Chapter 1

Skin

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Skin diseases are very frequent in children. Most of them, including the most common disorders, such as atopic dermatitis, hemangiomas, nevi, acne, or bacterial and viral infections, are readily diagnosed through an adequate anamnesis and clinical examination. However, some skin tumors and inflammatory disorders may require a biopsy. The patient's age and relevant clinical history, in addition to the site from which the skin biopsy was obtained, should be known by the pathologist.

A sound basis of pediatric dermatological epidemiology is necessary, since the entities most frequently observed in children differ significantly from those seen in adults.

The specimens and biopsies most frequently sent for histopathological analysis in children are melanocytic nevi, inflammatory dermatoses such as Henoch–Schönlein purpura, psoriasis, pityriasis lichenoides, pityriasis rosea, lichen planus, pityriasis rubra pilaris, erythema multiforme, atopic dermatitis, granuloma annulare, and pigmented purpuric dermatosis, as well as infections, vascular anomalies and benign tumors/hamartomas/cysts. Genodermatosis and malignancies are rarely seen.

In this chapter, we will be dealing with the histopathology features of the most commonly biopsied skin diseases in children.

Inflammatory skin disorders

We will follow the pattern analysis approach and discuss an important example in each pattern.

Spongiotic dermatitis

Spongiotic dermatitis (SD) is defined by the presence of intraepidermal intercellular edema. Pronounced spongiosis results in the formation of intraepithelial spongiotic vesicles. When large enough, these vesicles can be grossly appreciated. These vesicles contain lymphocytes and/or Langerhans cells in most cases, but sometimes eosinophils or neutrophils can be the dominant element. spongiotic dermatitis is further subclassified into acute, subacute, and chronic. As the lesions progress, the spongiosis decreases and parakeratosis appears. In the late stage the spongiosis is mild to absent, but there is pronounced irregular acanthosis, hyperkeratosis, and parakeratosis.

The pattern of SD is caused by a variety of clinical conditions. These include atopic dermatitis, allergic/contact dermatitis, nummular dermatitis, dyshidrotic dermatitis, seborrheic dermatitis, drug reactions, Id reaction, dermatophytosis, miliaria, Gianotti–Crosti syndrome, and pityriasis rosea (1). The differential diagnosis of spongiotic dermatitis is shown in Table 1.1.

Atopic dermatitis is the most prevalent cause of spongiotic dermatitis, and is generally diagnosed clinically; however, some atypical cases can occasionally undergo biopsy.

Atopic dermatitis (AD)

Atopic dermatitis is a chronic, eczematous condition of the skin, often related to atopic states (including asthma, hay fever, and other allergic diseases).

Clinical presentation: Atopic dermatitis affects 5–15% of children in the industrialized world. Its prevalence has increased steadily in recent years, to become the most prevalent skin disease in children. The main clinical features include a combination of eczema, prurigo, and lichenification. It usually runs a chronic course with exacerbations. Most cases of AD begin in infancy with head and face eczema that can spread to the extensor areas of the limbs and trunk. By the age of two, the typical flexural involvement

Essentials of Surgical Pediatric Pathology, ed. Marta C. Cohen and Irene Scheimberg. Published by Cambridge University Press.

Table 1.1 Spongiotic dermatitis

Usual type spongiotic dermatitis (spongiosis distributed randomly through the epidermis with no specific localization)
- Contact dermatitis
- Pompholyx
- Juvenile plantar dermatosis
- Autoeczematization ("id" reaction)
- Papular acrodermatitis of childhood (Gianotti–Crosti)
- Spongiotic drug reactions

Miliarial spongiosis (intraepidermal edema centered on the acrosyringium)
- Miliaria rubra

Follicular spongiosis (intercellular edema in the follicular infundibulum)
- Infundibulofolliculitis
- Atopic dermatitis
- Apocrine miliaria
- Eosinophilic folliculitis

Pityriasiform spongiosis (microvesicles within areas of spongiosis that contain lymphocytes, histiocytes, and Langerhans cells)
- Pityriasis rosea
- Pityriasiform drug reaction
- Erythema annulare centrifugum
- Nummular dermatitis
- Lichen striatus

Neutrophilic spongiosis
- Pustular psoriasis
- Pemphigus foliaceus
- IgA pemphigus
- Infantile acropustulosis
- Acute generalized exanthematous pustulosis
- Palmoplantar pustulosis
- Staphylococcal toxic shock syndrome
- Dermatophytoses and candidiasis
- Pustular contact dermatitis
- Periodic fever syndromes

Eosinophilic spongiosis
- Pemphigus
- Bullous pemphigoid
- Allergic contact dermatitis
- Atopic dermatitis
- Arthropod bites
- Eosinophilic folliculitis
- Incontinentia pigmenti (first stage)
- Drug reactions
- Autoeczematization ("id" reaction)
- Still's disease
- Wells' syndrome

affecting mainly the elbow and knee folds is patent. Chronic disease and a vicious circle of itch and scratch lead to a typical thickening of the skin named lichenification. Prurigo lesions, consisting of papules and papulo-vesicles scattered throughout the skin surface are also common in older children and adolescents (2).

