Classic Findings, Mimickers, and Distinguishing Features in Primary Blistering Skin Disease

Suzanne J. Tintle, MD, MPH; Allison R. Cruse, MD; Robert T. Brodell, MD; Buu Duong, MD

- **Context.**—Blistering diseases comprise a large group of clinically polymorphic and sometimes devastating diseases. During the past few decades, we have developed an elegant understanding of the broad variety of blistering diseases and the specific histopathologic mechanism of each.

- **Objective.**—To review examples of the classic findings of specific blistering diseases and emphasize the importance of considering unrelated conditions that can mimic the classic finding.

Blistering diseases comprise a large group of clinically polymorphic and sometimes devastating diseases. Historically, pemphigus and pemphigoid were broad terms used in the clinical description of blistering. Today, we have an elegant understanding of the broad variety of blistering diseases and the specific histopathologic mechanism of each. Often, clinical diagnosis is dependent on the skin biopsy and careful histopathologic evaluation to determine the exact location of the blister in relationship to the epidermis.

In approaching blistering diseases, there are 3 fundamental criteria to consider: (1) the site or level of the blister (or the lowest level of vesiculation): subcorneal, midepidermis, suprabasal, subepidermal; (2) the findings that implicate the mechanism of blister formation (spongiosis, acantholysis, blistering degeneration, or epidermolysis); and (3) the type of inflammation (neutrophilic, lymphocytic, eosinophilic, mixed), if present. A “top-down” approach (evaluating the histopathologic specimen beginning at the stratum corneum and moving inferiorly through the epidermis to the basement membrane zone [BMZ] and then the dermis) is recommended to characterize blistering processes with respect to these 3 criteria. Of course, any histopathologic diagnosis must be considered in the context of the clinical stage of disease, the stage of the blister, and the location of biopsy (perilesional, lesional, or nonlesional). For example, in a patient with bullous pemphigoid, a subepidermal blister that is 72 hours old may appear intradermal when re-epithelialization has begun. In contrast, intraepidermal blisters can appear subepidermal if the blister “blows out” into the subepidermal zone or if there is prominent papillary dermal edema.

Biopsy technique also plays a role in the histopathologic evaluation of blistering diseases. Autoimmune blistering diseases are associated with autoantibodies that target specific components of the stratified epithelia or BMZ. In these cases, direct immunofluorescence (DIF) is often critical in sample analysis. Optimally, the clinical characteristics of the blister and the histologic differential diagnosis will be considered in the approach to biopsy. For example, in the setting of widespread tense blisters, 1 of 3 approaches is recommended: (1) choose a small (1–2 mm) blister and remove in entirety with an 8-mm punch with the blister at the center of the punch. Bisect and submit half for hematoxylin–eosin (H&E) staining and half for DIF; (2) biopsy the edge of a large blister using a 6- or 8-mm punch, after using a marker to delineate the line along which the specimen is bisected to provide half for H&E and half for DIF; or (3) take 2 biopsies. The first biopsy is taken at the edge of a blister, including approximately 10% blister and 90% perilesional skin, and the specimen is bisected at the bedside to demonstrate the “take-off” point of the blister for H&E. The second biopsy is taken from perilesional skin (1 cm from lesional skin) and is submitted for DIF (Figure 1). In each situation, the H&E specimen is placed in formalin and the DIF specimen is placed in Zeus or Michel media.

Pathologists and clinicians must work together to ensure that the appropriate techniques and media are used. However, clinicians should be aware of the possibility of a degenerated stratum corneum and/or stratified epithelium.
which makes both H&E sections and DIF difficult for the pathologist to interpret.

This article reviews examples of the classic findings of specific blistering diseases and emphasizes the importance of considering unrelated conditions that can mimic the classic finding.

PEMPHIGUS FOLIACEUS MIMICKED BY STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Two subcorneal blistering diseases produce widespread superficial desquamation: pemphigus foliaceus (PF) and staphylococcal scalded skin syndrome (SSSS). When the latter disease shows acantholysis, it can mimic the former (Table 1).

