Chapter 10
Bullous Dermatitis

Keywords Pemphigus • Transient acantholytic dermatosis • Grover's disease • Bullous pemphigoid • Cicatricial pemphigoid • Pemphigoid gestationis • Dermatitis herpetiformis • Bullous lupus erythematosus • Linear IgA disease • Epidermolysis bullosa acquisita • Porphyria cutanea tarda • Pseudoporphyria

The bullous dermatitis pattern is characterized by intraepidermal or subepidermal blister formation (Figs. 10.1 and 10.2). This discussion will be limited to diseases in which blister formation is the primary manifestation rather than blisters as a secondary phenomenon (i.e., blisters secondary to contact dermatitis, as discussed in Chap. 2). An understanding of the concept of acantholysis is paramount to any discussion of the intraepidermal vesicular disorders. Acantholysis is the result of loss of appropriate keratinocyte–keratinocyte adherence. This adherence is mediated by tight junctions, adherens junctions, gap junctions, and desmosomes. Desmosomes are critical to keratinocyte adhesion, and they are the last structures to split when acantholysis occurs. Acantholytic disorders that have been well characterized develop as sequelae of desmosomal dysfunction or disruption of the desmosomal connections with the intracellular keratin structural matrix. Keratinocyte–keratinocyte adhesion is a dynamic process because the relationship of one keratinocyte to another must change during epidermal maturation. Thus, acantholysis may be viewed as a loss of equilibrium between the formation and dissolution of junctions. This dysequilibrium may occur primarily when the adhesion junctions are impaired directly or secondarily when keratinocytic viability is affected. Histologically, acantholytic keratinocytes are rounded with condensed eosinophilic cytoplasm, large nuclei, peripheral marginated chromatin and prominent nucleoli. In intraepidermal blistering disease, the blister forms as the result of acantholysis within the epidermis.

In contrast, with subepidermal blistering disease, the split occurs at the dermal-epidermal junction. The integrity of dermo-epidermal adhesion is maintained thorugh focal attachment sites with the cutaneous basement membrane zone known

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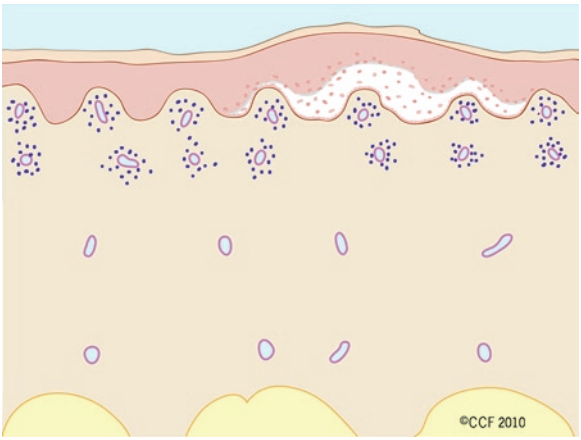

Fig. 10.1 *Schematic representation of intraepidermal blister*. Intraepidermal bullous dermatoses are characterized by formation of an intraepidermal blister via acantholysis. The basal layer remains attached to the basement membrane

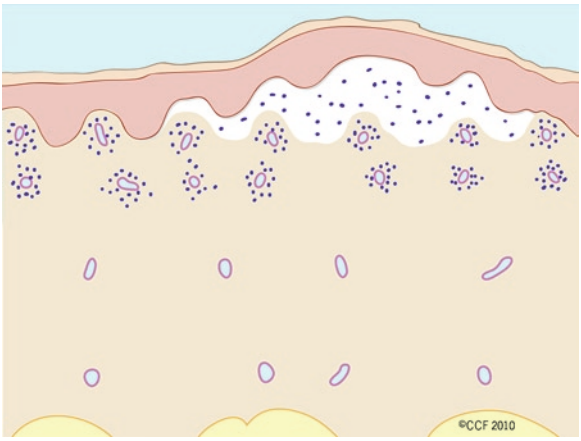

Fig. 10.2 *Schematic representation of subepidermal blister*. In subepidermal bullous dermatoses the entire epidermis is separated from the underlying dermis

as anchoring complexes. Patients with acquired autoimmune subepidermal blistering disorders have autoantibodies directed against components of the anchoring complex, resulting in disruption of the basement membrane zone and blister formation. Location of the level of blister formation, the composition of the inflammatory infiltrate, and correlation with direct immunfluorescence is required for definitive diagnosis. This chapter will focus on intraepidermal and subepidermal blistering disorders that are of importance to the general surgical pathologist. Where relevant, the underlying pathogenesis of the blistering disorder is discussed, as this aids in understanding the histologic findings.

In the evaluation of autoimmune blistering disease, examination of biopsies with direct immunofluorescence is often required for confirmation of the diagnosis. These biopsies should be perilesional (between 0.5 and 1 cm away from an adjacent bliser). Importantly, the specimen should be placed in Michel's solution rather than formalin. Formalin fixation results in autofluorescence, thereby resulting in nonspecific positivity.

Intraepidermal Vesicular Dermatitis

Pemphigus Vulgaris

Clinical Features

Pemphigus vulgaris presents as large, flaccid bullae on a normal, or erythematous base. Lesions typically involve oral mucosa, face, scalp, central chest, and intertriginous zones in older individuals. Oral lesions are the first manifestation in 10–15% of patients and almost invariably develop during the course of the disease. Blisters break easily leaving large eroded and crusted ulcers. Pemphigus vulgaris is a severe disease, that, if left untreated, can often lead to death.

Microscopic Features

The antibodies in pemphigus vulgaris are directed against desmoglein 3, a desmosomal cadherin that mediates cell binding. Desmoglein 3 is expressed in greater concentration in the lower epidermis, the location of the suprabasal acantholytic blister of pemphigus vulgaris. More than half of sera from patients with pemphigus vulgaris also have circulating antibodies against desmolglein 1.

Established lesions of pemphigus vulgaris demonstrate suprabasilar acantholysis with frequent involvement of follicular external root sheaths (Fig. 10.3). The basal keratinocytes separate from one another but remain attached to the dermis, reminiscent of a "row of tombstones" (Fig. 10.4). Acantholytic cells may be arranged as solitary units or groups of cells separated from the adjacent keratinocytes (Fig. 10.5). Nuclei are pyknotic, hyperchromatic, and often surrounded by a perinuclear halo. In the superficial dermis, there is typically a superficial perivascular lymphoid infiltrate with occasional eosinophils. Rarely, lesions in pemphigus vulgaris may demonstrate eosinophilic spongiosis (i.e., eosinophils within the overlying epidermis).

All patients with active pemphigus have IgG autoantibodies directed against the cell surface of keratinocytes detectable by direct and often indirect immunofluorescence. Direct immnofluorescence demonstrates intercellular squamous staining of IgG and, in most cases, complement C3 (Fig. 10.6). Pemphigus should not be diagnosed if only C3 is present. About 30% of patients exhibit deposition of IgM and/or IgA. (Table 10.1 highlights key microscopic and immunofluorescence features).

Table 10.1 Key microscopic features: pemphigus vulgaris

- Suprabasilar blister with acantholysis which extends into the follicular epithelium
- Basal layer spared ("tombstone")
- Rarely, eosinophilic spongiosis observed
- DIF: IgG and possibly C3 deposited in the intercellular regions of the epidermis

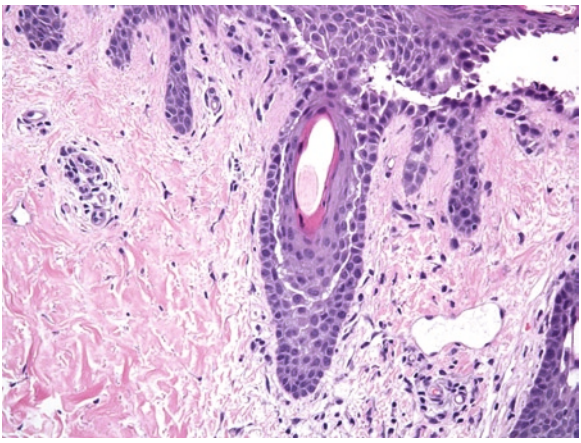

Fig. 10.3 *Pemphigus vulgaris* is characterized by acantholysis. Extension down follicles is common