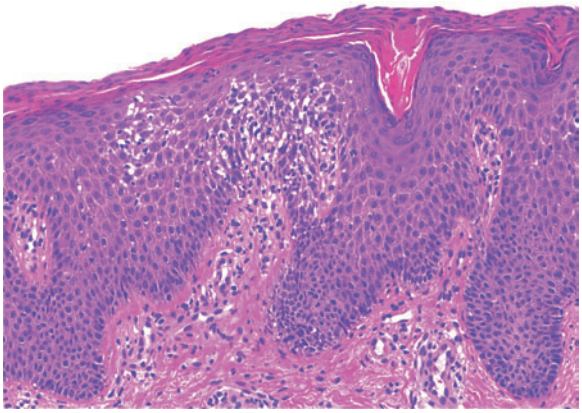

Figure 1.1 Atopic dermatitis. Subacute lesion showing mild spongiosis, exocytosis of lymphocytes, and parakeratosis, in a perifollicular distribution.

Genetics: Atopic dermatitis is due to a genetic defect in the skin barrier. In about 40% of patients, a semi-dominant genetic defect in the FLG gene, encoding the epidermal protein filaggrin, is responsible. Deficient filaggrin function leads to weaker corneocytes and skin barrier derangement, thus leading to an increased passage of irritants and allergens throughout the epidermis, and to a higher adherence of bacteria due to impaired natural immunity (3,4).

Classification: Atopic dermatitis is a heterogeneous disease; different types of genetic defects are supposed to result in an epidermal barrier defect. Most types of eczema in infants are regarded as "atopic," although there may be clinical differences that might reflect different genetic backgrounds.

Histology: Atopic dermatitis cannot be reliably or consistently distinguished from other forms of eczematous dermatitis based on assessment of histopathological features alone. Biopsies of atopic dermatitis are usually taken from subacute or chronic lesions, so parakeratosis, epidermal hyperplasia, and superimposed features of lichen simplex chronicus are typical, rather than prominent spongiosis (Figure 1.1). Secondary impetiginization with Staphylococcus aureus or secondary herpes simplex virus infection (eczema herpeticum) may occur.

Psoriasiform dermatitis

Psoriasiform dermatitis is characterized by the presence of regular epidermal hyperplasia, elongation of the rete ridges, hyperkeratosis, and parakeratosis. Thinning of the suprapapillary plates, a superficial

Table 1.2 Psoriasiform dermatitis

- Psoriasis
- Psoriasiform drug eruption
- Pityriasis rubra pilaris
- Lichen simplex chronicus
- Chronic spongiotic dermatitides
- Erythroderma
- Pityriasis lichenoides chronica
- Inflammatory linear verrucous epidermal nevus
- Chronic fungal infections
- Lamellar ichthyosis
- Secondary syphilis
- Pellagra and other nutritional deficiencies

perivascular inflammatory cell infiltrate, and dilated, tortuous blood vessels within these papillae are also present. Numerous conditions can result in psoriasiform dermatitis (Table 1.2).

Psoriasis

Psoriasis is a common, chronic, relapsing, papulosquamous disorder of the skin with highly variable presentation.

Clinical presentation: Psoriasis is very common, and around 20% of cases begin in childhood or adolescence. The main clinical feature is the psoriatic plaque. It appears as an erythematous, flat-topped plaque, with thick, adherent scales, generally on the extensor surfaces of the elbows and knees, but areas such as the scalp, trunk, arms, legs, and virtually any part of the skin surface can be affected. The extension of the disease may range from a very few plaques to whole skin involvement (5).

Genetics: Psoriasis' heterogeneity and multiple gene involvement make it difficult to establish a clear genetic base of the disease. Certain genes are known to predispose to psoriasis, and there is a strong relationship with genes involved in the immune response.

Classification: Plaque-type psoriasis is the most common variant. Other variants include pustular psoriasis, with a predominance of pustules usually arranged in arcs and annuli; erythrodermic psoriasis, with erythema and scales covering more than 95% of the body surface; palmo-plantar psoriasis, with variable presentations including plaques and pustules; and psoriatic arthritis, among many others.

Histology: Fully developed lesions exhibit parakeratosis with neutrophils, hypogranulosis, psoriasiform hyperplasia, thinning of suprapapillary plates, tortuous blood vessels within papillary dermal tips, and superficial perivascular predominantly lymphocytic dermal infiltrates. Neutrophilic spongiosis, intraepidermal spongiform pustules (of Kogoj), and neutrophil aggregates in the stratum corneum (Munro microabscesses) can also be present.

Table 1.3 Interface dermatitis

Interface dermatitis, vacuolar-type
- Erythema multiforme
- Erythema multiforme-like drug eruption
- Fixed drug eruption
- Lichen sclerosis et atrophicus
- Erythema dyschromicum perstans
- Lupus erythematosus
- Dermatomyositis
- Viral exanthemas
- Phototoxic dermatitis
- Acute radiation dermatitis
- Acute graft vs. host disease

Interface dermatitis, lichenoid-type
- Lichen planus
- Lichenoid drug eruption
- Lupus erythematosus
- Chronic graft vs. host disease
- Lichen nitidus
- Pigmented purpuric dermatosis
- Pityriasis lichenoides chronica
- HIV dermatitis
- Syphilis
- Mycosis fungoides
- Urticaria pigmentosa

Interface dermatitis

Interface dermatitis is characterized by epidermal basal cell damage, which may be manifested by cell death, basal vacuolar change, or both. The basal cell death usually presents in the form of Civatte bodies (shrunken eosinophilic cells with pyknotic nuclear remnants) scattered along the epidermal basal layer. Based on the pattern of inflammation, interface dermatitis can be divided in two groups: vacuolar and lichenoid. Vacuolar interface dermatitis (such as erythema multiforme) is characterized by sparse inflammation along the dermo-epidermal junction. Lichenoid interface reactions (such as pityriasis lichenoides) are characterized by a denser band-like infiltrate (6). Differential diagnosis of interface dermatitis in pediatric patients is displayed in Table 1.3.