Pemphigus foliaceus classically produces subcorneal blistering with acantholysis. Individual acantholytic cells can be identified floating in the blister lumen and may cling to the underside of the stratum corneum (“cling-ons”; Figure 2). This disease is caused by autoantibodies to desmoglein 1 (Dg1), a component of the desmosome, the adhesion molecule necessary for intercellular (keratinocyte-to-keratinocyte) adhesion. Because Dg1 is found primarily
in the granular layer (stratum granulosum), epidermal acantholysis in PF is mostly confined to the upper layers of the stratified epithelium. A “Acantholytic hypergranulosis,” a newly described finding of PF, refers to acantholytic keratinocytes in the superficial portion of the epidermis associated with large keratohyaline granules and may be seen in about one-third of cases.4

Essentially all patients with PF have positive DIF results demonstrating intercellular immunoglobulin (Ig) G throughout the epidermis, with heavier deposits characteristically seen in the upper epidermis.5

Pemphigus foliaceus is seen primarily in otherwise healthy middle-aged to elderly adults and presents with recurrent crops of fragile, flaccid bullae that are often ruptured by the time of presentation.1 Thus, exfoliative characteristics may predominate on exam, with superficial erosions and a peripheral, adherent scale crust resembling corn flakes. Patients may complain of burning, pain, or pruritus. Systemic symptoms are notably absent.6

Like PF, SSSS is characterized by subcorneal blistering (Figure 3). Staphylococcal scalded skin syndrome is also due to the disruption of Dg1, although in SSSS Dg1 is cleaved by exfoliative toxin A, a serine protease released by certain strains of Staphylococcus aureus.7

Although the clinical appearance of intact blisters and bullae in SSSS and PF is very similar, the 2 have otherwise distinct clinical characteristics and patient populations. Staphylococcal scalded skin syndrome is seen in neonates (ages 3–7 days) with immature kidneys, adults with renal disease, and immunosuppressed patients with kidneys that do not adequately excrete exfoliative toxin A.8,9 These patients often have acute systemic symptoms of infection (fever, irritability, and malaise) compared with the chronic and nonsystemic course of PF.8 Staphylococcal scalded skin syndrome is a more rapidly evolving and widespread disease in which the skin desquamates in sheets. Bacteria are not absent on cutaneous histopathology because the source of infection is not skin but a distant site (such as the umbilicus, nasopharynx, or urine).8

On H&E, the subcorneal and intragranular pattern of acantholysis is identical in SSSS and PF.10 However, epidermal inflammation in SSSS is typically sparse because bullae are sterile. In contrast, PF typically shows a more prominent inflammatory infiltrate in the upper dermis, including eosinophils.11 Direct immunofluorescence on perilional skin may be required to differentiate between these 2 entities, revealing intercellular IgG with or without complement 3 (C3) in PF and negative findings in SSSS.10

It should be noted that pemphigus erythematosus, which combines clinical features of PF with immunologic features of lupus erythematosus, histologically appears identical to pemphigus foliaceus (subcorneal blister containing acantholytic cells).12

PEMPHIGUS VULGARIS MIMICKED BY HAILEY-HAILEY DISEASE

Acantholysis within the epidermis leading to intraepidermal blistering is the characteristic finding of pemphigus vulgaris (PV), the most common subtype of pemphigus. Pemphigus vulgaris is usually seen in middle-aged adults and presents with flaccid, fragile vesicles and bullae most commonly involving the face, neck, axillae, and groin.13 Pemphigus vulgaris is related to formation of antibodies to desmoglein 1 (Dg1), another component of the desmosome (linking keratinocytes to one another).14 Dg3 is thought to be more prominent than Dg1 in mucosal epithelium. For this reason, mucosal involvement is almost always seen in PV (in contrast to PF) and precedes cutaneous involvement in a significant majority of patients.14

