnostic (arachidonic acid/eicosatrienoic acid ratio >0.4 or linoleic acid/arachidonic acid ratio >2.3). The horny layer of the skin contains microscopic cracks, the barrier function of the skin is disturbed, and transepidermal water loss is increased. Topical application of linoleic acid, which is present in sunflower seed and safflower oils, may ameliorate the clinical and biochemical skin manifestations, although absorption can be inconsistent. Oral and/or parenteral therapy can also be considered. Appropriate nutrition should be provided, with the recommendation that 1–4% of total calories should be from linoleic acid.

KWASHIORKOR

Severe protein and essential amino acid deprivation in association with adequate caloric intake can lead to **kwashiorkor**, particularly at the time of weaning to a diet that consists primarily of corn, rice (or rice milk), or beans (see Chapter 64). Children can be fed such a restricted diet for cultural reasons or because of misdiagnosis on the part of the child's parents or healthcare providers of perceived food allergies. Diffuse, fine, reddish-brown scaling (enamel/flaky paint sign) is the classic cutaneous finding. In severe cases, erosions and linear fissures develop (Fig. 712.3). Nails are thin and soft, and hair is sparse, thin, and depigmented, sometimes displaying a "flag sign" consisting of alternating light and dark bands that reflect alternating periods of adequate and inadequate nutrition. The cutaneous manifestations may closely resemble those of acrodermatitis enteropathica; however, edema of the extremities and face ("moon facies") and a protuberant abdomen ("pot belly") are key features uniformly observed in kwashiorkor. The serum zinc level is often deficient; in some cases, skin lesions of kwashiorkor heal more rapidly when zinc is applied topically. See Chapter 64 for treatment recommendations.

CYSTIC FIBROSIS

See Chapter 454.

Protein-calorie malnutrition develops in 5–10% of patients with cystic fibrosis. Rash in infants with cystic fibrosis and malnutrition is rare but may appear by age 6 months. The initial eruption consists of scaling, erythematous papules and progresses in 1-3 months to extensive desquamating plaques. The rash is accentuated around the mouth and perineum and on the extremities (lower greater than upper). Alopecia may be present, but mucous membranes and nails are uninvolved.

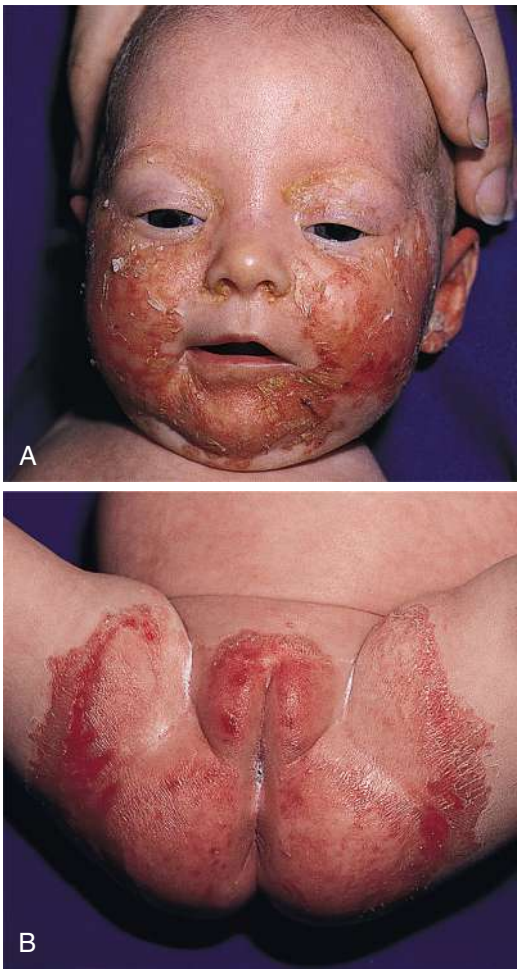

Fig. 712.1 A, Periorificial eruption. B, Diaper rash. The skin findings are typical of zinc deficiency, in this case caused by low levels of zinc in breast milk. *(From Eichenfield LF, Frieden IJ, Esterly NB. Textbook of Neonatal Dermatology. Philadelphia: Saunders; 2001: Fig. 14.14.)*

PELLAGRA

See Chapter 67.3.