Erythema multiforme (EM)

Erythema multiforme (minor) is an acute, self-limited, and sometimes recurring reactive condition of the skin due to direct infection by herpes simplex virus (HSV).

Clinical presentation: Target lesions, consisting of a central papule or vesicle, a surrounding pale elevation and peripheral erythema, are the hallmark of the disease. They appear in attacks of cropped lesions, affecting mainly the cheeks, forearms, hands, and palms, but they may also involve the elbows, knees, and feet. The lesions usually disappear in 2–3 weeks without scarring. They may be preceded or coincide with a typical HSV on the lips, but may appear without any visible HSV infection or recurrence; polymerase chain reaction (PCR) has revealed HSV viral DNA in erythema multiforme lesions.

Classification: There has been considerable confusion and overlapping with two other conditions, erythema multiforme major and Stevens–Johnson syndrome (SJS). In erythema multiforme major, mucosal involvement of at least three different mucosae is seen, mainly the oral, eye, and genital mucosae. Some cases of erythema multiforme major in children are related to HSV infection, but also to mycoplasma and drugs. Stevens–Johnson syndrome shows preferential mucosal involvement with purpuric target-like lesions that resemble toxic epidermal necrolysis (TEN); in fact, SJS and TEN are part of the same disease spectrum. Toxic epidermal necrolysis is the most severe reaction, defined as widespread sloughing of the epidermal surface on greater than 10% of the total body surface area. The cause of TEN and SJS is drug intake, but there may be cases of SJS related to HSV (7,8).

Histology: Erythema multiforme is the prototypical vacuolar interface dermatitis showing a lymphocytic infiltrate along the dermo-epidermal junction associated with vacuolar degeneration and apoptotic basal keratinocytes. Because most cases present acutely, there is usually "basket weave" orthokeratosis. Occasionally, severe papillary edema is present. A mild-to-moderate lymphocytic infiltrate around the superficial vascular plexuses is also seen. As the lesions progress, partial-to-full-thickness epidermal necrosis or subepidermal blisters may appear (Figure 1.2). In TEN there is always progression to full-thickness epidermal necrosis and subepidermal blistering.

Differential diagnosis: Erythema multiforme, SJS, and TEN cannot be reliably distinguished from one another on histopathological grounds alone; distinction requires clinical context. Prodromal upper respiratory tract syndrome, mucous membrane involvement, extensive exfoliation, and association with medication use are features of SJS/TEN. The most important clinical differential diagnosis of TEN is staphylococcal scalded skin syndrome (SSSS), the latter exhibiting a superficial intraepidermal cleavage plane, akin to that observed in pemphigus foliaceus.

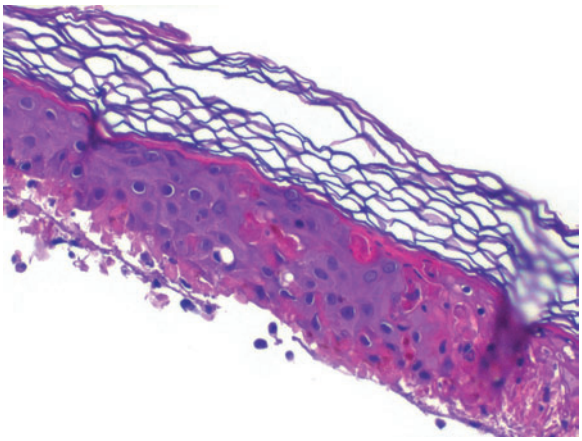

Figure 1.2 Erythema multiforme. Subepidermal blister formation.

Pityriasis lichenoides (PL)

A papulo-squamous disease of the skin of unknown origin, PL can range from a relatively mild chronic form to a more severe acute eruption.

Clinical presentation: Pityriasis lichenoides appears as a generalized exanthema of discrete, red-brown papules, affecting mainly the trunk and flexor surface of the arms and forearms, although a widespread distribution can occur. Shortly after, the papules develop a round, pale-brown scale that can be easily shed. Finally, when the lesions eventually disappear, hypopigmented areas appear (9,10).

Classification: There is an acute and a chronic form. In the acute form, also known as PLEVA (pityriasis lichenoides et varioliforme acuta), there is an acute onset of lesions, usually developing a hemorrhagic and vesicular component leading to small dark crusts. In chronic PL (CPL), there are recurrent attacks of less severe lesions leading to a long-lasting eruption that can even span through many months. The possible relation of PL with cutaneous lymphoma is virtually absent in children.

