

REVIEW ARTICLE

Mimickers of classic acantholytic diseases

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ABSTRACT

Acantholysis is a commonly encountered histological pattern which typically generates a differential of the pemphigus variants, Hailey–Hailey, Darier’s and Grover’s diseases. In addition to these diseases, the dermatologist and dermatopathologist must be aware of entities that mimic classic acantholytic dermatoses and of rare disease variants, which are characterized by acantholysis.

Key words: acantholysis, acantholytic dyskeratosis, epidermolysis bullosa, Galli–Galli disease, mimickers.

INTRODUCTION

Acantholysis is a histological phenomenon defined by loss of intercellular cohesion between keratinocytes, resulting in cell separation and a rounded cellular outline. It may or may not be accompanied by clinically apparent blisters. Keratinocyte junctions include the desmosomal junction, adherens junctions and tight junctions (Fig. 1). Of these, disruption of the desmosomal junction results in the histological pattern of acantholysis. The desmosomal junction is characterized by linkage of specialized transmembrane cadherin proteins, called desmosomes and desmocollins, to the keratin intermediate filament system (KIF) via a set of desmosomal plaque proteins (Fig. 1). Desmoglein (DSG) and desmocollin (DSC) have intercellular and intracytoplasmic components. The intercellular DSG–DSC complex of one keratinocyte interacts with that of adjacent keratinocytes, leading to cell stabilization. Plaque proteins desmoplakin, plakoglobin and plakophilin form the intermediary link between DSG–DSC and the KIF. Diseases affecting any of these structures may potentially lead to acantholytic disease.

In a given dermatosis, simple acantholysis may be the major pathological finding (“bland acantholysis”) (Fig. 2) or accompanied by significant dyskeratosis (Fig. 3). The classic cell types associated with this dyskeratotic acantholysis include corp ronds and grains. Corp ronds demonstrate a rounded basophilic nucleus with a clear perinuclear halo, surrounded by intensely eosinophilic cytoplasm. Grains are thought to represent older corp ronds and are characterized as elongate cells, with small hyperchromatic nuclei and a brightly eosinophilic cytoplasm. Some diseases primarily exhibit “bland” acantholysis, typified in the autoimmune-mediated pemphigus group (Fig. 2), while others are characterized by varying degrees of acantholytic dyskeratosis as seen in the genodermatoses Darier’s and Hailey–Hailey diseases (Fig. 3). Grover’s disease (transient acantholytic dermatosis, TAD) may demonstrate bland or dyskeratotic acantholysis, often with a mixture of both

patterns. Acantholysis is also commonly present in epidermal malignancies and premalignant conditions such as squamous cell carcinomas and actinic keratoses (Fig. 4). The keratinocytic dysplasia and typical architecture of these entities usually allow for easy distinction from inflammatory and heritable acantholytic diseases. Additionally, despite these classic and widely appreciated disease associations, certain uncommon acantholytic dermatoses and rare acantholytic variants of genodermatoses, which are typically devoid of this feature, have been described (Table 1). This paper will review these entities along with diseases that may demonstrate acantholysis and mimic primary acantholytic dermatoses.

INFLAMMATORY AND INFECTIOUS DISEASES

Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) is a papulosquamous disorder with characteristic clinical and histopathological findings. Classic disease occurs in elderly patients who present with erythematous patches and thin plaques demonstrating intervening islands of normal appearing skin (islands of sparing). The rash begins on the head and spreads caudally. Lesions exhibit a peculiar red-orange hue with focal areas of follicular prominence. Palmoplantar keratoderma (PPK) is common. Six variants have been described including classic adult, atypical adult, classic juvenile, circumscribed juvenile and HIV-associated onset.¹ Histopathologically, PRP is characterized by hyperkeratosis with alternating layers of ortho- and parakeratosis, follicular plugging, mild to moderate psoriasiform epidermal hyperplasia and mild spongiosis. In comparison with psoriasis, the granular layer is typically preserved, though focal hypogranulosis may be observed. Occasionally, acantholysis can be seen (Fig. 5). Though initially reported to be suprabasilar in location, acantholysis at all levels of the epidermis has been documented.^{2–4} Both bland and dyskeratotic acantholysis have been reported with cases resembling pemphigus vulgaris,

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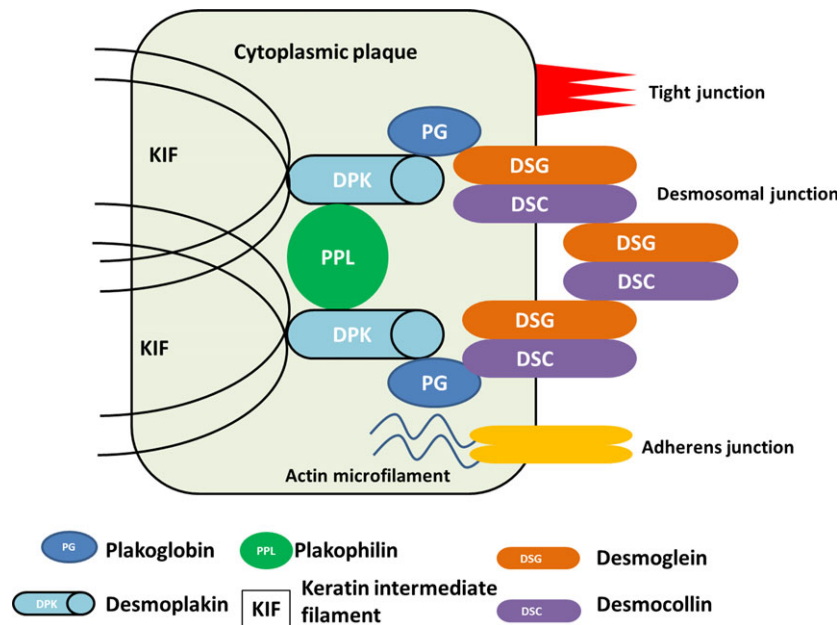


Figure 1. Keratinocyte junctions. Note desmosomal, adherens and tight junctions. The desmosomal junction is characterized by specialized transmembrane cadherin proteins (desmogleins and desmocollins), linked to the keratin intermediate filament system via a combination of plaque proteins (desmoplakin, plakoglobin and plakophilin). Diseases affecting any of these proteins may lead to acantholysis.