Intraepidermal acantholysis in PV is diffuse and suprabasal,1 classically leaving a “tombstone row” of basal cells attached to the dermal papillae (resembling gastrointestinal “villi”; Figure 4). Occasional dyskeratosis is seen, and inflammation is relatively minimal. Although follicular involvement has historically been associated with PF, See et al recently found a much higher percentage (up to 84%) of PV cases displaying follicular acantholysis.4 Direct immunofluorescence can confirm the diagnosis and characteristically shows a “chicken-wire” pattern of IgG and complement staining within the intercellular spaces, particularly intense in the lower epidermis.15

A histologic mimicker with some clinical similarities is Hailey-Hailey disease, formerly known as benign familial pemphigus (Table 2). As its historical name suggests, Hailey-Hailey disease is a benign, autosomal dominant condition with a clinical picture that mimics PV: fragile, flaccid vesicles that progress to flaccid bullae with subsequent rupture and crusting.16 Hailey-Hailey disease typically is composed of smaller vesicles and involves intertriginous areas, primarily the axillae, as well as flexures and sides of the neck (like PV).17 Lesions have usually ruptured by the time of presentation, appearing instead as painful, well-demarcated, macerated, or crusted plaques with reticulated...
Table 2. Pemphigus Vulgaris and Its Mimicker Hailey-Hailey Disease (Confusing Feature: Both Can Show Suprabasal Blistering)

<table>
<thead>
<tr>
<th>Blistering Disease</th>
<th>Common Histopathologic Findings</th>
<th>Pathophysiology</th>
<th>Distinguishing Features</th>
<th>Clinical</th>
<th>Histologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td>“Tombstone row” of basal cells attached to dermal papillae</td>
<td>Target Ag: desmoglein 3; Ag-Ab complex produces inflammatory cascade that dissolves cement substance</td>
<td>Middle-aged adults; involvement of face</td>
<td></td>
<td>Focal dyskeratosis; “chicken-wire” pattern of IgG and complement staining within intercellular spaces, particularly intense in the lower epidermis; follicular involvement</td>
</tr>
<tr>
<td>Hailey-Hailey disease</td>
<td>Full-thickness acantholysis; “dilapidated brick wall”</td>
<td>Altered calcium metabolism in keratinocytes leading to disruption of the tight junction (mutation in ATP2C1 gene)</td>
<td>Familial history (autosomal dominant with incomplete penetrance); young adults; axillary involvement</td>
<td></td>
<td>Extensive, pronounced acantholysis that spares follicles; negative DIF</td>
</tr>
</tbody>
</table>

Abbreviations: Ab, antibody; Ag, antigen; DIF, direct immunofluorescence; IgG, immunoglobulin G.
fissuring. The mechanism of acantholysis appears to be related to altered calcium metabolism in keratinocytes that disrupts the adherens junction (tight junction).

Histologically, early lesions of Hailey–Hailey disease show suprabasal clefting and the formation of intraepidermal lacunae lined by single or clumped acantholytic cells. As disease progresses, intercellular edema between keratinocytes with partial acantholysis results in a “dilapidated brick wall” appearance (Figure 5). The acantholysis of Hailey–Hailey disease is characterized more extensively (full-thickness) than that of PV. In addition, the dyskeratotic cells of Hailey–Hailey disease usually show a well-defined nucleus and preserved cytoplasm, versus the degenerating dyskeratosis of PV. Hailey–Hailey disease typically spares adnexal epithelium, as opposed to prominent follicular involvement in PV. Epidermal hyperplasia is common in Hailey–Hailey disease, along with a mixed inflammatory cell infiltrate. Although eosinophils may be present, these are more characteristic of PV. A negative DIF argues against the diagnosis of PV and supports (but does not confirm) the diagnosis of Hailey–Hailey disease.