Histology: Pityriasis lichenoides et varioliforme acuta lesions are characterized by a wedge-shaped superficial and deep dermal lymphocytic infiltrate, interface dermatitis with lymphocyte exocytosis, papillary dermal hemorrhage, parakeratotic neutrophilic crust, and variable death of epidermal keratinocytes (Figure 1.3). Epidermal necrosis may involve

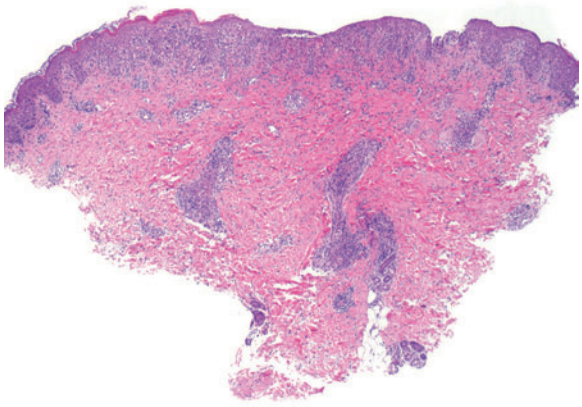

Figure 1.3 Pytiriasis lichenoides. An interface dermatitis with lymphocyte exocytosis and a wedge-shaped superficial and deep dermal lymphocytic infiltrate.

scattered single cells or sheets of cells, resulting in confluent necrosis. Fully developed lesions have a lichenoid infiltrate. Dense infiltrates of lymphocytes in and around blood vessels is often noted, but a true vasculitis, with fibrin within vessel walls, is only occasionally present. In CPL, neutrophilic crust, necrosis of keratinocytes, and erythrocyte extravasation may be minimal or absent, and the perivascular lymphocytes are usually sparser and superficial.

Bullous dermatitis

This pattern is characterized by intraepidermal or subepidermal blister formation, resulting from a defect, congenital or acquired, in the adhesion of keratinocytes. A blister is a fluid-filled space within or beneath the epidermis that can be primary or appear as a secondary event caused by different factors (infections, burns, ischemia, etc.). Assessment of the associated inflammatory infiltrate, identification of the mechanism of tissue split, and determination of the histologic plane of the blister are the first steps in the histopathological diagnosis of a vesiculo-bullous disorder.

The blister may be subcorneal/intracorneal, intraspinous, suprabasilar, or subepidermal. See Table 1.4 for differential diagnosis.

Table 1.4 Bullous dermatitis, differential diagnosis according to blister location

Subcorneal/intracorneal blister
- Miliaria crystallina
- Bullous impetigo
- Staphylococcal scalded skin syndrome
- Subepidermal pustular dermatosis
- Pustular psoriasis
- Acropustulosis of infancy
- Transient neonatal pustular melanosis
- Erythema toxicum neonatorum
- Acute generalized exanthematous pustulosis
- Pemphigus foliaceus

Intraspinous blister
- Pemphigus variants
- Hailey–Hailey disease
- Darier's disease
- Grover's disease
- Spongiotic vesicles
- Herpetic dermatitis
- Friction
- Edema

Suprabasilar blister
- Pemphigus vulgaris
- Darier's disease

Subepidermal blisters
- Linear IgA bullous dermatosis
- Epidermolysis bullosa
- Dermatitis herpetiformis
- Bullous pemphigoid
- Burns and cryotherapy
- Toxic epidermal necrolysis
- Bullous urticaria
- Bullous acute vasculitis
- Bullous lupus erythematosus
- Sweet's syndrome
- Epidermolysis bullosa acquisita
- Suction blisters
- Blisters overlying scars
- Drug reactions
- Kindler's syndrome
- Wells' syndrome
- Arthropod bites

Bullous pemphigoid (BP) and linear IgA disease of childhood (LAD)

Bullous pemphigoid and LAD are bullous diseases due to the development of autoantigens directed to certain structures of the basal membrane. In BP, the autoantigens are usually IgG, IgM, and sometimes IgA type, whereas in LAD, antigens are IgA type. There is considerable overlap between these two entities, and thus they are discussed together (11,12).

Clinical presentation: Both are infrequent. Bullous pemphigoid usually presents as an annular, urticarial eruption; later, a few vesicles develop within the urticarial plaques, and finally, a striking bullous eruption appears. The perioral region, neck, trunk, limbs, and especially hands and feet may be involved. In LAD there is predominant perineal involvement. Bullae

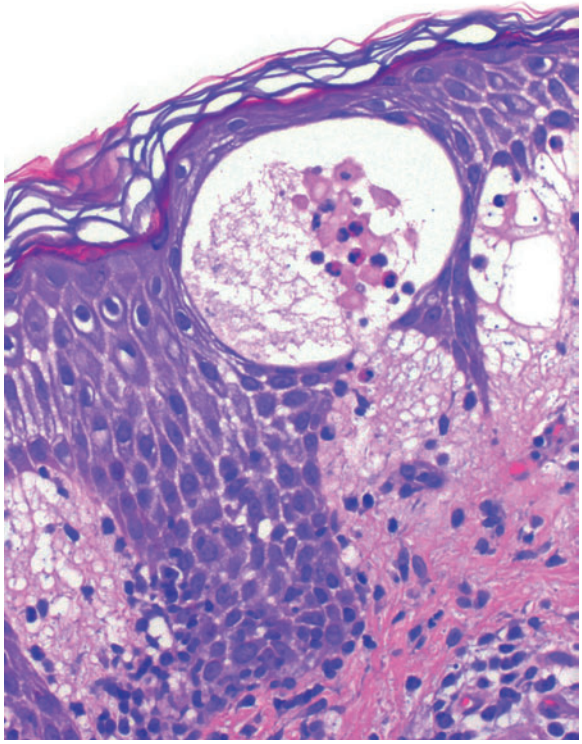

Figure 1.4 Bullous penphigoid. Eosinophilic spongiosis is frequently seen in the erythematous non-bullous skin.

often show a typical peripheral beading, with blisters surrounding a central area of erythema. Both BP and LAD run a chronic course, but eventually the disease disappears in most cases.