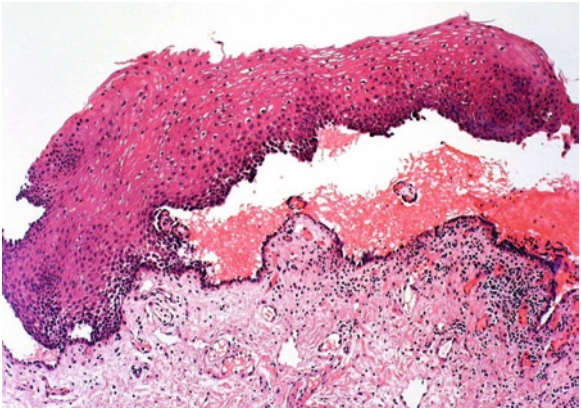

Fig. 10.4 *Pemphigus vulgaris*. This is a biopsy from the oral mucosa involved by pemphigus vulgaris. Note the suprabasilar blister formation with sparing of the basal layer of keratinocytes. The basal keratinocytes cling to the basement membrane in a tombstone pattern. This case has relatively little suprabasilar acantholysis

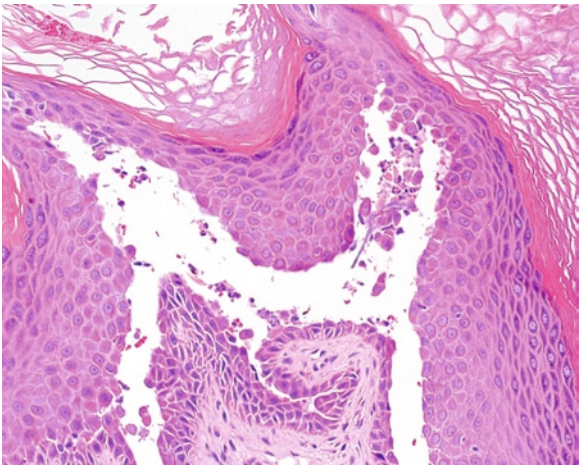

Fig. 10.5 *Pemphigus vulgaris*. This higher power image from a case of pemphigus vulgaris demonstrates the acantholysis and the tombstone pattern of basal layer

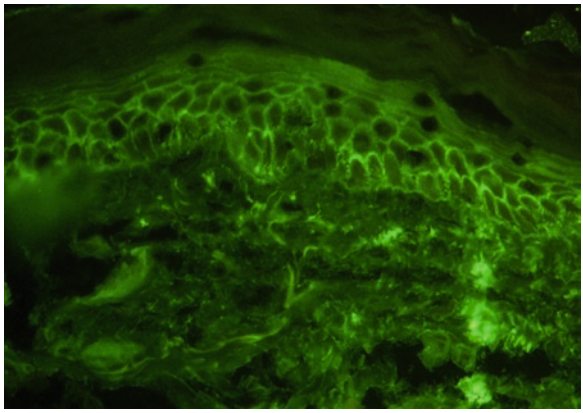

Fig. 10.6 *Pemphigus vulgaris direct immunofluorescence*. Direct immunofluorescence of perilesional skin demonstrates intercellular staining of IgG resulting in a net-like or chicken wire staining pattern of the epidermis

Differential Diagnosis

Although the clinical and histopathologic features of pemphigus vulgaris are often distinctive, other acantholytic disorders including pemphigus foliaceus, drug-induced pemphigus, IgA pemphigus, paraneoplastic pemphigus, familial benign pemphigus, focal acantholytic dyskeratosis, herpesvirus infection, and acantholytic variants of actinic keratosis may enter into the differential diagnosis.

In pemphigus foliaceus, the majority of the authoantibodies are directed against desmoglein 1, which is expressed in higher concentrations in the upper epidermis. Histologically, this manifests as superficial intraepidermal blister formation, often with loss of the stratum corneum and granular layer (Fig. 10.7) in contrast to the suprabasilar cleaveage of pemphigus vulgaris. A clear association with a drug may be necessary to separate drug-induced pemphigus from pemphigus vulgaris. IgA pemphigus differs from pemphigus vulgaris by demonstrating subcorneal or intraepidermal neutrophilic pustules with mininimal or no acantholysis and positive immunoreactivity for intraepidermal intercellular IgA. Paraneoplastic pemphigus is distinctive because of a close relationship with an underlying maligiancy, the clinical heterogeneity of the eruption, and striking mucocutaneous involvement. Histologically, the presence of interface alteration and dyskeratosis (erythema multiforme-like pattern), coupled with acantholysis, and both intercellular and basement membrane zone patterns of immunofluorescence distinguish paraneoplastic pemphigus from pemphigus vulgaris. Familial benign pemphigus (Hailey–Hailey disease) is differentiated from pemphigus by the presence of acanthosis, acantholysis involving at least half of the epidermis in a diffuse pattern, occasional dyskeratosis, lack of appendageal involvement, and negative immunofluorescence results. Other acantholytic disorders that fall in the differential diagnosis include Darier's disease and Grover's disease. In contrast to Darier's and Grover's disease, pemphigus vulgaris exhibits greater breadth of involvement of the epidermis with periappendageal extension. In contrast, Grover's disease involves smaller, more discrete foci of epithelium; Darier's disease demonstrates dyskeratotic cells (see Table 10.2). Occasionally, pemphigus vulgaris may mimic herpesvirus infection by

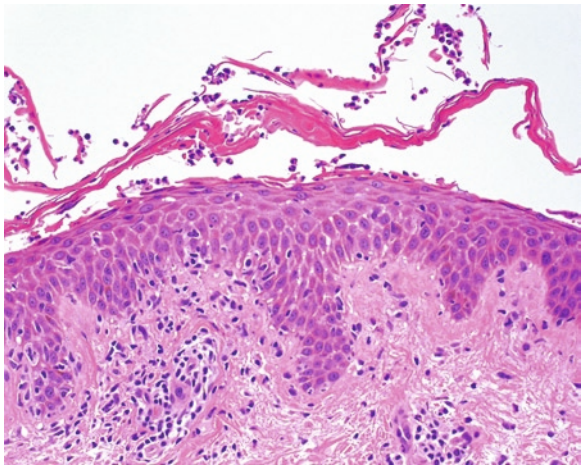

Fig. 10.7 *Pemphigus foliaceus*. In pemphigus foliaceus the blister formation is superficial, occurring at the stratum corneum or granular layer

Table 10.2 Practical tips: pemphigus vulgaris

- The clinical and histologic/direct immunofluorescence findings are usually distinctive
- If presenting in intertriginous areas consider Hailey–Hailey disease
- Other acantholytic disorders to be considered include Darier's disease and Grover's disease
  - In contrast to Darier's and Grover's disease, pemphigus vulgaris involves broad areas of the epidermis with periadnexal extension. In contrast, Grover's disease involves smaller more discrete foci of epithelium; Darier's disease demonstrates dyskeratotic cells
- Not all histologic features are necessarily seen in a given biopsy

showing acantholysis and alterations suggesting viral cytopathic changes of herpes ("ground glass" nucleus). Acantholytic variants of actinic keratosis are distinguished from pemphigus vulgaris by the presence of parakeratosis, crowding and atypia of the basilar keratinocytes, as well as clinical presentation.

Transient Acantholytic Dermatosis (Grover's Disease)

Clinical Features

Also known as Grover's disease, transient acantholytic dermatosis is characterized by pruritic discrete papulovesicles on the chest, back, and thighs, usually in middle-aged or elderly males.