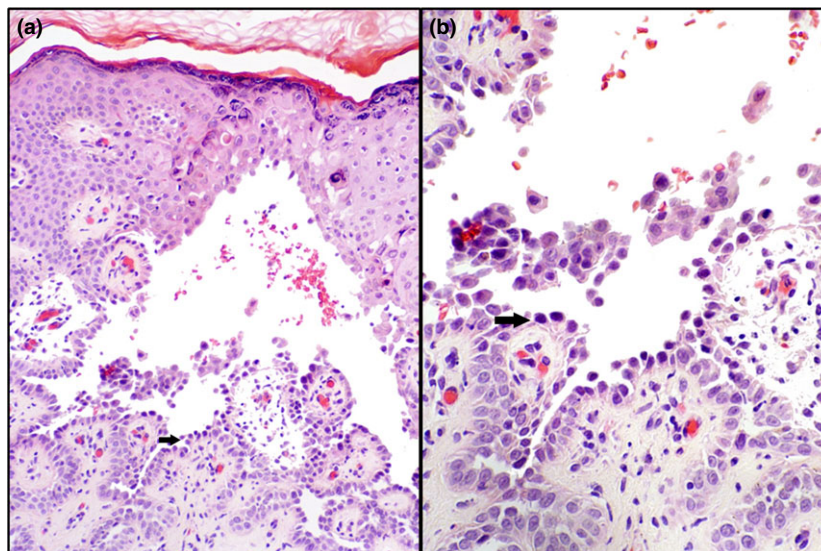


Figure 2. (a,b) Suprabasal acantholysis with “tombstoning” (arrow) characteristic of pemphigus vulgaris. Note minimally dyskeratotic “bland acantholysis” (hematoxylin–eosin, original magnifications: [a] ×100; [b] ×200).

pemphigus foliaceus (PF), Darier’s or Hailey–Hailey diseases.^{2–7} Acantholysis in PRP may predate the development of characteristic histopathological features, often leading to the incorrect diagnosis of a primary acantholytic disease.⁷ No association between the presence of acantholysis and disease severity has been reported.

Bullous impetigo

Impetigo is a contagious superficial pyoderma, most commonly seen in children. It is caused by infection with *Staphylococcus aureus* or group A β-hemolytic streptococcus, often following minor trauma, an arthropod bite, shallow abrasions or superficial burns. Non-bullous (common impetigo) and

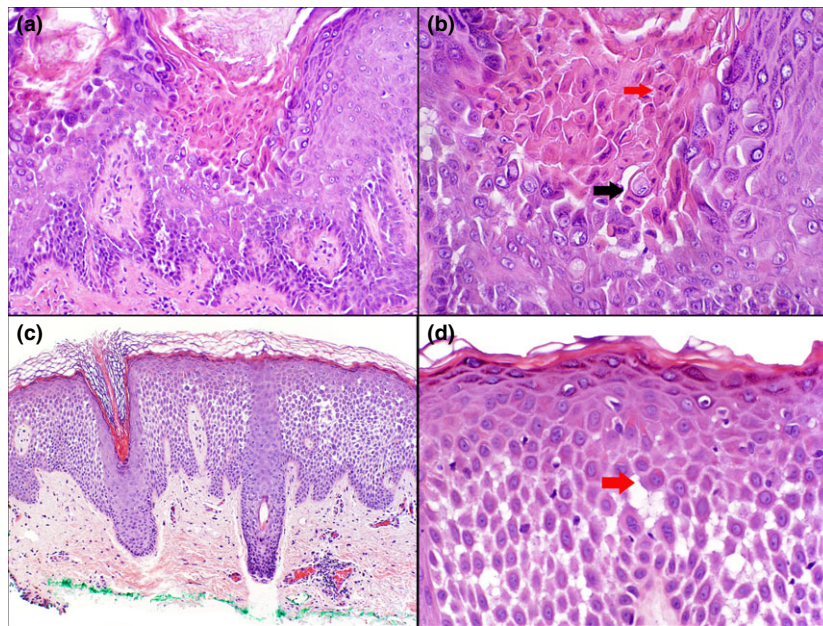


Figure 3. Acantholytic dyskeratosis. (a,b) Darier-type pattern with suprabasal acantholysis and well-formed corp ronds (black arrow) and grains (red arrow) and (c,d) Hailey-Hailey-type pattern with intraepidermal and suprabasal acantholysis, a “dilapidated brick wall” appearance and mild dyskeratosis (red arrow) without prominent corp ronds or grain formation (hematoxylin–eosin, original magnifications: [a] $\times 100$; [b] $\times 200$; [c] $\times 40$; [d] $\times 100$).

bullous forms are seen. Bullous impetigo is only seen with *S. aureus* infection. Common impetigo presents with shallow erosions covered by honey-colored crusts, frequently affecting the perioral and perinasal face as well the extremities. Bullous impetigo occurs in a similar distribution but also frequently involves the perineum. Histologically, common impetigo displays intra- and subcorneal collections of neutrophils and basophilic debris. Rare acantholytic cells may be present near the roof of the pustule but acantholysis is subtle in this subtype. A superficial perivascular lymphocytic infiltrate and interstitial neutrophilic infiltrate is noted. Gram-positive cocci are seen within the neutrophils and extracellularly. Bullous variants show a subcorneal blister, which may contain neutrophils, keratinocytic debris and occasional Gram-positive cocci. Subcorneal/intragranular acantholysis (Fig. 6) is more prominent than in common impetigo due to lysis of DSG1 by locally produced staphylococcal exfoliatin toxins A and B.⁸ This pattern of acantholysis is identical to PF. In PF, subcorneal neutrophils and debris are less prominent than in impetigo and bacterial colonies are not common, though secondary impetiginization may occur. A milder superficial perivascular lymphocytic infiltrate with occasional eosinophils and eosinophilic exocytosis may also point to an autoimmune etiology. Most importantly, the characteristic clinical presentation of impetigo should lead to the correct diagnosis. In the highly improbable scenario that the clinical data does not definitively differentiate these entities, direct immunofluorescence performed on perilesional skin will reveal

intercellular immunoglobulin G with/without C3 in PF and will be negative in bullous impetigo.

Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome (SSSS) is an uncommon staphylococcal exfoliatin toxin-mediated disease, which most commonly affects infants and young children. Unlike bullous impetigo, the widespread blistering seen in SSSS is caused by hematogenous dissemination of the toxins, often from a nasopharyngeal, conjunctival or perianal focus.⁹ Clinical features include sheet-like flaccid blisters with predilection for the flexural areas and perioral face. Mucosal involvement is absent. Exfoliatin toxins A and B cleave DSG1 as in bullous impetigo, leading to PF-type acantholysis.¹⁰ Unlike bullous impetigo, subcorneal neutrophils, debris and bacterial colonies are often absent, even further mimicking PF (Fig. 6). In the absence of a sample for immunofluorescence, the clinical data is most important in distinguishing these entities. Widespread sheet-like flaccid blistering is not a feature of PF. Additionally, childhood PF is exceedingly rare, except in areas where endemic PF (Fogo Selvagem) occurs. Adult cases without the benefit of a sample for immunofluorescence may present diagnostic challenges in the absence of detailed clinical data, as “widespread blistering” in this age group is more commonly attributed to PF than to SSSS. In these cases, clinician–pathologist communication and careful review of the morphology and distribution of the disease, as well as a search for comorbidities, such as chronic renal disease and causes of

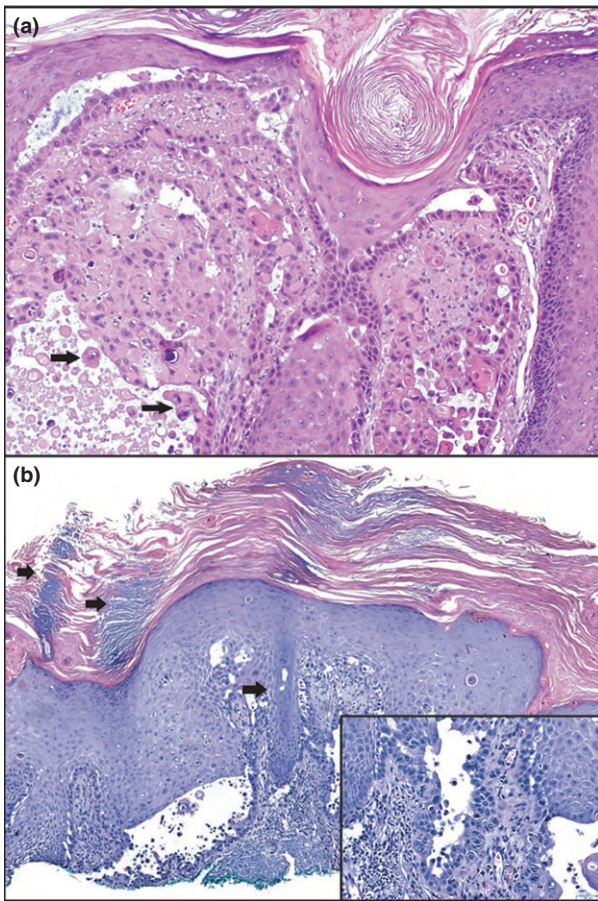


Figure 4. (a) Acantholytic squamous cell carcinoma and (b) acantholytic actinic keratosis. Note acantholytic cells with marked cytological atypia in squamous cell carcinoma (a, arrows) and (b) typical acrosyringal and follicular sparing (arrows) in the actinic keratosis (hematoxylin–eosin, original magnifications: [a] $\times 100$; [b] $\times 40$; insert, $\times 200$).

immunosuppression, which increase the risk of adult SSSS, should clarify doubt and obviate the need for immunofluorescence testing.

Viral infections

Human herpes viruses (HHV) frequently involve the skin. Of the eight HHV, HHV-1 (herpes simplex virus 1, HSV-1), HHV-2 (HSV-2) and HHV-3 (varicella zoster virus, VZV) are characterized by an intraepidermal blister. In well-developed lesions, recognition of reticular and ballooning degeneration of keratinocytes, multinucleate keratinocyte giant cells exhibiting nuclear molding and a characteristic steel-gray nucleus which lacks a nucleolus and demonstrates chromatin margination, allow for easy diagnosis. Though readily appreciated in the company of well-developed viral cytopathic change, acantholysis is often overlooked as a diagnostic clue. Its usefulness increases in two settings: that of an eroded vesicle or old lesion where obvious viral cytopathic features are obscured by

Table 1. Dermatoses exhibiting acantholysis

Dermatoses which exhibit acantholysis	
<ul style="list-style-type: none"> ● Heritable <ul style="list-style-type: none"> ○ Darier's disease ○ Hailey–Hailey disease ○ Familial dyskeratotic comedones ○ Lethal acantholytic epidermolysis bullosa ○ Epidermolysis bullosa simplex Dowling–Meara type ○ Acantholytic epidermolysis bullosa (Weber–Cockayne-like syndrome) ○ Striate palmoplantar keratoderma ○ Galli–Galli disease ○ Mal de Meleda keratoderma ● Inflammatory (acantholysis commonly seen) Autoimmune <ul style="list-style-type: none"> ○ Pemphigus vulgaris <ul style="list-style-type: none"> ■ Pemphigus vegetans ■ Pemphigus herpetiformis (subset) ○ Pemphigus foliaceus <ul style="list-style-type: none"> ■ Fogo selvagem ■ Pemphigus erythematosus ■ Pemphigus herpetiformis (subset) ○ IgA pemphigus <ul style="list-style-type: none"> ■ Subcorneal pustular dermatosis type ■ Intraepidermal neutrophilic type Non-autoimmune <ul style="list-style-type: none"> ○ Grover's disease 	<ul style="list-style-type: none"> ● Inflammatory (uncommonly exhibits acantholysis) <ul style="list-style-type: none"> ○ Pityriasis rubra pilaris ○ Acantholytic dermatosis of the genitocrural area ○ Relapsing linear acantholytic dermatosis ● Infectious <ul style="list-style-type: none"> ○ Bullous impetigo > common impetigo ○ Staphylococcal scalded skin syndrome ○ HSV/VZV infection ● Physical agents <ul style="list-style-type: none"> ○ Cantharidin and pederin dermatitis ○ Thermal acantholysis ○ EMLA® acantholysis ● Hamartomatous/neoplastic <ul style="list-style-type: none"> ○ Warty dyskeratoma ○ Acantholytic dyskeratotic acanthoma ○ Squamous cell carcinoma ○ Actinic keratoses ○ Acantholytic dyskeratotic epidermal nevus ● Incidental focal acantholytic dyskeratosis

IgA, immunoglobulin A; HSV, herpes simplex virus; VZV, varicella zoster virus.

secondary changes and in herpetic folliculitis. In our experience, the clinical impression of a solitary eroded vesicle is often that of a non-melanoma skin cancer. Though easily overlooked, the recognition of rare acantholytic cells at the edge of an eroded lesion (Fig. 7) is crucial to avoid misdiagnosis. Examination of additional levels will often reveal focal diagnostic viral cytopathic change, though multiple recuts may be required. In the case of herpetic folliculitis, acantholytic cells within follicular epithelium, especially if accompanied by individually necrotic keratinocytes, should raise suspicion for involvement by HSV/VZV. Demonstration of classic herpetic change is usually possible on deeper levels. Care must be taken however not to overdiagnose herpetic folliculitis, as many cases of conventional bacterial folliculitis may also