Classification: In BP and LAD, certain basal membrane antigens are targeted by autoantibodies. Antibodies against the BP230 antigen are typically present in BP patients' serum, and in both BP and LAD, different epitopes of the BP180 antigen (corresponding to collagen XVII) are targeted.

Histology: In LAD, also known as chronic bullous dermatosis of childhood, the blister is subepidermal and neutrophils are usually the predominant cells in the infiltrate. Papillary microabscesses are seen in some cases, making the lesion indistinguishable from dermatitis herpetiformis on light microscopy. Direct immunofluorescence reveals a homogeneous linear pattern of IgA deposition along the basement membrane of non-lesional skin. IgG, IgM, and/or C3 may also be present.

In BP there is also a subepidermal blister, but eosinophils are the predominant cell in the dermis and blister cavity. Eosinophilic spongiosis may be seen in the clinically erythematous skin surrounding the blister (Figure 1.4). Direct immunofluorescence shows a linear deposition of IgG and/or C3 along the basement membrane. IgM and IgA can sometimes be positive. In early stages of the disease only C3 may be present.

Vasculitis

Vascular diseases can be classified as non-inflammatory purpuras, vascular occlusive diseases, urticarias, neutrophilic dermatoses, and vasculitis. Schönlein–Henoch purpura (SHP) is the most commonly biopsied condition in this heterogeneous group of disorders (13,14).

Schönlein–Henoch purpura

Schönlein–Henoch purpura is a peculiar type of leukocytoclastic vasculitis, mediated by IgA immune complexes that can affect the skin and internal organs.

Clinical presentation: Usually an infectious episode precedes the skin eruption. Palpable purpura is the hallmark of SHP, and appears as small purpuric papules surrounded by a halo of flat purpuric erythema. These lesions usually appear on the ankles, feet, and legs, but can also affect the thighs, buttocks, arms, and, rarely, the face. IgA immune complexes deposit in the vessel walls leading to necrotizing vasculitis and blood extravasation, visible as purpura. Vasculitis can affect other organs such as joints, gastrointestinal tube, kidneys, and, more rarely, central nervous system (CNS), lungs, and virtually any other organ. Accompanying symptoms include fever, malaise, joint swelling, gastrointestinal hemorrhage, and proteinuria. Schönlein–Henoch purpura usually affects children and adolescents. In infants, a similar vasculitic condition called acute hemorrhagic edema of infancy is recognized. It shows large purpuric macules with acral distribution and edema of ankles, wrists and ears, but usually there is no systemic involvement.

Histology: Recent lesions are characterized by small-vessel neutrophilic vasculitis affecting the superficial dermal plexus. Fragmented nuclei (leukocytoclasia) around small vessels are typical (Figure 1.5). Focal intravascular fibrin and thrombosis can be present. The dermis shows variable edema and extravasation of red blood cells. In some cases, the subepidermal edema is pronounced, resulting in vesiculo-bullous lesions. In resolving lesions, there is usually a mild perivascular infiltrate of lymphocytes and some

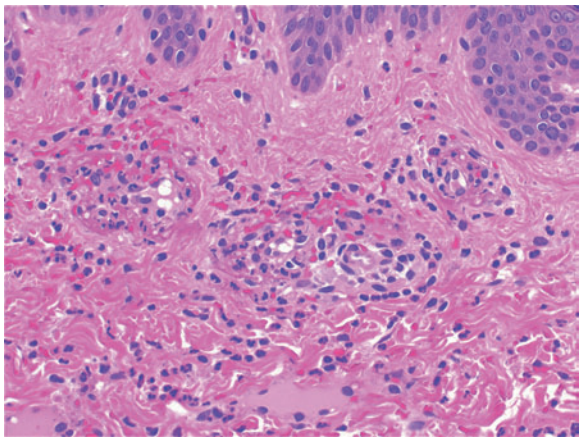

Figure 1.5 Schönlein–Henoch purpura. Neutrophilic vasculitis with leukocytoclasia and fibrinoid necrosis involving dermal postcapillary venules.

eosinophils. In most cases biopsied early in the course of the disease IgA can be demonstrated in vascular walls of involved and uninvolved skin. In infantile acute hemorrhagic edema the histopathology is the same, but IgA deposition is negative (15).

Granulomatous dermatitis

Granulomas are discrete collections of histiocytes or epithelioid histiocytes with variable numbers of admixed multinucleate giant cells and other inflammatory cells. Different histological patterns of granulomas are recognized: sarcoid ("naked" granulomas), epithelioid, or tuberculoid, necrobiotic (collagenolytic), suppurative and foreign-body granulomas. Some granulomas do not fit neatly into one of the above categories. Differential diagnosis is shown in Table 1.5.