Microscopic Features

Four histologic patterns have been described. These include Darier-like, Hailey–Hailey, pemphigus-like and spongiosis with acantholysis. Regardless of the pattern,

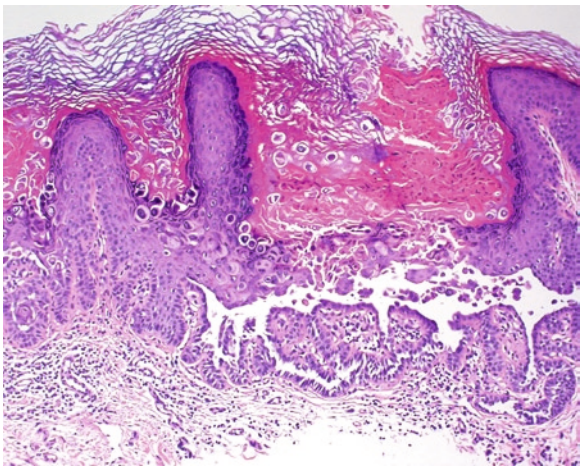

Fig. 10.8 *Transient acantholytic dermatosis (Grover's disease)*. Sharply circumscribed foci of suprabasilar acantholysis (pemphigus pattern) with hyperkeratosis, parakeratosis, and dyskeratotic round cells with abundant keratohyaline granules (corps ronds/Darier pattern)

Table 10.3 Key microscopic features: transient acantholytic dermatosis (Grover's disease)

- Discrete foci of acantholytic dyskeratosis (focal acantholytic dyskeratosis)
- Four histologic patterns have been described: Darier's-like, Hailey–Hailey-like pemphigus vulgaris-like (most common) and spongiotic dermatitis
- Superficial perivascular lymphocytic infiltrate in the dermis

all lesions are characterized by the circumscribed, focal nature of histologic changes, often, only several rete wide. Moreover, any or all of these histologic patterns may be present in an individual biopsy from an individual patient. The most common pattern is pemphigus vulgaris-like, followed by Darier-like. The pemphigus-type is characterized by discrete foci of suprabasilar acantholysis. Darier-like lesions demonstrate a suprabasilar split with corps ronds and corps grains and elongation of rete ridges. The patterns frequently coexist (Fig. 10.8). Given the focal nature of the process in a given biopsy specimen, multiple levels may be needed to reveal the characterisitic findings. Key microscopic features of Grover's disease are highlighted in Table 10.3.

Differential Diagnosis

Given the different patterns described with transient acantholytic dyskeratosis, the differential diagnosis includes Darier's disease, Hailey–Hailey disease, pemphigus, and a spongiotic dermatitis. Transient acantholytic dermatosis is distinguished from the latter entities based on the presence of two or more histologic patterns and limitation to small foci, often only several rete wide. Clinical information is also of value as the clincial presentation is distinctly different from the other acantholytic diseases in the histologic differential diagnosis. Important clues to the diagnosis of Grover's disease are summarized in Table 10.4.

Table 10.4 Practical tips: transient acantholytic dermatosis (Grover's Disease)

- The focal nature of the acantholytic process is a clue to the diagnosis
- Multiplicity of histologic patterns is a clue to the diagnosis
- Multiple levels may be necessary to establish the diagnosis
- The pattern of focal acantholytic dyskeratosis may be seen as an incidental finding in otherwise benign keratoses
- Direct immunofluorescence negative

Subepidermal Vesicular Dermatitis

The subepidermal blistering disorders are defined by the presence of a blister beneath the epidermis. They can also be subdivided as to the nature of the associated inflammatory cells, or lack thereof.

Subepidermal Vesicular Dermatitis with Predominant Eosinophils

Bullous Pemphigoid

Clinical Features

Bullous pemphigoid (BP) is the most common autoimmune blistering disorder. It affects elderly patients and is characterized by tense bullae arising on normal skin or an erythematous base. The sites of predilection are the groin and lower abdomen. Oral mucosal involvement develops in one third of patients. Pruritus is a common feature at presentation. In the early stages of the eruption, there are urticarial papules and plaques.

Microscopic Features

Patients with BP have circulating IgG autoantibodies against two BMZ antigens: BPAg1, a 230-kD protein, and BPAg2, a 180-kD protein. Fully developed lesions of bullous pemphigoid are characterized by a subepidermal vesicle with eosinophils and other inflammatory cells in and around the vesicle (Fig. 10.9). Rarely, the inflammatory process can be neutrophil- predominant or cell-poor. Early urticarial forms of bullous pemphigoid demonstrate eosinophilic spongiosis and/or a perivascular lymphoid infiltrate with eosinophils (Fig. 10.10). Eosinophils tagging the basal layer can be a clue to the diagnosis in the urticarial phase. Direct immunofluorescence of perilesional skin shows linear deposition of C3 (100%) and IgG (65–95%) along the dermoepidermal junction (Fig. 10.11). Indirect immunofluorescence examination with patient's sera applied to normal human skin as substrate

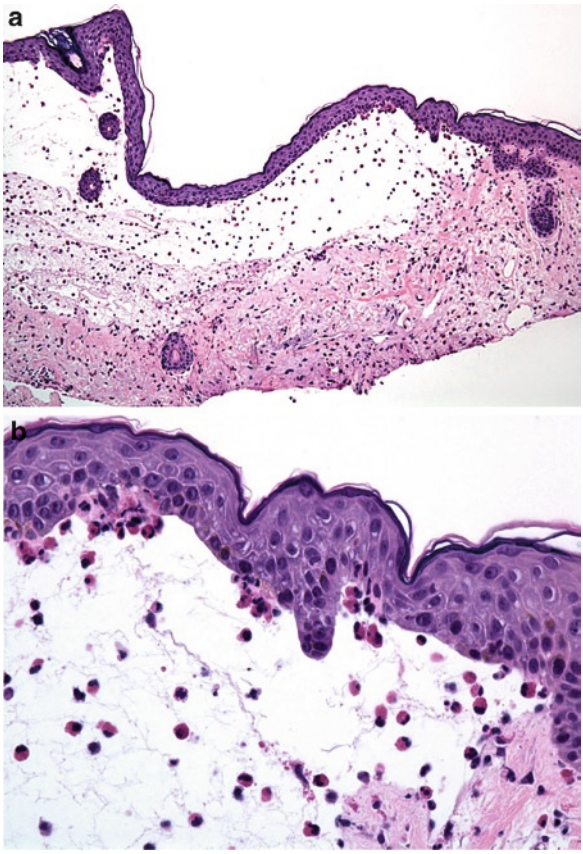

Fig. 10.9 (**a**) *Bullous pemphigoid* is characterized by a subepidermal blister. (**b**) The higher power image demonstrates eosinophils in the blister cavity

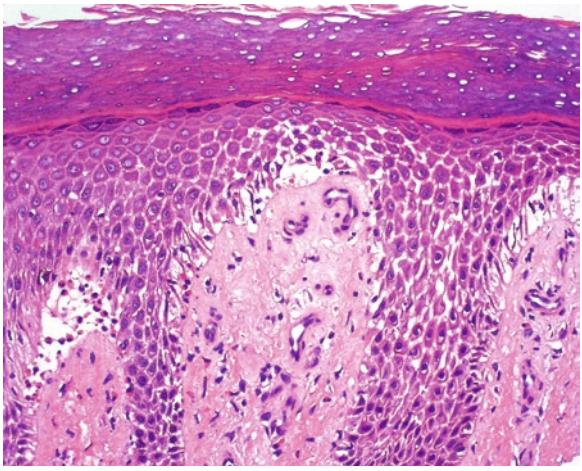

Fig. 10.10 *Urticarial bullous pemphigoid*. Biopsies from urticarial (pre-bullous) lesions of bullous pemphigoid demonstrate eosinophilic spongiosis and eosinophils tagging the epidermis along the dermoepidermal junction and in papillary dermis

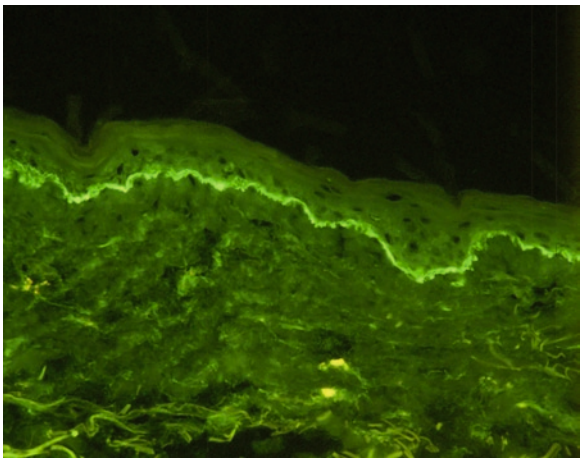

Fig. 10.11 *Direct immunofluorescence of bullous pemphigoid*. Direct immunofluorescence of perilesional skin demonstrating strong linear deposition of complement C3

Table 10.5 Key microscopic features: bullous pemphigoid

- Subepidermal blister with eosinophils and other inflammatory cells in and around the blister
- Rarely the inflammatory process can be neutrophil-predominant or cell-poor
- Dermal infiltrate is generally confide to the papillary dermis and is composed of lymphocytes, eosinophils and rarely neutrophils
- Urticarial forms of bullous pemphigoid may show eosinophilic spongiosis and eosinophils tagging the basal layer
- Direct immunofluorescence of perilesional skin demonstrates linear C3 (100%) and IgG (65–95%) at the dermoepidermal junction
- Direct immunofluorescence of perilesional salt-split skin usually demonstrates IgG along the epidermal side (roof) of the split

demonstrates circulating IgG antibodies to the basement membrane zone in 65–80% of the cases with active disease. Key microscopic and direct immunofluorescence features are summarized in Table 10.5.