Pellagra manifests as edema, erythema, and burning of sun-exposed skin on the face, neck, and dorsal aspects of the hands, forearms, and feet. Lesions of pellagra may also be provoked by burns, pressure, friction, and inflammation. The eruption on the face frequently follows a butterfly distribution, and the dermatitis encircling the neck has been termed "Casal's necklace." Blisters and scales develop, and the skin increasingly becomes dry, rough, thickened, cracked, and hyperpigmented. Skin infections may be unusually severe. Pellagra develops in patients with insufficient dietary intake or malabsorption of niacin and/or tryptophan. Administration of isoniazid, 6-mercaptopurine, or 5-fluorouracil may also produce **pellagra**. **Hartnup disease** (see Chapter 105), caused by a pathogenic gene variant in *SLC6A19,* which encodes a neutral amino acid transporter, is a rare autosomal recessive disorder that presents in infancy with a "pellagra-like syndrome" as a result of decreased absorption of tryptophan. Nicotinamide supplementation and sun avoidance are the mainstays of therapy in pellagra. See Chapter 67.3 for treatment recommendations.

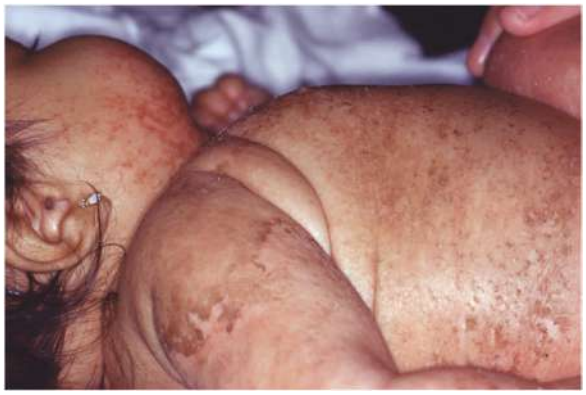

Fig. 712.3 Erosions and scaling in kwashiorkor.