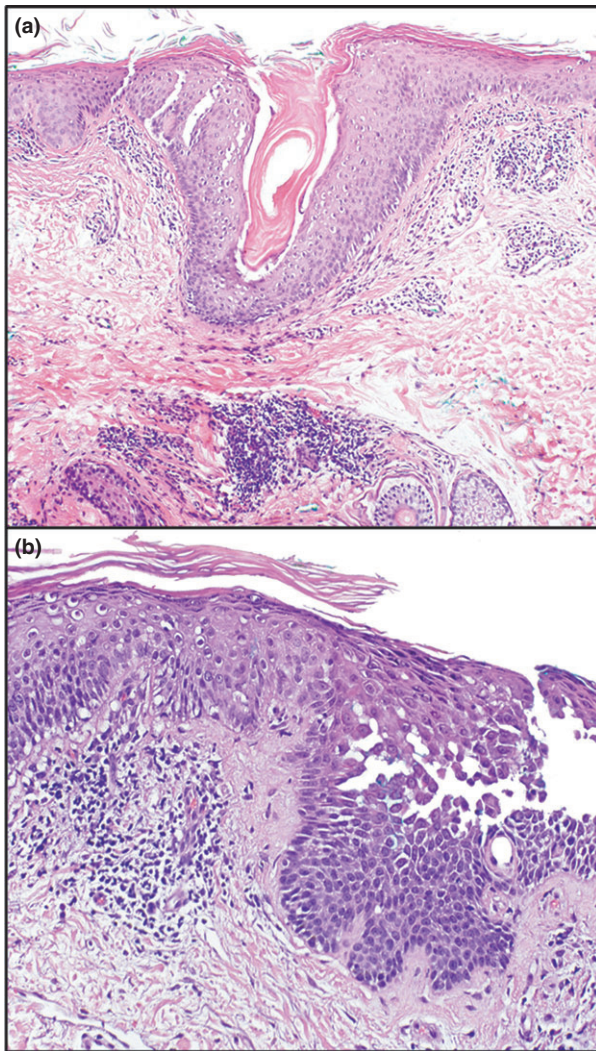


Figure 5. (a) Classic changes of pityriasis rubra pilaris exhibiting hyperkeratosis, a retained granular layer, acanthosis and follicular plugging. (b) Other areas in the biopsy demonstrate intraspinous acantholysis with mild dyskeratosis. This pattern closely resembles that of Hailey–Hailey disease (hematoxylin–eosin, original magnifications: [a] $\times 100$; [b] $\times 200$).

demonstrate HSV-like acantholysis and even keratinocyte multinucleation. Though nuclear molding may occur, multinucleate cells in non-herpetic folliculitis retain their normal nuclear microanatomy, preserving their nucleoli and lacking the steel-gray color and chromatin margination characteristic of HSV infection.

ACANTHOLYTIC VARIANTS OF RARE GENODERMATOSES

Much attention has been paid to the prototypical acantholytic (and dyskeratotic) genodermatoses including Darier's disease and Hailey–Hailey disease. Other rare, but important,

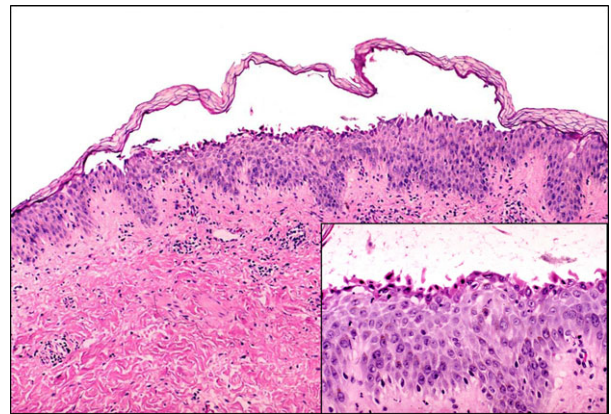


Figure 6. Bullous impetigo demonstrating a subcorneal blister with subtle bland acantholysis (insert). Note the lack of inflammatory cells and bacterial colonies within the blister cavity. This pattern of acantholysis is identical to that seen in pemphigus foliaceus and staphylococcal scalded skin syndrome (hematoxylin–eosin, original magnifications: $\times 40$; insert, $\times 200$). Reproduced from Bhawan J, Sau P and Byers R (2001, www.dermthatlas.com) with permission.

genodermatoses may at times manifest acantholytic changes and lead to diagnostic confusion. Most of these diseases result from mutations in structures affecting desmosomal plaque proteins or the KIF cytoskeleton. Why some variants with near identical genetic aberrations display acantholysis and others do not is currently a mystery.

ACANTHOLYSIS IN INHERITED EPIDERMOLYSIS BULLOSA

Heritable epidermolysis bullosa (EB) groups of disorders are rare autosomal dominantly or recessively inherited mechanobullous diseases. Acantholysis is not frequently associated with EB.¹¹ Classically divided into EB simplex (EBS), junctional EB (JEB) and dystrophic EB (DEB), EB subtype designation is dependent on the ultrastructural level of blister formation. EBS is characterized by intraepidermal cleavage, most often very low within basal keratinocytes, giving the appearance of a subepidermal blister, though less commonly superficial variants occur. JEB demonstrates a split through the lamina lucida, while DEB exhibits a sublamina densa plane of cleavage. Intraepidermal EB (EBS) is associated with cell-poor blister formation, typically in the absence of acantholysis.¹² Exceptionally, acantholysis is a prominent finding and may occur in three subtypes of EBS, namely, lethal acantholytic EB (LAEB), Dowling–Meara (DM) and an acral acantholytic Weber–Cockayne-like subtype.^{13–15}

Lethal acantholytic EB is an exceptionally rare form of EBS. Patients present with generalized cutaneous denudation beginning at birth with associated mucosal involvement. Numerous epithelial surfaces may be involved including respiratory, gastrointestinal and genitourinary tracts. Additional clinical findings include generalized alopecia, anonychia and natal teeth.^{14,16,17} Death typically results from massive transepithelial fluid loss and cardiac decompensation.^{14,17} A mutation in the gene