Differential Diagnosis

The histologic pattern of an eosinophil-rich, subepidermal vesicular dermatitis most is quite characteristic of bullous pemphigoid. Occasionally, arthropod bite reactions can have prominent papillary dermal edema that histologically mimics a blister. In those cases, the depth of the infiltrate and clinical presentation should readily allow distinction.

There are two other pemphigoid diseases, cicatricial pemphigoid and pemphigoid gestationis, (also known as herpes gestationis) that figure into the differential diagnosis. In all three forms of pemphigoid, autoantibodies are directed against the same target basement membrane proteins. The three disorders share similar histologic features; however, they differ in their clinical presentations. Pemphigoid (herpes) gestationis is histologically indistinguishable from bullous

pemphigoid. Lesions of pemphigoid that demonstrate a mixture of eosinophils and neutrophils must be differentiated from inflammatory-rich epidermolysis bullosa acquisita. Neutrophil-predominant cases of bullous pemphigoid must be distinguished from dermatitis herpetiformis, bullous lupus erythematosus, and linear IgA disease. These entities are discussed in detail below.

Occasionally, bullous pemphigoid is relatively noninflammatory. In cases of cell-poor bullous pemphigoid, the differential diagnosis includes epidermolysis bullosa acquisita (see below). Although there are clinical differences between the two entities, the histologic and direct immunofluorescence features may be identical. Distinction between the two disorders requires the salt-split direct immunofluorescence technique to more precisely identify the location of the autoantibody. In this technique, the biopsy is placed in a sodium chloride solution that induces split within the basement membrane complex. The biopsy is then evaluated by direct immunofluorescence. With salt-split, clinically normal-appearing perilesional skin, the antibodies predominantly bind to the epidermal side (roof) of the blister in bullous pemphigoid and the dermal side (floor) of the blister in epidermolysis bullosa acquisita (Fig. 10.12). As in all bullous dermatoses, obtaining a proper biopsy for direct immunofluorescence examination is critical. With regard to bullous pemphigoid, false negative results may be seen in biopsies obtained from the lower extremities or lesional skin (see Table 10.6).

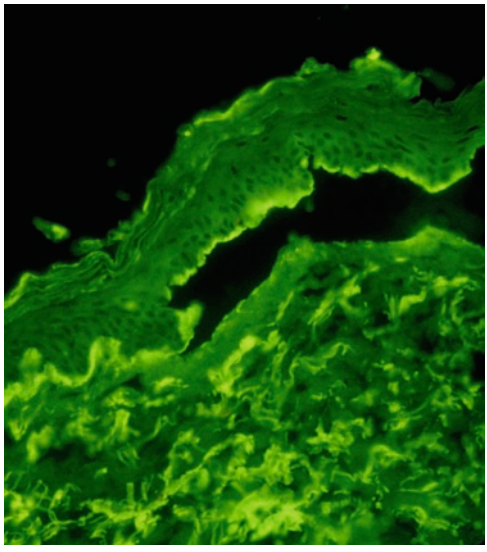

Fig. 10.12 *Salt-split direct immunofluorescence of bullous pemphigoid*. In a salt-split direct immunofluorescence of bullous pemphigoid, the deposits are (predominantly) on the roof of the blister

Table 10.6 Practical tips: bullous pemphigoid

- For accurate direct immunofluorescence examination, use perilesional skin
- False negative direct immunofluorescence results may be seen in biopsies from the lower extremities and lesional skin
- Always consider urticarial bullous pemphigoid when a biopsy from an elderly patient demonstrates eosinophilic spongiosis

Cicatricial Pemphigoid

Clinical Features

Cicatricial pemphigoid is a chronic blistering disorder involving mucous membranes including mouth, eye, nasopharynx, larynx, esophagus and genitalia. Lesions generally heal with scarring which can lead to decreased vision, blindness and supraglottic stenosis. Generalized skin lesions resembling bullous pemphigoid may occur, but are uncommon.

Microscopic Features

The two major antigens associated with cicatricial pemphigoid are BPAG2 and epiligrin (laminin-5). Intact mucosal lesions demonstrate separation of the epithelium from the basement membrane, accompanied by a slight number of inflammatory cells including eosinophils in the subepithelial stroma. A dermal scar may be evident if the biopsy is taken at the sight corresponding to previous blister formation (Fig. 10.13). The majority of lesions, however, are ruptured at the time of biopsy and therefore the subepithelial separation may be found just at the edge of an otherwise nonspecific ulcer (Table 10.7). In the majority of cases, direct immunofluorescence demonstrates linear IgG and C3 along the basement membrane zone. Indirect immunofluorescence demonstrates circulating autoimmune antibodies in more than half of patients.

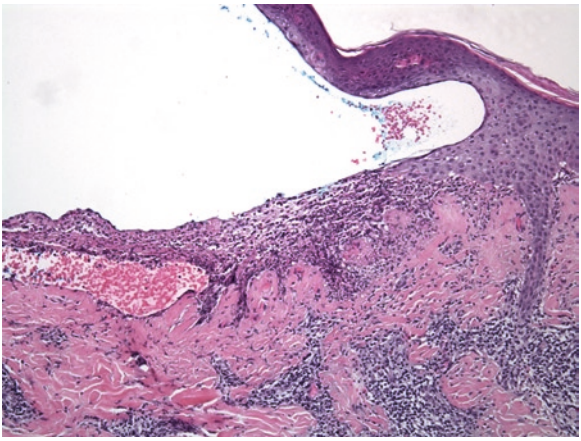

Fig. 10.13 *Cicatricial pemphigoid*. There is subepidermal separation of epidermis from dermis consistent with partial re-epithelialization. Also observed is a mixed inflammatory infiltrate in the papillary dermis composed of eosinophils, neutrophils, and lymphocytes. Note the fibrosis of the papillary dermis

Table 10.7 Key microscopic features: cicatricial pemphigoid

- Resembles bullous pemphigoid
- Scarring

Differential Diagnosis

As mentioned above, the differential diagnosis is bullous pemphigoid. Histologically, with the exception of the presence of scarring, the two diseases are indistinguishable. Clinical presentation of disease primarily restricted to mucous membranes is distinctive in cases where scarring is not histologically evident. In general, findings of pemphigoid (subepidermal blister with eosinophils with or without fibrosis) on a mucosal surface of an elderly individual should prompt consideration of the diagnosis (Table 10.8).

Table 10.8 Practical tips: cicatricial pemphigoid

- Involves mucosa
- Findings of pemphigoid on mucosal surface should prompt consideration of the diagnosis

Pemphigoid (Herpes) Gestationis

Clinical Features

Pemphigoid gestationis was originally named herpes gestationis on the basis of the morphologic similarity to herpetic blisters; however, this term is a misnomer as pemphigoid gestationis is not related to, or associated with any active or prior herpes virus infection. Pemphigoid gestationis is a pregnancy-associated autoimmune disease that occurs in 1 of 3,000 to 1 of 10,000 pregnancies. The eruption typically manifests during the second or third trimester of pregnancy and is characterized by an abrupt onset of severely pruritic papules and plaques. Blisters may develop and are often distributed in a herpetiform pattern. Lesions are distributed on the abdomen and trunk often in a characteristic periumbilical pattern. As the disease progresses, the eruption may spread peripherally, often sparing the face, palms and soles. Clinical course is variable. Exacerbation at delivery or immediately postpartum is classic, although it may resolve in the latter part of gestation with a flare at delivery. Most patients experience spontaneous regression over weeks to months postpartum. Complications that may be associated with the disorder include trophoblastic tumors, autoimmune diseases (e.g., Graves disease), transient skin eruptions in infants of affected mothers, and increased risk of prematurity and small-for-gestational age births.