Table 1.5 Granulomatous dermatitis

Sarcoidal granulomas (epithelioid histiocytes and giant cells with a paucity of surrounding lymphocytes)
- Sarcoidosis and Blau's syndrome
- Foreign body reactions
- Secondary syphilis
- Crohn's disease
- Orofacial granulomatosis
- Granuloma annulare (sarcoidal type)
- Immunodeficiencies

Tuberculoid granulomas (epithelioid histiocytes and Langhans giant cells with a rim of lymphocytes and a central "caseation" necrosis).
- Tuberculosis
- Tuberculids
- Leprosy
- Late syphilis
- Leishmaniasis
- Rosacea
- Lupus miliaris disseminatus faciei
- Perioral dermatitis
- Crohn's disease
- Idiopathic facial aseptic granuloma

Necrobiotic granulomas (usually poorly formed and composed of histiocytes, lymphocytes and giant cells with associated 'necrobiosis'. The inflammatory component may form a palisade around the necrobiosis)
- Granuloma annulare
- Necrobiosis lipoidica
- Rheumatoid nodules
- Rheumatic fever nodules
- Crohn's disease
- Immunodeficiencies
- Reactions to foreign materials and vaccines

Suppurative granulomas (epithelioid histiocytes and multinucleate giant cells with central collections of neutrophils).
- Non-tuberculous mycobacterial infections
- Fungal infections (chromomycosis and pheohyphomycosis, sporotrichosis, blastomycosis, paracoccidioidomycosis, coccidioidomycosis,
- Nocardiosis and actinomicosis
- Ruptured cysts and follicles
- Cat-scratch disease
- Lymphogranuloma venereum
- Pyoderma gangrenosum

Foreign body granulomas (epithelioid histiocytes, foreign body-type giant cells, and variable numbers of other inflammatory cells with identifiable foreign material)
- Endogenous materials (calcium deposits, keratin, hair)
- Exogenous materials (tattoo material, cactus bristles, wood splinters, suture material, injected hyaluronic acid, bovine collagen, insect mouth parts, pencil lead, etc.)

Granuloma annulare (GA)

Granuloma annulare is a fairly common benign inflammatory skin condition of unknown etiology, which most often affects children and young adults (16).

Clinical presentation: There are four main clinical variants: localized, subcutaneous, disseminated, and perforating. Localized lesions usually appear on the distal extremities of children and young adults as smooth, flesh-colored to erythematous, firm papules that may coalesce into an annular papule or plaque. Subcutaneous GA is characterized by firm or hard asymptomatic nodules in the deep dermis or subcutaneous tissues; they are prevalent on the anterotibial zone, ankles, dorsal feet, buttocks, hands, scalp, and eyelids (17). Disseminated GA occurs predominantly in adults. In the rarer variant called perforating GA, there is a variety of superficial umbilicated papules with or without discharge, that heal with scarring. Localized disease is generally self-limited and resolves within one to two years, whereas disseminated disease

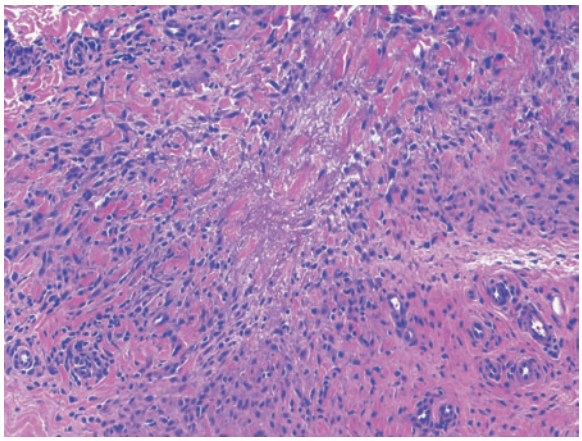

Figure 1.6 Granuloma annulare. Necrobiotic dermis surrounded by palisading granulomatous inflammation.

lasts longer. Granuloma annulare may be associated with diabetes, but association with other systemic disease is rare.

Histology: The fully developed GA lesions reveal foci of degenerative collagen with palisading granulomatous inflammation (Figure 1.6). Necrobiotic areas frequently show a pale, homogeneous, light-blue appearance due to the presence of mucin. There are associated perivascular and interstitial lymphocytes, occasionally neutrophils and nuclear dust. In the incomplete or interstitial variant, there is only an interstitial histiocytic infiltrate with minimal or absent palisading or increased mucin. In subcutaneous GA the palisading granulomas are located in the subcutaneous fat. In the perforating variant of GA there is transepidermal elimination of abnormal collagen fibers.

Panniculitis

The panniculitides include a group of disorders of varied etiology that manifest as inflamed nodules in the subcutaneous tissue. They are rarely seen in infants and children (18,19). Panniculitides can be classified into three distinct categories: septal panniculitis, lobular panniculitis, and panniculitis associated with large-vessel vasculitis. Septal panniculitides with no vasculitis include erythema nodosum, necrobiosis lipoidica, deep morphea, subcutaneous granuloma annulare, and rheumatoid nodule. Lobular panniculitides without vasculitis comprise a large series of disparate disorders, including sclerema neonatorum, subcutaneous fat necrosis of the newborn, post-steroid panniculitis, lupus erythematosus profundus, pancreatic panniculitis, α-1 antitrypsin deficiency panniculitis, subcutaneous Sweet syndrome, infective panniculitis, factitial panniculitis, traumatic panniculitis, etc.(20). Lobular panniculitis with vasculitis is represented by erythema induratum of Bazin (21). Finally, polyarteritis nodosa can mimic a primary panniculitis, and many serial sections are needed in some cases to definitely rule out vascular involvement.