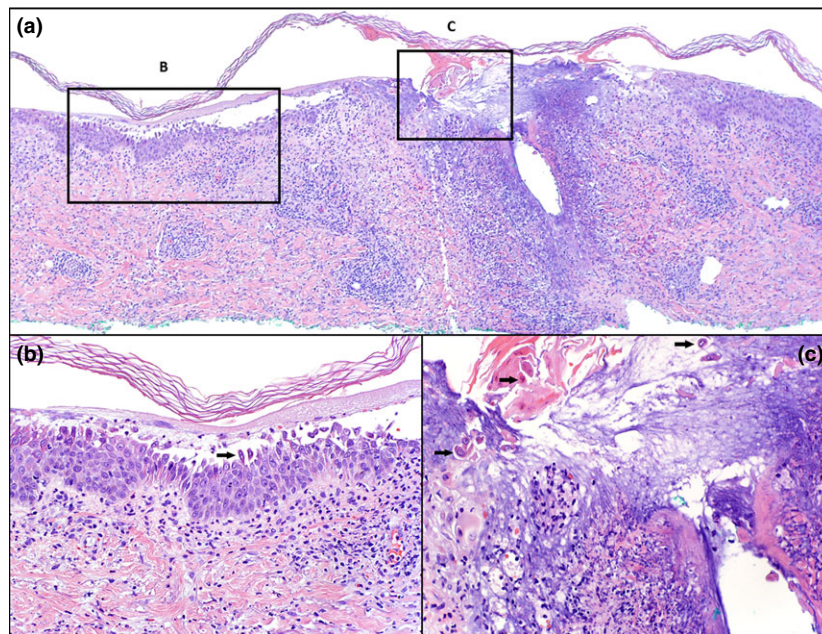


Figure 7. (a,c) Herpetic infection exhibiting subcorneal acantholysis closely mimicking bullous impetigo, staphylococcal scalded skin syndrome or pemphigus foliaceus. Note subtle steel gray nucleus (b, arrow) and chromatin margination (arrows, b and c) diagnostic for herpetic viral cytopathic change. Acantholysis and necrosis of follicular epithelium should prompt examination for changes of herpetic infection (hematoxylin–eosin, original magnifications: [a] $\times 40$; [b,c] $\times 200$).

encoding the cytoplasmic plaque protein desmoplakin is suspected to cause LAEB.^{16,17} As the protein desmoplakin serves as a link between transmembrane cadherin proteins DSG and DSC and the KIF system via plakoglobin attachment, mutations in this gene leads to loss of desmosomal cell–cell adhesion resulting in acantholysis (Fig. 1). This loss of adhesion leads to retraction of the KIF, further demonstrated by a clumped perinuclear localization of keratin filaments on immunofluorescence microscopy, as opposed to the normal diffuse pattern.¹⁴ The histopathological correlate is diffuse bland suprabasal acantholysis, with tombstoning of basal keratinocytes and involvement of adnexal epithelium, closely mimicking pemphigus vulgaris.^{14–18} Lack of maternal pemphigus, intercellular keratinocyte deposition of immunoreactants and circulating antibodies against DSG proteins should clarify the diagnosis.

Rare cases of DM-EBS with prominent acantholysis have been reported.^{13,19} DM-EB is a severe type of classic EBS, resulting from mutations in genes encoding basal keratinocyte intermediate filaments 5 and 14 (*KRT5/14*) with the unique ultrastructural abnormality of clumped tonofilaments, as seen on electron microscopy.^{13,19–21} Patients present with widespread, often hemorrhagic, blistering at birth, sometimes displaying arciform or grouped configurations. Nail, hair and dentition abnormalities are also present.^{13,19–21} A case with clinical and ultrastructural features consistent with DM-EBS has been reported, with prominent acantholysis-mimicking pemphigus vulgaris or LAEB.¹⁹ Though the exact mechanism of acantholysis is not clearly understood, additional findings of dyskeratosis due to tonofilament clumping, somewhat similar to that seen in Darier’s disease, and the observation that

severe keratin mutations downregulate other cell junction proteins, including desmosomal proteins, may suggest that severe keratin mutations induce acantholysis indirectly.²²

A single case described as “acantholytic epidermolysis bullosa” reported a kindred with an acraly distributed mechanobullous disease closely resembling Weber–Cockayne EBS. Suprabasal pemphigus vulgaris-like acantholysis was noted, and electron microscopy revealed tapered microvilli, sparse desmosomes and thickened tonofilaments.¹⁵

Acantholysis in heritable PPK

The inherited PPKs are a rare group of genodermatoses characterized by excessive hyperkeratosis of the palms and soles. Various clinicopathological classifications exist, the most useful of which delineates causes of diffuse versus focal keratodermas as well as the association of additional associated cutaneous and extracutaneous findings. Whereas distinct PPK variants associated with epidermolytic hyperkeratosis are well appreciated, less common acantholytic variants are also described. In particular, the focal variant striate PPK (SPPK), due to mutations in desmosomal protein DSG1 (*DSG1*), is associated with marked hyperkeratosis and acantholysis. Like PF, which demonstrates antibodies against *DSG1*, acantholysis in *DSG1*-associated SPPK is limited to the upper spinous and granular layers. Significant dyskeratosis did not seem to be a feature in these reports.^{23,24} Widening of spinous layer intercellular spaces was also noted in biopsies from patients with desmoplakin-mutation associated SPPK.²⁵ The reason for excessive hyperkeratosis rather than frank vesiculobullous disease in these keratodermas is currently unclear, though as

previously discussed, the presence of acantholysis is unsurprising given the importance of the desmosome in keratinocyte adhesion. The cardiomyopathy woolly hair-PPK diseases, Carvajal syndrome and Naxos disease, are also caused by mutations of genes encoding desmoplakin and another desmosomal protein plakoglobin, respectively. Frank acantholysis has been reported in a patient with a Carvajal syndrome-like presentation.²⁶ Additionally, a single case report documents a case of a desmoplakin mutation-associated epidermolytic bullous dermatosis with lethal cardiomyopathy in the absence of hair or teeth findings, which displayed bland acantholysis affecting the epidermal spinous layer.²⁷

Interestingly, a case clinically diagnosed as the rare trans-grediens Mal de Meleda PPK (AR mutation in *SLURP-1*) has also been reported with Hailey–Hailey-like acantholysis.²⁸ The genesis of this change is unclear at this time.