Microscopic Features

The main antigenic target is the extracellular NC16A domain of the 180-kD BPAg2; however, autoantibodies also react (less frequently) with BP 230 (BPAg1). Pemphigoid gestationis is histologically indistinguishable from bullous

pemphigoid (Table 10.9). Direct immunofluorescence examination of perilesional skin demonstrates deposits of C3 (100% of cases) and IgG (27% of cases) at the basement membrane zone. Circulating complement-fixing autoantibodies ("HG factor") can be detected in most patients by indirect immunofluorescence on intact or salt-split skin.

Table 10.9 Key microscopic features: pemphigoid gestationis

- Microscopic features are histologically indistinguishable from bullous pemphigoid (both cell rich and urticarial forms)

Differential Diagnosis

As mentioned previously above, the histologic differential diagnosis is that of bullous pemphigoid. Clinical presentation generally allows distinction (Table 10.10). In rare cases, indirect immunofluorescence can be pursued, but this is rarely needed for diagnosis.

Table 10.10 Practical tips: pemphigoid gestationis

- Clinical presentation of periumbilical plaques in second or third trimester of pregnancy characteristic
- Common inflammatory disorders of pregnancy (atopic dermatitis, drug eruption) should be considered in the histologic differential of urticarial phase bullous pemphigoid

Subepidermal Vesicular Dermatitis with Predominantly Neutrophils

Dermatitis Herpetiformis

Clinical Features

Dermatitis herpetiformis is a rare, chronic subepidermal blistering disorder characterized by exquisitely pruritic, grouped urticarial plaques, papules and vesicles. Elbows, knees and shoulders are classically involved. The majority of patients have associated gluten sensitive enteropathy that is indistinguishable from celiac disease. Both dermatitis herpetiformis and celiac disease are associated with HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2. The majority of patients with dermatitis herpetiformis have no gastrointestinal symptoms, but greater than 90% have a gluten-sensitive enteropathy demonstrable on bowel biopsy. Although often difficult to accomplish due to compliance, 80% of

patients with dermatitis herpetiformis have improvement of skin disease when put on a gluten-free diet.

Microscopic Features

Recent studies suggest that epidermal transglutaminase (eTG) 3 is the predominant autoantigen of dermatitis herpetiformis. eTG is a cytosolic enzyme involved in cell envelope formation during keratinocyte differentiation. It has been demonstrated that sera from most patients with dermatitis herpetiformis demonstrate autoantibodies against eTG and tissue transglutaminase (TG2), which is found in the gut. IgA immune complexes containing eTG and IgA have been demonstrated in the papillary dermis in patients with dermatitis herpetiformis. These data suggest that development of this disorder is a complex, multifactorial process: a genetic predisposition to the disease, combined with a diet high in gluten, leads to formation of IgA antibodies to gluten-TG2 complexes. These antibodies cross-react with eTG, thus leading to papillary dermal deposition of IgA/eTG complexes and cutaneous lesions of DH.

In early lesions of dermatitis herpetiformis, neutrophils are observed at the tips of dermal papillae – so-called papillary microabscesses (Fig. 10.14). Fibrin may be present near the tips of dermal papillae giving a "necrotic" appearance. Subepidermal vesiculation with neutrophils is seen in older lesions (Fig. 10.15.). Blood vessels in the upper and mid dermis are surrounded by an infiltrate of lymphocytes, histiocytes, neutrophils and eosinophils. Direct immunofluoresence of perilesional skin demonstrates granular, thread-like deposits of IgA along the dermoepidermal junction with accentuation at the dermal papillary tips (Fig. 10.16). Complement C3 deposition may also be present. Key microscopic features and direct immunofluorescence profile are summarized in Table 10.11.

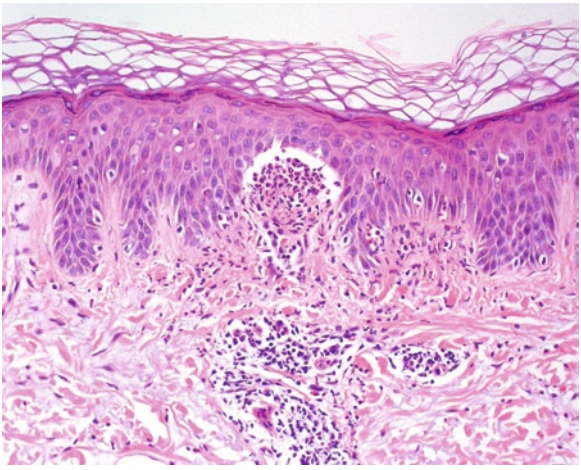

Fig. 10.14 *Dermatitis herpetiformis*. In early lesions of dermatitis herpetiformis there are neutrophilic microabscesses in the dermal papillae

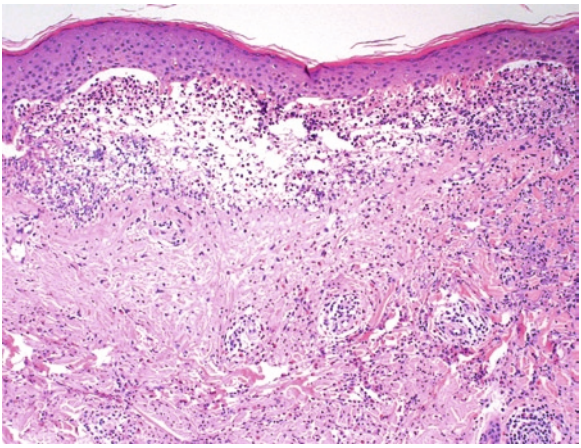

Fig. 10.15 *Dermatitis herpetiformis*. In established lesions there is subepidermal blister formation. Neutrophils are the predominant inflammatory cell in the blister cavity

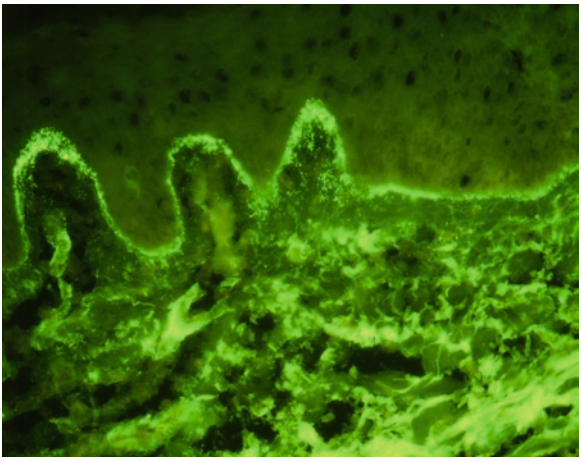

Fig. 10.16 *Dermatitis herpetiformis*. Direct immunofluorescence of perilesional skin demonstrate granular deposits of IgA along the dermoepidermal junction. Staining is frequently most intense in the tips of the dermal papillae

Table 10.11 Key microscopic features: dermatitis herpetiformis

- Early lesions: neutrophils at the tips of dermal papillae ("papillary microabscesses")
- Well-developed lesions: subepidermal vesiculation with neutrophils
- Direct immunofluorescence examination demonstrates IgA deposited in a granular fashion along the basement membrane
- IgA deposits often more prominent at the dermal papillary tips

Differential Diagnosis

The histologic differential diagnosis includes linear IgA disease and bullous lupus erythematosus (see below). The former is essentially indistinguishable from dermatitis herpetiformis. Bullous lupus erythematosus often has other histologic features of lupus erythematosus. Direct immunofluorescence allows distinction between these entities (see Table 10.12). Clinically, excoriated eczematous dermatitis

Table 10.12 Practical tips: dermatitis herpetiformis

- Significant overlap with bullous lupus erythematosus, linear IgA disease and inflammatory-rich cases of epidermolysis bullosa acquisita
- In the absence of direct immunofluorescence, sign out descriptively
- Clinically, dermatitis herpetiformis and excoriated eczematous dermatitis can look alike

(see Chap. 2) can resemble lesions of dermatitis herpetiformis. Histologically, this is spongiotic dermatitis, not a blistering disease.