Specific panniculitides of children include subcutaneous fat necrosis of the newborn, post-steroid panniculitis, sclerema neonatorum, and cold panniculitis. The panniculitides of the newborn represent a unique response of the infant's fat to different injuries, and are a specific type of panniculitis that is only seen in neonates and very young infants (18).

Subcutaneous fat necrosis of the newborn (SFNN)

SFNN is a self-limited panniculitis, present at birth or appearing in the first few days of life.

Clinical presentation: Subcutaneous fat necrosis of the newborn is an uncommon disorder, usually affecting healthy, full-term children that undergo some form of obstetric trauma such as meconium aspiration, asphyxia, hypothermia, or peripheral hypoxemia. In most cases, hypothermia is the common factor that leads to SFNN and extensive subcutaneous fat necrosis of the newborn has been described associated with therapeutic hypothermia (22). A not uncommon and life-threatening complication of SFNN is hypercalcemia (23).

Newborn fat has a lower fusion point than children's fat, and thus lower body temperatures lead to fat solidification, crystallization, and adipose tissue necrosis and inflammation. Clinically, erythematous or violaceous subcutaneous nodules appear on the back, shoulders, arms, or buttocks in newborns. Most cases resolve spontaneously, but in some patients the nodules melt and break, leading to external extrusion of the necrotized tissue. Prognosis is generally good, except for the development of hypercalcemia in severe cases (24).

Classification: There is considerable overlap with a condition called sclerema neonatorum, which is also a type of newborn panniculitis usually appearing in severely sick preterm newborns in which a diffuse induration of the back is the main symptom.

Histology: Subcutaneous fat necrosis of the newborn is characterized by necrosis of the subcutaneous fat with needle-shaped crystal formations within the adipose cells. This initiates a localized inflammatory process with foreign-body giant cell formation. There

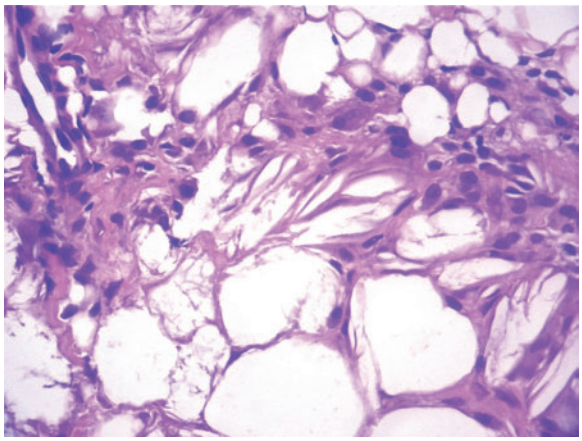

Figure 1.7 Subcutaneous fat necrosis of the newborn. Needle-shaped crystals and necrotic adipocytes.

is mostly lobular panniculitis, with a dense inflammatory infiltrate composed of lymphocytes, histiocytes, lipophages, and multinucleated giant cells. At a higher magnification, narrow needle-shaped clefts radially arranged are seen within the cytoplasm of the adipocytes and multinucleated giant cells (Figure 1.7).

Infectious disorders and bites

Bacterial skin infections are rarely biopsied; a clinical and microbiological diagnosis is usually made. Common viral infections, such as warts or molluscum contagiosum may require a skin biopsy for a correct diagnosis. Certain mycobacterial, parasitic, and fungal disorders are diagnosed on histopathological grounds, and thus a skin biopsy is required.

Warts

A wart (*verruca vulgaris*) is an epidermal proliferation induced by human papilloma virus (HPV) infection of the skin (25,26).

Clinical presentation: Warts are very common, especially in school-age children. They usually present as discrete verrucous papules that may appear in virtually every area of the skin surface. Palmar and plantar warts often take the form of translucent papules. Facial lesions may have a filiform shape. Mucosal lesions appear as moist masses, and are called condylomata. Different types of HPV cause different variants; both skin and mucosal types are recognized. Types 1, 2, and 4 are the most common in palms and soles, whereas types 6 and 11 are the most common mucosal types in children.

Histology: Warts show a papillomatous hyperplasia of the epidermis with hyperkeratosis and a prominent granular cell layer with enlarged keratohyaline granules and, sometimes, intracytoplasmic eosinophilic viral inclusions. Columns of parakeratosis overlie the tips of the papillomatous peaks. Koilocytes are frequent in the upper epidermis; they have a small, dark, hyperchromatic nucleus with irregular contours, surrounded by clear cytoplasm. Mild variation of the architecture and cytological features is seen in flat warts, myrmecial warts, and filiform warts. *In situ* hybridization or PCR studies can be used to detect HPV in paraffin-embedded tissue. In cases of warts involving genital or perianal skin, the possibility of sexual abuse may require investigation.

Molluscum contagiosum (MC)

This is a viral infection of the skin due to a poxvirus (27).

Clinical presentation: Molluscum contagiosum is very common in children, especially those attending swimming pools, atopic patients, and children affected by immunodeficiency. Individual lesions consist of small, discrete, pearly papules, sometimes with an umbilicated center. Their size ranges from 1 mm to 1 cm diameter nodules. There may be a single lesion to hundreds. The trunk, limbs, face, groin, and face are the most common sites. They are virtually never seen on mucosae, palms, or soles. In adolescents and adults, MC may be acquired throughout sexual contact (28,29).