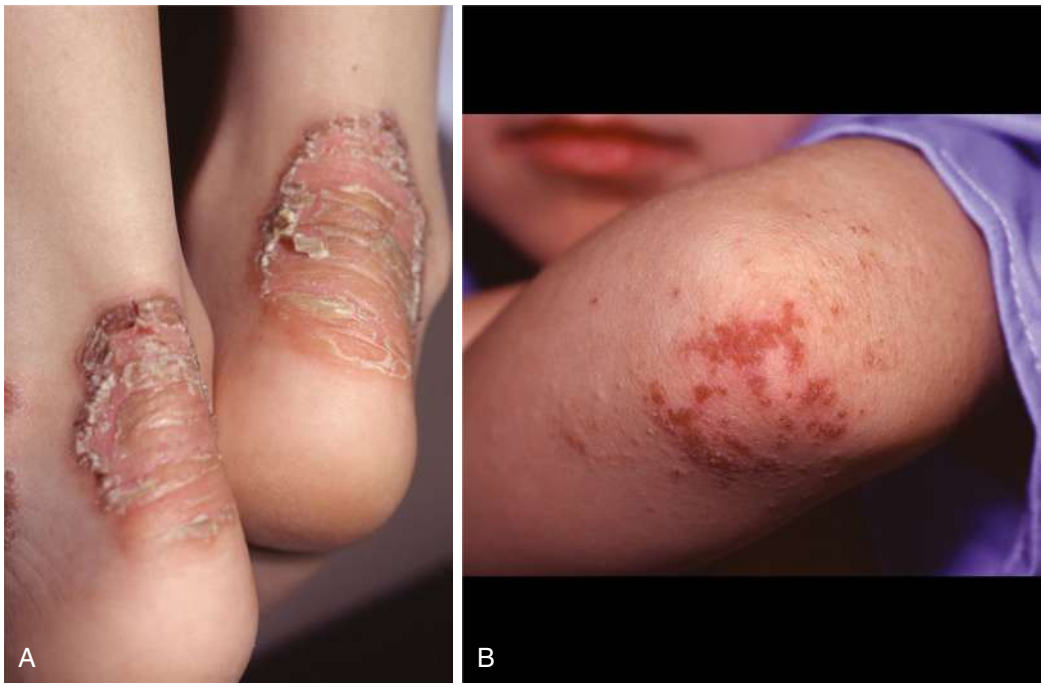

Fig. 712.2 A, Psoriasiform lesion of zinc deficiency dermatitis on the ankles. B, Similar lesions on the elbows.

SCURVY (VITAMIN C OR ASCORBIC ACID DEFICIENCY)

See Chapter 68.

Scurvy manifests initially as follicular hyperkeratosis, or coiling of the hair on the upper arms, back, buttocks, and lower extremities (Fig. 712.4). Other features are perifollicular erythema and hemorrhage, particularly on the legs and advancing to involve large areas of hemorrhage; swollen, erythematous gums (Fig. 712.5); stomatitis; and subperiosteal hematomas. In children, the most common risk factors are behavioral or psychiatric disease resulting in poor nutrition. The best method of confirmation of a clinical diagnosis of scurvy is a trial of vitamin C supplementation. Treatment is with 100-200 mg/day of vitamin C supplementation orally or parenterally for up to 3 months.

VITAMIN A DEFICIENCY

See Chapter 66.

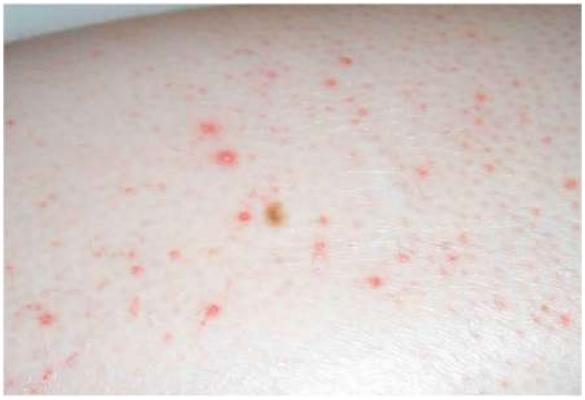

Fig. 712.4 Scurvy. *(Photo courtesy Albert Yan, MD.)*

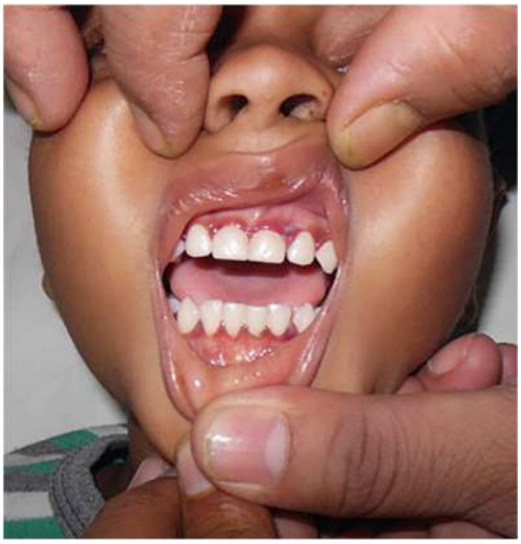

Fig. 712.5 Clinical photograph showing inflamed marginal gingiva in scurvy. *(From Agarwal A, Shaharyar A, Kumar A, et al. Scurvy in pediatric age group – a disease often forgotten? J Clin Ortho Trauma. 2015;6:101–107, Fig. 1, p. 103.)*

Vitamin A deficiency manifests initially as impairment of visual adaptation to the dark. Cutaneous changes include xerosis and hyperkeratosis and hyperplasia of the epidermis, particularly the lining of hair follicles and sebaceous glands. In severe cases, desquamation may be prominent. See Chapter 66 for treatment recommendations.

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