Bullous Lupus Erythematosus

Clinical Features

Bullous lupus erythematosus is a rare variant of systemic lupus erythematosus that most commonly affects African-American women. Patients fulfill the American College of Rheumatology criteria for systemic lupus erythematosus and present with non-pruritic tense vesicles and bullae involving the upper trunk, proximal arms, face and neck. Mucosal involvement may be seen. Lesions respond dramatically to dapsone.

Microscopic Features

Indirect immunofluorescence assay demonstrates circulating IgG autoantibodies to the basement membrane zone. These autoantibodies target a 209-kDa protein which represents the NC1 domain of type VII collagen.

There is a subepidermal vesicle accompanied by a band-like neutrophilic inflammatory infiltrate in the upper dermis (Fig. 10.17). Leukocytoclasia and leukocytoclastic vasculitis may be present. Mucin deposition may also be observed.

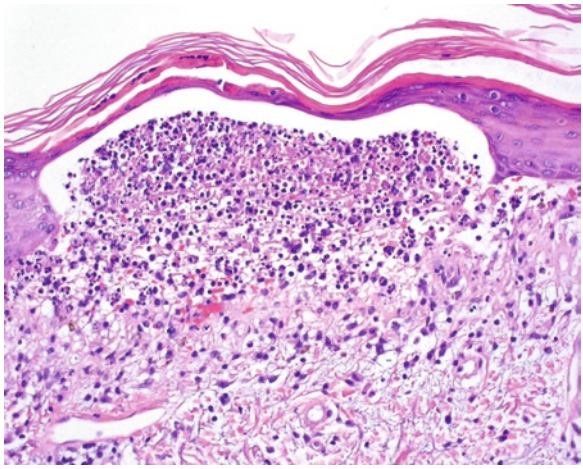

Fig. 10.17 *Bullous lupus erythematosus* is characterized by a subepidermal vesicle with a band-like neutrophilic infiltrate in the underlying dermis. Note the presence of dermal mucin between the collagen bundles, a clue to the diagnosis

Table 10.13 Bullous lupus erythematosus: key microscopic features

- Subepidermal vesicle associated with band-like neutrophilic infiltrate in the dermis
- Papillary neutrophilic microabscesses
- Leukocytoclasia
- Leukocytoclastic vasculitis may be present
- Mucin deposition
- DIF: IgG and C3 along the dermal-epidermal junction; IgM (50%) and IgA (60%)
- Salt-split: dermal side (floor) of the split

Direct immunofluorescence examination demonstrates granular and/or linear staining of IgG and C3 along the dermal-epidermal junction. IgM (50%) and IgA (60%) deposition may also be observed. Salt-split direct immunofluorescence demonstrates deposits on the dermal side of the split. See Table 10.13 for summary of key microscopic and direct immunofluorescence features.

Differential Diagnosis

The histologic differential diagnosis of bullous lupus erythematosus includes dermatitis herpetiformis, linear IgA bullous dermatosis, and inflammatory epidermolysis bullosa acquisita. Histologic evidence of other features of lupus erythematosus (e.g., mucin deposition) can allow for recognition. Clinical information is also very useful. For example, bullous lupus erythematosus is nonpruritic, unlike dermatitis herpetiformis which is intensely pruritic in essentially all cases. Direct immunofluorescence examination will also allow distinction. See Table 10.14 for clues to distinguishing bullous lupus from other neutrophil-rich subepidermal vesicular dermatoses.

Table 10.14 Practical tips: bullous lupus erythematosus

- Clinical presentation is characteristic
- There may be considerable histologic overlap with dermatitis herpetiformis. In bullous lupus, neutrophils tend to extend more deeply and in around vessels
- Presence of other histologic findings of lupus erythematosus (e.g. dermal mucin) can be a clue
- DIF allows distiniction between dermatitis herpetiformis, IgA bullous disease and epidermolysis bullosa acquisita

Linear IgA Disease

Clinical Features

Linear IgA dermatosis is a clinically heterogeneous disorder, with both adult and childhood forms described. Lesions may clinically simulate bullous pemphigoid, dermatitis herpetiformis, cicatricial pemphigoid and epidermolysis bullosa acquisita. Classic IgA disease presents as erythematous patches rimmed by tense blisters at the edges (“string of pearls”). There are a number of associated conditions that

have been described with linear IgA disease including inflammatory bowel disease (ulcerative colitis/Crohn's disease), lymphoproliferative disorders, and drugs (with vancomycin being the most common culprit).

Microscopic Features

Patients with linear IgA disease have circulating antibodies against components of the epidermal basement membrane including bullous pemphigoid antigen 1 and/or bullous pemphigoid antigen 2. Linear IgA is characterized by a subepidermal vesicle with neutrophils aligned along the dermal-epidermal junction (Fig. 10.18). Occasional eosinophils may be present. Later stage lesions may demonstrate basal vacuolization and papillary dermal edema. Direct immunofluorescence of perilesional skin demonstrates homogenous linear deposition of IgA along the dermoepidermal junction (Fig. 10.19). Table 10.15 summarizes key microscopic and direct immunfluorescence features.

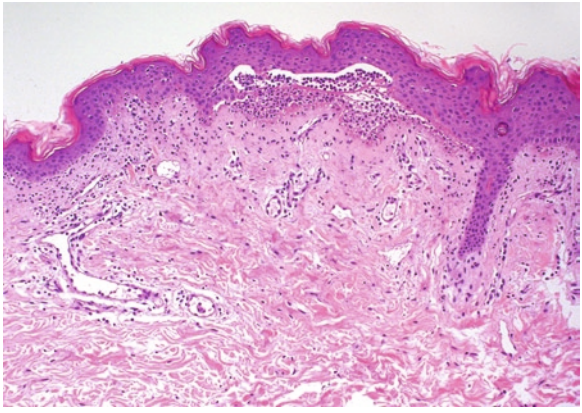

Fig. 10.18 *Linear IgA disease*. Subepidermal vesicle with neutrophils aligned upon the dermal-epidermal junction

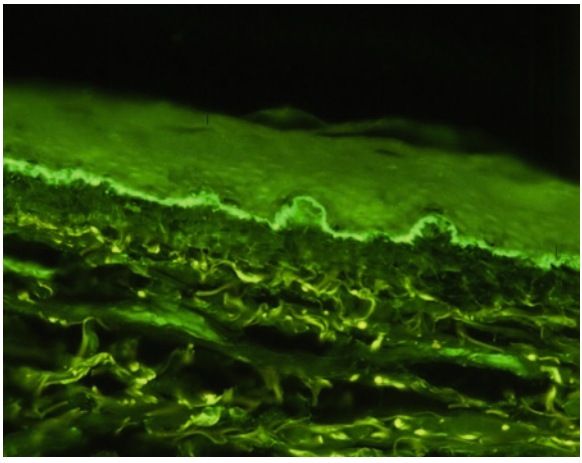

Fig. 10.19 *Linear IgA Disease*. Direct immunofluorescence of perilesional skin demonstrating linear IgA deposition along the dermal-epidermal junction

Table 10.15 Linear IgA disease: key microscopic features

- Subepidermal vesicle with neutrophils
- Papillary microabscesses may be seen (dermatitis herpetiformis-like)
- Direct immunofluorescence of perilesional skin demonstrates linear deposition of IgA along the basement membrane zone of non-lesional skin

Differential Diagnosis

The main differential diagnostic entity to consider is dermatitis herpetiformis. As discussed previously, classic lesions of dermatitis herpetiformis are characterized by fairly discrete papillary dermal microabscesses whereas the neutrophilic infiltrate in linear IgA is more diffuse in nature. In reality, however, there may be considerable histologic overlap between the two entities and direct immunofluorescence examination is required for definitive diagnosis. Other diagnostic considerations include bullous pemphigoid, inflammatory-rich epidermolysis bullosa acquisita, and bullous systemic lupus erythematosus. Non-autoimmune disorders that also fall into the differential diagnosis includes bullous arthropod bite reaction or bullous drug eruption. These are not typically neutrophil rich. Table 10.16 highlights clues in differentiating linear IgA disease from its closest histologic mimic, dermatitis herpetiformis.