Galli–Galli disease (acantholytic Dowling–Degos disease)

The Dowling–Degos family of diseases (DDD) is most commonly due to AD mutations in *KRT5*.²⁹ Key features include adolescent onset of reticulate hyperpigmentation of the flexures and perioral acneiform scars. Elongation of rete ridges, increased basal keratinocyte pigmentation and occasional horn-cysts characterize typical DDD. Galli–Galli disease (GGD) presents with identical findings, often with the addition of erythematous, scaly papules. In addition to typical histological changes of DDD, GGD demonstrates subtle suprabasal acantholysis with focal dyskeratosis on biopsy (Fig. 8).^{30–32} Recent data has confirmed shared *KRT5* mutations in GGD and DDD.³³ The frequently truncal location of the papules of GGD and the presence of subtle acantholysis (Fig. 8) may easily lead to a misdiagnosis of Grover’s disease (TAD). Recognition of the peculiar seborrheic keratosis-like elongation of the rete ridges, often with intervening epidermal atrophy and increased basal layer keratinocyte pigmentation, are valuable clues in distinguishing these entities. When present, “antler-like” bifurcations of a bulbous rete are also a helpful clue (Fig. 8).

Familial dyskeratotic comedones

Familial dyskeratotic comedones is an uncommon comedonal dermatosis inherited in an AD fashion and presents as small

hyperkeratotic and crateriform papules with predilection for the limbs. Histological features include hyperkeratosis, a crateriform epidermal invagination, acantholysis and grain-type dyskeratosis.^{34–36}

ACANTHOLYSIS DUE TO PHYSICAL AGENTS

Thermal burns

It is not uncommon to see blisters in a thermal injury. Typically, blisters are seen in second-degree burns and are usually subepidermal in location.³⁷ However, rarely intraepidermal blistering occurs with acantholysis as observed in the biopsy of a man with heat injury due to overnight contact with a heating pad. The resulting suprabasal acantholysis closely mimicked pemphigus vulgaris, which could lead the unwary pathologist astray (Fig. 9). A useful clue to the thermal etiology of the acantholysis is elongate or spindly morphology of the acantholytic cells.

Blister beetle dermatitis (including cantharidin-induced acantholysis)

From the order Coleoptera, three families of beetles, Meloidae, Oedemeridae and Staphylinidae (“blister beetles”) are known to secrete vesicant chemicals.^{38–40} Insects from both Meloidae and Oedemeridae families produce cantharidin, in contradistinction to those of the family Staphylinidae, which release pederin.³⁸ The most well-known of these beetles is the cantharidin-producing meloid *Lytta (cantharis) vesicatoria* (Spanish fly), followed by the Staphylinidae pederin-producing beetles of the genus *Paederus*. Cantharidin-associated eruptions typically present as bullae arising on non-inflamed skin, whereas those caused by *Paederus* are characterized by a significant inflammatory component, often with a vesiculopustular appearance and prominent urtication.³⁸ All blister beetle dermatitis is characterized by epidermal necrosis with significant acantholysis.^{38–40} In the setting of a sudden vesiculobullous eruption, the histological picture closely imitates that of pemphigus vulgaris, including a superficial perivascular lymphocytic infiltrate with scattered eosinophils. Clinical data detailing localized, linear or a mirror image or “kissing lesion” distribution and morphology, as well as negative immunofluorescence studies, help to clarify the diagnosis. Additionally, cantharidin has been used for many conditions by both folk and traditional medicine, being employed frequently in

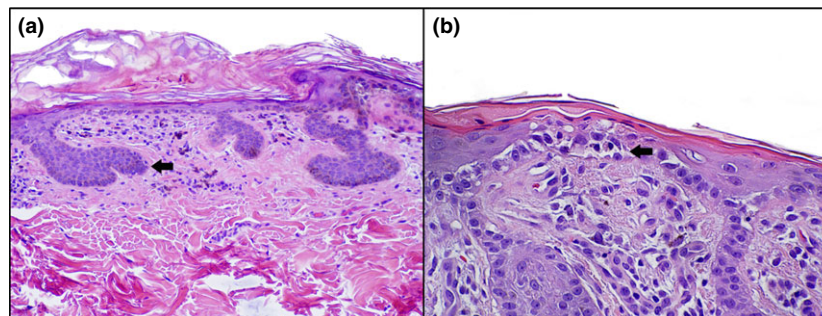


Figure 8. (a) Galli–Galli disease with “antler-like” bifurcation of bulbous rete ridges (arrow), intervening epidermal atrophy and (b) subtle suprabasal acantholysis (arrow) and dyskeratosis (hematoxylin–eosin, original magnifications: [a] $\times 100$; [b] $\times 200$).

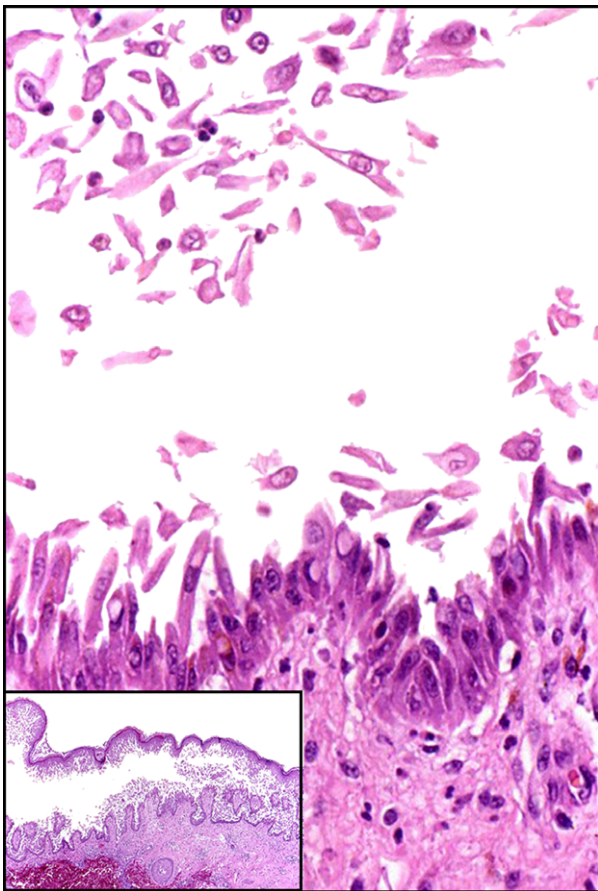


Figure 9. Heat-induced acantholysis. Note intraepidermal blister (insert) with suprabasal acantholysis and “tombstoning” appearance of basal keratinocytes. Elongation of keratinocytes including acantholytic cells is an important clue to avoid misdiagnosis of pemphigus vulgaris (hematoxylin–eosin, original magnifications: $\times 200$; insert, $\times 40$).

the treatment of verruca vulgaris and molluscum contagiosum.^{41,42} Biopsy of a lesion treated in this way will demonstrate typical findings of blister beetle vesiculation.