Histology: Lesions appear as cup-shaped invaginations of the epidermis into the dermis. Eosinophilic inclusion bodies (Henderson–Patterson bodies) form in the cytoplasm of keratinocytes just above the basal layer. They accumulate and progressively enlarge, replacing the entire cell. These molluscum bodies are eventually extruded with keratinous debris into dilated ostia, which lead to the surface. Some lesions show a florid dense lymphocytic inflammatory infiltrate.

Leishmaniasis

Cutaneous leishmaniasis is due to infestation of the skin by protozoa of the genus Leishmania.

Leishmaniasis is present worldwide, with great species and clinical variation according to geographical distribution. It is endemic in the Middle East, North Africa, and in parts of Asia. Most cases in Europe are restricted to the Mediterranean basin, in relation with the vector mosquito population. Dogs are the most

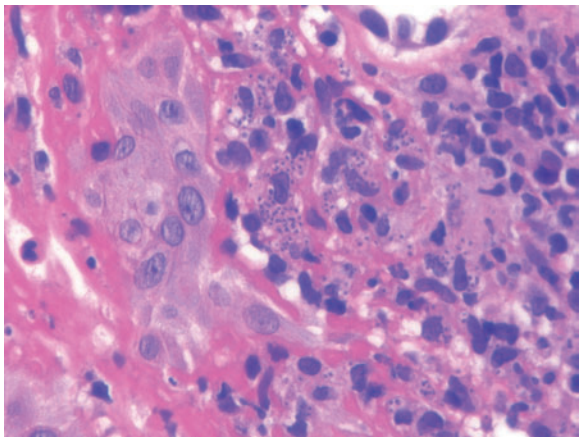

Figure 1.8 Leishmaniasis. Amastigotes within the cytoplasm of hystiocytes.

common reservoirs; mosquitoes act as vectors, and inoculate Leishmania on the human skin (30).

Clinical presentation: Leishmania growth within macrophages leads to an erythematous papule topped by a grayish, adherent crust that usually lasts for many months and is resistant to topical corticosteroids and antibiotics. There is usually a single lesion, most commonly on the cheeks. Rarely, multiple lesions can develop on the face.

Histology: Depending in the clinical type and stage, the epidermis may be either ulcerated with marked secondary changes and epidermal reaction, or it may be quite unremarkable or even atrophic. In *acute* lesions there is a massive dermal infiltrate of parasitized macrophages intermixed with lymphocytes, epithelioid cells and plasma cells. There may be a few eosinophils and variable numbers of neutrophils. The infiltrate may surround neurovascular bundles akin to lepromatous leprosy. Although Leishmanias can be seen in H-E stained sections (Figure 1.8), the morphological details are better seen on Giemsa stain. The parasites are 2–4 μm round to oval basophilic structures, with an eccentrically located kinetoplast. Leishmania organisms are difficult to find late in the disease, when there is a resolving granulomatous and sclerotic inflammatory reaction. Polymerase chain reaction is the most sensitive method for diagnosis and can be used to demonstrate the presence of amastigotes in tissue sections or lesional scrapings (31,32).

Differential diagnosis: Cutaneous leishmaniasis is frequently misdiagnosed in areas where it is not endemic, particularly if organisms are not seen. It may be misinterpreted as sarcoidosis, foreign-body reaction, granulomatous rosacea, and even granuloma annulare. When organisms are present, the lack of a capsule in Leishmanias is helpful in distinguishing them from *Histoplasma capsulatum*.

Melanocytic lesions

Melanocytic nevi (MN) are benign proliferations of nevocytes 3. that are present virtually in every person. Recognizing the many variants of MN avoids confusion with malignant melanoma (MM), which is very uncommon in children.

Dermal melanocytosis (DM)

DMs are cutaneous hyperpigmented lesions characterized by scattered pigmented dendritic melanocytes in the reticular dermis.

Clinical presentation: At least three different types are recognized: Mongolian spot, nevus of Ito, and nevus of Ota. Mongolian spots appear as one or multiple hyperpigmented patches on the lower posterior trunk with predilection for the sacro-gluteal region. Nevus of Ito typically involves the supraclavicular, deltoid, or scapular area. Nevus of Ota usually involves the sclera, conjunctiva, and skin around the eye, and zygomatic and temporal areas.

Histology: All types of DM are histologically similar. The epidermis appears unremarkable, but may show increased melanin in basal cells and a mild increased number of basal melanocytes. Scattered dendritic or spindle-shaped, often deeply pigmented melanocytes are recognized in the superficial and mid-dermis. Melanophages in the papillary dermis may be seen.

Simple lentigo (SL)

Simple lentigo is a common, benign lesion showing basal melanocyte proliferation.

Clinical presentation: Simple lentigo may appear anywhere on the skin surface as small, sharply demarcated macules about 3–5 mm in diameter, with a uniform light to dark-brown color. Sun-exposed skin of the trunk and extremities in individuals with white complexion is most frequently involved.

Histology: Simple lentigo is characterized by basal hyperpigmentation and increased melanocytes in the basal layer. The melanocytes are usually single and cytologically normal. Small junctional nests are sometimes seen. Epidermal acanthosis and melanophages in the papillary dermis are additional histological features.