Table 10.16 Practical tips: linear IgA disease

- Subepidermal neutrophilic infiltrate tends to be more dispersed in linear IgA vs. dermatitis herpetiformis
- Eosinophils may predominate in drug-associated cases of linear IgA
- Unequivocal distinction from dermatitis herpetiformis impossible without direct immunofluorescence examination

Subepidermal Vesicular Dermatitis with Little to No Inflammation

Epidermolysis Bullosa Acquisita

Clinical Features

Three different clinical forms of epidermolysis bullosa acquisita have been described. In the most common (noninflammatory) variant, patients present with trauma-induced acrally distributed blisters and erosions that heal with scarring. There may be associated nail dystrophy and alopecia. The inflammatory variant of epidermolysis bullosa acquisita presents as a generalized blistering eruption resembling bullous pemphigoid. The third form of epidermolysis bullosa acquisita predominantly involves mucous membranes and can result in significant scarring and dysfunction, similar to cicatricial pemphigoid.

Microscopic Features

Patients with epidermolysis bullosa aquisita have circulating IgG autoantibodies against the noncollagenous (NC1) domain of type VII collagen, the major component of anchoring fibrils that maintain the structural integrity of epidermal-dermal attachment. The histology of epidermolysis bullosa acquisita is that of a subepidermal blister with fibrin and only a few inflammatory cells in the lumen (Fig. 10.20). In non-inflammatory lesions, there is a sparse superficial lymphocytic infiltrate around the vessels of the superficial vascular plexus, while in inflammatory lesions, there is a heavy upper dermal inflammatory infiltrate composed of lymphocytes, neutrophils and eosinophils. In older lesions, there will be some dermal scarring and milia. Direct immunofluorescence of perilesional skin or mucosa demonstrates linear deposition of IgG along the basement membrane zone, similar to bullous pemphigoid. Salt-split perilesional skin demonstrates IgG along the dermal side (floor) of the split (Fig. 10.21). Approximately, 50% of patients have circulating IgG antibodies to the BMZ by indirect immunofluorescence assay. Table 10.17 highlights key microscopic features and direct immunofluorescence profile.

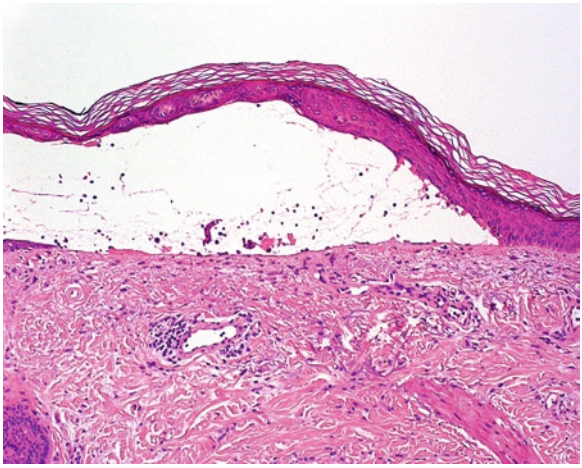

Fig. 10.20 *Epidermolysis bullosa acquisita* is characterized by an inflammatory-poor subepidermal vesicle

Differential Diagnosis

In classic, noninflammatory lesions, the differential diagnosis includes other cell-poor subepidermal blistering disorders including cell-poor bullous pemphigoid, porphyria cutanea tarda and pseudoporphyria. Cell poor bullous pemphigoid is differentiated by the location of the autoantibody on salt-split skin direct immunofluorescence as mentioned previously above. In epidermolysis bullosa acquisita, the autoantibodies are on the floor of the salt-split blister.

Porphyria cutanea tarda and pseudoporphyria are discussed in more detail below. Briefly, these entities have rigid dermal papillae protruding into the blister

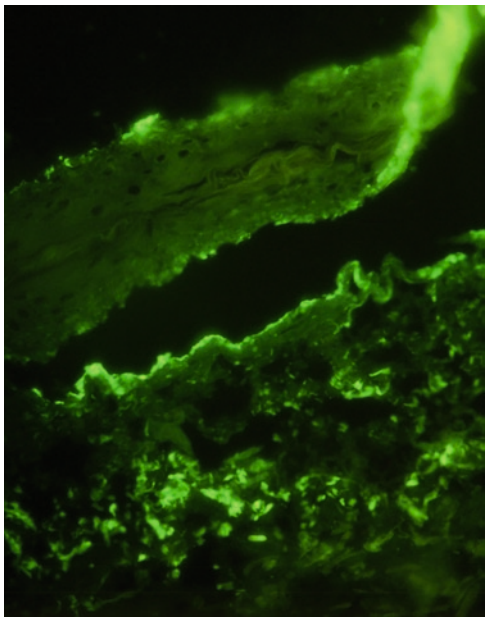

Fig. 10.21 *Salt-split direct immunofluorescence of epidermolysis bullosa acquisita*. Salt-split perilesional skin demonstrating linear IgG deposition along the dermal side (floor) of the split

Table 10.17 Key microscopic features: epidermolysis bullosa acquisita

- The most common pattern is that of a subepidermal blister with fibrin and only a few inflammatory cells in the lumen (non-inflammatory pattern)
- Occasional cases may demonstrate a heavy upper dermal inflammatory infiltrate composed of lymphocytes, neutrophils and eosinophils (inflammatory pattern)
- Older lesions may demonstrate dermal scarring and milia
- DIF profile: linear IgG and C3 at the dermal-epidermal junction; in salt-split skin examination, antibodies bind to the dermal side (vs. epidermal side for bullous pemphigoid)

cavity and thick-walled superficial dermal blood vessels. In addition to basement membrane deposits of antibodies, there are waxy vascular deposits seen on direct immunofluorescence that are not seen in epidermolysis bullosa acquisita. Inflammatory lesions of epidermolysis bullosa acquisita may overlap histologically with bullous lupus erythematosus and bullous pemphigoid. (see Table 10.18 for tips in distinguishing epidermolysis bullosa acquisita from other minimally inflammatory subepidermal blistering disorders).

Table 10.18 Practical tips: epidermolysis bullosa acquisita

- Noninflammatory subepidermal blister should prompt consideration
- Blisters tens to be on trauma prone areas
- No festooning of dermal papillae like in porphyria cutanea tarda

Porphyria Cutanea Tarda

Clinical Features

Porphyria cutanea tarda is a disease associated with underlying defects in porphyrin metabolism. It can be hereditary or acquired as a result of underlying liver disease. The latter is more common. Clinical manifestations include acral blisters and erosions, skin fragility, milia, scars, and hypertrichosis. Cutaneous manifestations are exacerbated by ultraviolet light. The dorsal hands are the most common locations for the blisters.

Microscopic Features

The blister of porphyria cutanea tarda is a pauci-inflammatory subepidermal blister, classically with festooning of the dermal papillae (Fig. 10.22). This latter feature presents as the dermal papillae sticking into the blister cavity as finger-like projections. Festooning of the dermal papillae is frequently but not invariably present. Eosinophilic, segmented collections of basement membrane material, referred to as caterpillar bodies, may be seen along the roof of the blister. The vascular changes in the underlying dermis are useful diagnostic features. The papillary dermal blood vessels have relatively thick walls due to deposition of glycoproteins. In some cases, the deposits are best appreciated with PAS stains.

Direct immunofluorescence demonstrates deposition of IgG, complement C3 and fibrinogen along the basement membrane zone. IgM deposition is also sometimes seen. Characteristic features are the waxy vascular deposits in the superficial dermal blood vessels. Table 10.19 for summarizes of key microscopic features for porphyria cutanea tarda and pseudoporphyria.