EMLA[®]-induced acantholysis

EMLA[®] (eutectic mixture of 2.5% lidocaine and prilocaine in oil and water; APP Pharmaceuticals, Schaumburg, IL, USA) is used as a topical anesthetic agent. Side-effects are uncommon, though irritant, allergic and purpuric reactions have been reported.^{43–45} A recent case series identified three patients with vulvar lichen planus in whom EMLA[®] was applied prior to performing a biopsy. Two of the patients' biopsies demonstrated acantholysis while the third showed full-thickness epidermal necrosis and congestion of papillary dermal vessels. The superficial acantholysis was present in both cases and one case demonstrated suprabasal acantholysis.⁴⁶ Recognition of this entity is important to avoid diagnostic pitfalls, as a clinical history of mucosal erosions and the pathological finding of acantholysis may lead to misdiagnosis of an autoimmune

blistering disease, prompting unnecessary additional investigations and increased patient anxiety.

UNCOMMON DERMATOSES CHARACTERIZED BY ACANTHOLYSIS WITH DYSKERATOSIS

As stated earlier, the finding of acantholytic dyskeratosis is most commonly associated with Darier's, Hailey–Hailey and Grover's diseases. This finding, however, is not unique to the aforementioned entities and is a key finding in other less commonly encountered diseases. These are outlined below.

Relapsing linear acantholytic dermatosis

This rare condition is characterized by a blaschkolinear papular eruption, which undergoes an unusual waxing and waning pattern, with reports of complete resolution followed by recurrent crops of lesions.⁴⁷ The majority of cases are reported in children though one case was reported in an 81-year-old man. Histology is identical to Hailey–Hailey disease, with spinous layer acantholysis and subtle dyskeratosis.^{47,48} The exact relationship with Hailey–Hailey is unknown, though the clinical presentation is somewhat unusual for classic variants of the disease.

Acantholytic dermatosis of the genitocrural area

Also known as papular acantholytic dermatosis of the vulvocru-ral area, this entity has been described in males.⁴⁹ Clinically, it presents as white to tan papules (and occasionally as a solitary lesion) on the labia majora, scrotum, penis, perianal area and upper medial thighs.^{50,51} Biopsies demonstrate acantholytic dyskeratosis of the Darier or Hailey–Hailey type, with some lesions demonstrating the cup-shaped epidermal architecture of a warty dyskeratoma (Fig. 10).^{49–51} Patients do not have a family history or other features of an acantholytic dyskeratotic genodermatosis, and recognition of this entity is imperative to avoid overdiagnosis of these entities. These lesions can share histopathological features similar to acantholytic dyskeratotic acanthoma (see below) but the location is important in differentiating these entities.

Warty dyskeratoma

This relatively common benign tumor typically presents as a solitary umbilicated papulonodule on the head and neck of adults. Rare cases of multiple lesions have been reported.⁵² The histopathological features are striking, demonstrating a cup-shaped epidermal invagination filled with keratotic debris, grains, corp ronds and prominent suprabasal acantholysis with the formation of “villi” (Fig. 11). A mild superficial lymphocytic infiltrate is often present. This pattern of acantholytic dyskeratosis is identical to that seen in Darier's disease. Recognition of the solitary nature of the lesion and the prominent cup-shaped architecture help to avoid misdiagnosis.

Acantholytic dyskeratotic acanthoma

These are commonly encountered entities in the dermatopathology setting, though often unfamiliar to persons in clinical practice. Lesions present as solitary papules on the

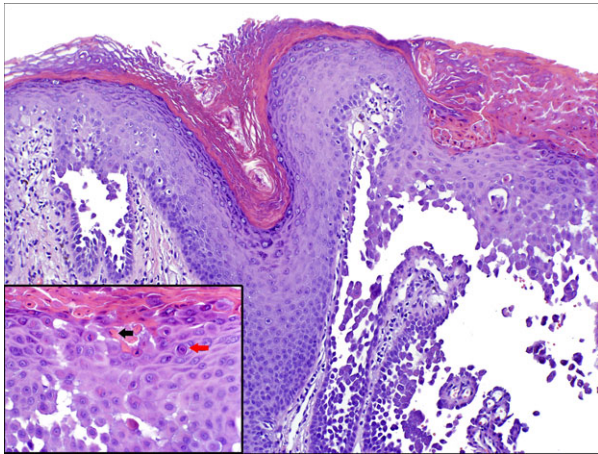


Figure 10. Papular acantholytic dermatosis of the genitocrural area. Note Darier-like acantholytic dyskeratosis with subtle corp rone (red arrow) and grain formation (black arrow) (hematoxylin–eosin, original magnifications: $\times 40$; insert, $\times 200$).

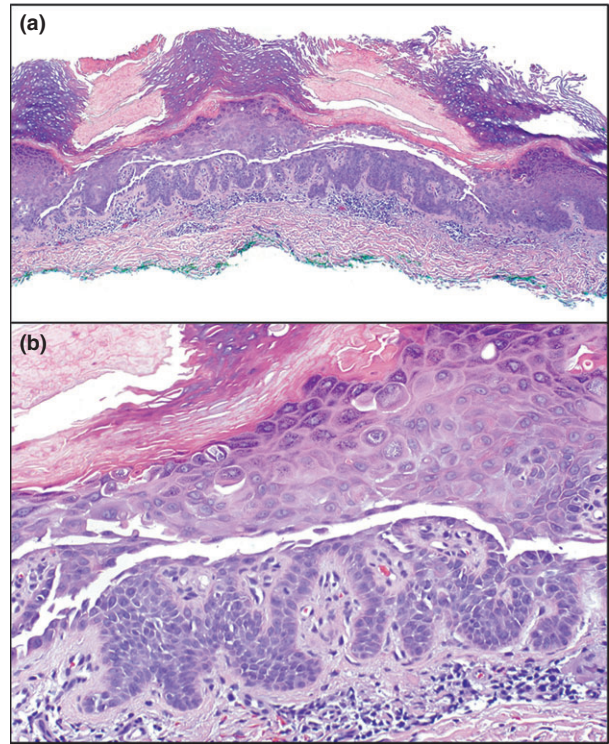


Figure 12. (a,b) Acantholytic acanthomas demonstrate hyperkeratosis, acanthosis (often seborrheic keratosis-like) and in the example Darier-type acantholytic dyskeratosis. Note the lack of a cup-shaped invagination separating this entity from warty dyskeratoma (hematoxylin–eosin, original magnifications: [a] $\times 40$; [b] $\times 200$).

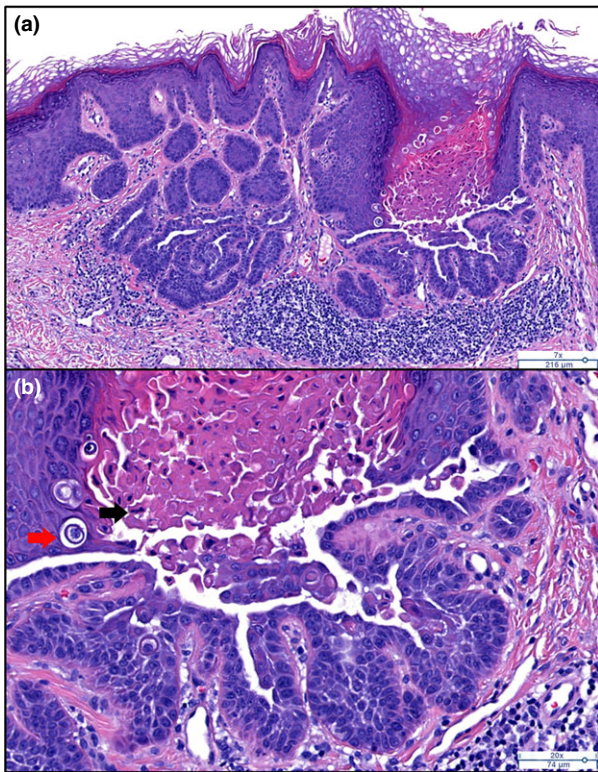


Figure 11. (a) Cup-like architecture with prominent Darier-type acantholytic dyskeratosis characteristic of warty dyskeratoma. (b) Note corp rone (red arrow) and grain (black arrow) formation. In the absence of good clinical data, the misdiagnosis of Darier's disease may occur (hematoxylin–eosin, original magnifications: [a] $\times 70$; [b] $\times 100$).

trunk or occasionally as longitudinal erythronychia.⁵³ The lesions are commonly clinically suspected to be basal cell carcinomas.^{53,54} Hyperkeratosis, well-demarcated, regular acanthosis and Darier-type acantholytic dyskeratosis at all levels of the epidermis comprise the histological picture (Fig. 12). Variants with bland acantholysis, mimicking pemphigus vulgaris or foliaceus have also been described.⁵⁵

Acantholytic dyskeratotic epidermal nevus

A handful of case reports highlighting Darier-like acantholytic dyskeratosis within linear epidermal nevi have been published.^{56–58} In addition to acantholytic dyskeratosis, the lesions demonstrated typical histological changes of epidermal nevus including hyperkeratosis and papillomatous epidermal hyperplasia. These lesions were often congenital and exhibited blaschkolinearity. The patients did not have other features of Darier's disease. Because genetic testing was not performed in all cases, the relationship to type 1 mosaic linear Darier's disease cannot be clearly defined, though the congenital nature, lack of family history and the absence of typical genetic aberrations in those tested does seem to support the existence of a distinct acantholytic dyskeratotic epidermal nevus. Clinico-pathological correlation and genetic testing may be required to

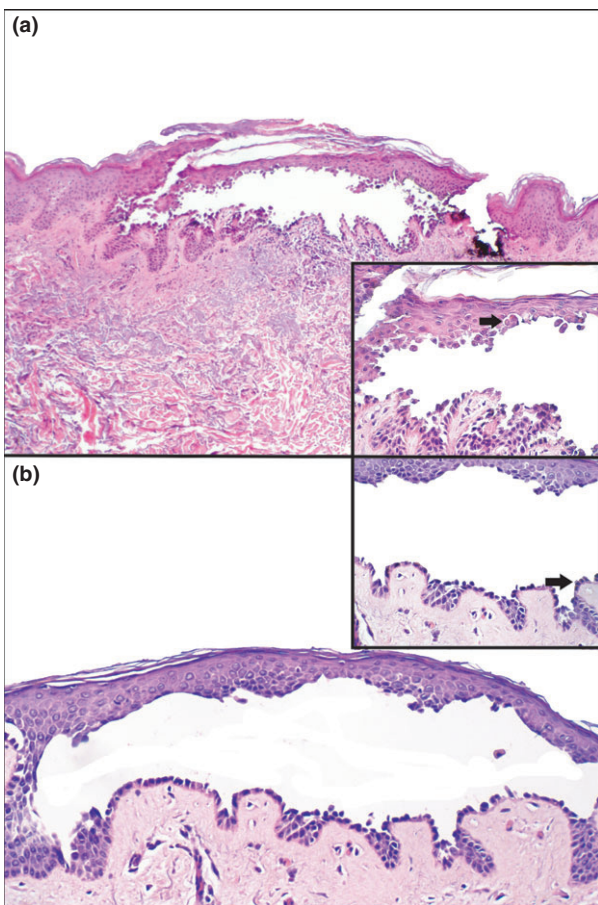


Figure 13. (a,b) Focal (incidental) acantholytic dyskeratosis. Both examples show suprabasal acantholysis (a) exhibiting mild Hailey-Hailey type dyskeratosis (arrow) and (b) more closely resembling the bland acantholysis of pemphigus vulgaris (arrow) (hematoxylin-eosin, original magnifications: [a] $\times 40$; inset, $\times 100$; [b] $\times 40$; inset, $\times 100$).

distinguish mosaic Darier's disease from this non-syndromic hamartoma.

Focal acantholytic dyskeratosis

Acantholytic dyskeratosis is a not infrequent finding in otherwise normal skin. Acantholysis in these cases is often of the Darier or Hailey-Hailey type, though pemphigus vulgaris or even foliaceus change can be seen less commonly. The term focal acantholytic dyskeratosis (FAD) is ascribed when this finding is seen incidentally, with no clinical correlate for the acantholysis. Many reports of acantholytic changes in the epidermis overlying or adjacent to a number of benign and malignant neoplasms have been reported including basal cell carcinoma (Fig. 13), dermatofibroma, keratoacanthoma, psoriasis, elastolytic granuloma, superficial fungal infections, leukocytoclastic vasculitis, angiomas and a verruciform xanthoma.⁵⁹⁻⁶² Some authors have suggested that the finding of FAD indicates generalized epidermal photodamage and is a precancerous

marker for mutagenesis and tumor development.⁶³ Conclusive evidence supporting this hypothesis is lacking, and further studies are needed to establish the relationship, if any, to photodamage-associated dysplasia.

CONCLUSION

In summary, acantholysis is a histological pattern, which may or may not be associated with dyskeratosis. When confronted with these patterns, the dermatopathologist must be able to generate a broad differential diagnoses which includes mimickers of classic acantholytic disorders and rare inflammatory, heritable and physical agent-associated acantholytic diseases.

CONFLICT OF INTEREST: None declared.

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