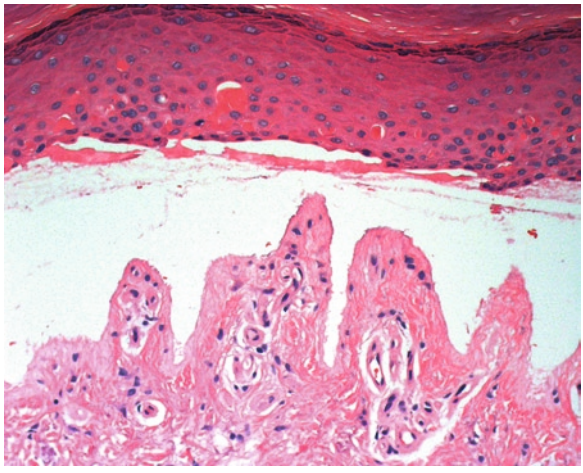

Fig. 10.22 *Porphyria cutanea tarda* (and pseudoporphyria) is characterized by a noninflammatory blister with festooning of the dermal papillae. Note the eosinophilic caterpillar bodies adjacent to the epidermis in the roof of the blister. The papillary dermal vessels have relatively thick walls

Table 10.19 Key microscopic features: porphyria cutanea tarda

- Noninflammatory subepidermal blister
- Festooning of dermal papillae
- Thick-walled papillary dermal blood vessels
- Caterpillar bodies
- Direct immunofluorescence demonstrates basement membrane and waxy vascular deposits (usually IgG)

Key microscopic features: pseudoporphyria

- Identical to porphyria cutanea tarda

Differential Diagnosis

The differential diagnosis includes epidermolysis bullosa acquisita and pseudoporphyria. Epidermolysis bullosa acquisita lacks the festooning of the dermal papillae and vascular deposits. On direct immunofluorescence, the presence of the vascular deposits seen in porphyria cutanea tarda is helpful. Pseudoporphyria is histologically indistinguishable form porphyria cutanea tarda. Differentiation is dependent on clinical factors (Table 10.20).

Table 10.20 Practical tips: porphyria cutanea tarda

- Most common on dorsal hands
- PAS stains can highlight glycoprotein deposits in vessel walls
- Acquired form associated with liver disease

Practical tips: pseudoporphyria

- Associated with renal disease
- Associated with NSAIDs and diuretics
- Discuss possibility with clinician

Pseudoporphyria

Clinical Features

Pseudoporphyria is clinically similar to porphyria cutanea tarda. It is associated with renal insufficiency or medications, especially nonsteroidal anti-inflammatory medications and diuretics. There is no underlying defect in porphyrin metabolism.

Microscopic Features

Pseudoporphyria is histologically indistinguishable from porphyria cutanea tarda.

Differential Diagnosis

The same comments regarding the differential diagnosis of porphyria cutanea tarda discussed above apply to pseudoporphyria.

Sample Reports

Sample Report: Pemphigus Vulgaris

Clinical history: Multiple vesicles and bullae on the groin of 75-year-old woman.
Diagnosis: Intraepidermal vesicular dermatitis, see comment.
Comment: There is prominent acantholysis with intraepidermal vesicle formation. Periadnexal extension of acantholysis is also observed. In the subjacent dermis, there is a slight superficial perivascular, predominantly lymphocytic inflammatory infiltrate with occasional eosinophils. Given the clinical presentation, the findings are strongly suspicious for pemphigus vulgaris. Recommend a biopsy of perilesional skin for direct immunofluorescence.
Note to reader: If the clinician suggests the possibility of pemphigus clinically, it would be acceptable to make the top line diagnosis as "pemphigus vulgaris" or "consistent with pemphigus vulgaris."

Sample Report: Transient Acantholytic Dermatosis

Example 1:
Clinical history: Pruritic papules on the chest; rule out folliculitis.
Diagnosis: Focal acantholytic dyskeratosis, see comment.
Comment: There are small, discrete foci of acantholytic dyskeratosis accompanied by a focal but brisk lymphocytic infiltrate in the underlying dermis. In this clinical setting, the findings are most compatible with Grover's disease (transient acantholytic dermatosis).

Example 2:
Clinical history: Keratotic lesion on the left arm; rule out basal cell carcinoma.
Diagnosis: Focal acantholytic dyskeratosis, see comment.
Comment: There is a solitary focus of acantholytic dyskeratosis. A slight superficial perivascular lymphocytic infiltrate is noted in the superficial dermis. Focal acantholytic dyskeratosis may be seen as an incidental finding in otherwise benign keratoses; however, in

the correct clinical setting (multiple lesions) the differential diagnosis includes Grover's disease. Clinical correlation is recommended.

Sample Report: Bullous Pemphigoid

Example 1: (fully developed lesion):
Clinical history: 70-year-old woman with vesicles and bullae on the lower abdomen.
Diagnosis: Eosinophil-rich subepidermal vesicular dermatitis, see comment.
Comment: Findings are strongly suspicious for bullous pemphigoid. A biopsy of perilesional skin for direct immunofluorescence is recommended for unequivocal diagnosis. The histologic differential diagnosis includes a bullous hypersensitivity reaction such as to drug or arthropod bite. Clinical correlation is recommended.
Note to reader: If the clinician suggests the diagnosis of bullous pemphigoid clinically, it would be acceptable to state the diagnosis as "consistent with bullous pemphigoid."

Example 2: (early urticarial lesion):
Clinical history: Urticarial papules and plaques on the thighs of a 65-year-old man.
Diagnosis: Eosinophil-rich spongiotic dermatitis, please see comment.
Comment: There is focal spongiosis of the epidermis accompanied by a perivascular and interstitial eosinophil-rich infiltrate. In foci, eosinophils are aligned along the dermal-epidermal junction. This histologic pattern may be seen with an eczematous hypersensitivity reaction such as to drug, contactant or arthropod bite. However, given the age of the patient, an urticarial/ non-bullous phase of bullous pemphigoid should be considered. If this is a clinical possibility, a biopsy of perilesional skin submitted in Michel's solution for direct immunofluorescence examination is recommended.

Sample Report: Pemphigoid Gestationis

Clinical history: 29-year-old woman in late second trimester of pregnancy presents with pruritic, urticarial papules on the abdomen, trunk and upper extremities.
Diagnosis: Eosinophil-rich spongiotic dermatitis, see comment.
Comment: There is slight spongiosis of the epidermis accompanied by an underlying mixed dermal inflammatory infiltrate composed of

lymphocytes and eosinophils surrounding the superficial vascular plexus. There is mild papillary dermal edema. These features may be seen with an eczematous hypersensitivity reaction such as to drug or contactant; however, in this clinical setting, pemphigoid gestationis must be excluded. Recommend punch biopsy of perilesional skin for direct immunofluorescence examination and unequivocal diagnosis.

Sample Report: Dermatitis Herpetiformis

Clinical history: Pruritic papules and vesicles around the elbows.
Diagnosis: Skin, punch biopsy: Subepidermal vesicle with neutrophils, see comment.
Comment: There is a subepidermal vesicle with papillary microabscesses in the dermal papillae. The clinical presentation in combination with the histologic features is strongly suggestive of dermatitis herpetiformis. The histologic differential diagnosis includes other autoimmune bullous disorders including bullous lupus erythematosus or linear IgA bullous dermatosis. Recommend punch biopsy of perilesional skin for direct immunofluorescence examination.

Sample Report: Linear IgA Disease

Clinical history: Bullae on the trunk.
Diagnosis: Subepidermal vesicle with neutrophils, see comment.
Comment: There is a subepidermal vesicle accompanied by a band-like neutrophilic infiltrate in the upper dermis. This histologic pattern raises consideration of linear IgA disease or, in the appropriate clinical setting, bullous lupus erythematosus. A biopsy of perilesional skin for direct immunofluorescence is recommended for unequivocal diagnosis.

Sample Report: Epidermolysis Bullosa Acquisita

Clinical history: Vesiculobullous lesions on the fingers of a 55-year-old man.
Diagnosis: Inflammatory poor subepidermal vesicular dermatitis, see comment.
Comment: There is a subepidermal vesicle with fibrin and few inflammatory cells in the lumen. The differential diagnosis includes

epidermolysis bullosa acquisita, cell-poor bullous pemphigoid or porphyria cutanea tarda/pseudoporphyria. Recommend biopsy for direct immunofluorescence evaluation.

Sample Report: Porphyria Cutanea Tarda/Pseudoporphyria

Clinical history: 45-year-old man with blisters on dorsal hands.
Diagnosis: Subepidermal vesicular dermatitis consistent porphyria cutanea tarda or pseudoporphyria, see comment.
Comment: Sections demonstrate a non-inflammatory subepidermal blister with festooning of the dermal papillae. The papillary dermal blood vessels have thick walls. The histologic features are consistent with porphyria cutanea tarda or pseudoporphyria. These entities are histologically indistinguishable. Distinction requires an appropriate clinical evaluation.

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