### ALLERGIC CONTACT DERMATITIS WITH RETICULAR DEGENERATION CAUSING INTRAEPIDEMIAL BLISTER MIMICKED BY PEMPHIGOID WITH RE-EPITHELIALIZATION

Eosinophilic spongiosis is a characteristic finding of both allergic contact dermatitis (ACD) and bullous pemphigoid (BP). If spongiosis in ACD is extensive, intraepidermal vesicles may coalesce to form intraepidermal spongiotic bullae (Figure 6). Bullous pemphigoid blisters are tense and sturdy. They can persist for many days or even weeks, long enough to completely re-epithelialize the base of the blister. Although BP is defined by subepidermal blistering, these re-epithelialized blisters may appear as intraepidermal bullae. Partial or complete re-epithelialization may be seen in up to 25% of cases of BP.

Differentiating factors between these 2 conditions include the presence of spongiosis, the location of eosinophils, and immunofluorescence results (Table 3). First, ACD displays spongiosis with reticular degeneration; intercellular edema causes keratinocytes to break open, but cell membranes remain connected and create a network of variably sized intraepidermal vesicles. In contrast, because the hemidesmosome is disrupted in BP, keratinocyte-to-keratinocyte cell membrane adhesion is intact, and hydropic degeneration (as opposed to spongiotic degeneration or vesiculation) is seen. Thus, in re-epithelialized BP, the floor of the blister will be cleanly split, with regenerative epithelium at the base (Figure 7).

Secondly, eosinophilic spongiosis (eosinophils within the epidermis with associated spongiosis) is characteristic of ACD (and other drug reactions). The inflammatory infiltrate in ACD also consists of a mild to moderately heavy infiltrate of lymphocytes, macrophages, and Langerhans cells in the upper dermis. Lymphocyte exocytosis may be present. Eosinophilic spongiosis in BP is often less prominent and has been described as more at the side of the bulla or at a distance more lateral within the specimen. In older BP lesions, scale crust, psoriasiform epidermal hyperplasia, and a denser inflammatory cell infiltrate are seen.

Finally, immunofluorescence can confirm the diagnosis of BP. Direct immunofluorescence shows IgG and complement deposited at the BMZ. Alternatively, enzyme-linked immunosorbent assay (ELISA) testing for bullous pemphigoid antigen 180 (BP180) and bullous pemphigoid antigen 230 (BP230), or indirect immunofluorescence (IIF) on human salt-split skin or monkey esophagus substrate can be performed. The IIF will demonstrate IgG at the dermal-epidermal junction (DEJ), specifically within the roof of the blister. Direct immunofluorescence, ELISA, and IIF are negative in ACD.

### EARLY ALLERGIC CONTACT DERMATITIS MIMICKED BY NONBULLOUS ECZEMATOUS OR URTICARIAL PEMPHIGOID

Nonbullous eczematous or urticarial BP can also closely resemble ACD, both clinically and histologically (Table 4). About 20% of BP cases follow a chronic, relapsing course that clinically resembles eczema or fixed urticaria. Like ACD, nonbullous BP clinically presents with pruritic, erythematos papules and plaques (which may progress to a vesicular, weeping, or bullous stage). The vast majority of these patients never develop clinically significant blistering.

With the exception of eosinophilic spongiosis, which is present in only about 8% of cases, histologic findings of nonbullous BP are nonspecific and consist of spongiosis, mild upper dermal edema, and a perivascular infiltrate with eosinophils (Figure 8). Similarly, early lesions of ACD show acute spongiotic dermatitis with papillary dermal edema and a mixed inflammatory perivascular infiltrate (lymphocytes, macrophages, and Langerhans cells). Eosinophils can be present in both the dermal infiltrate and

<table>
<thead>
<tr>
<th>Blistering Disease</th>
<th>Common Histopathologic Findings</th>
<th>Pathophysiology</th>
<th>Clinical Features</th>
<th>Histologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic contact dermatitis</td>
<td>Intraepidermal blister with eosinophilic spongiosis and reticular degeneration</td>
<td>Re-exposure to a contact allergen leading to delayed hypersensitivity reaction</td>
<td>Recent contact with an allergen; pruritic erythematous papules and vesicles</td>
<td>Spongiosis in epidermis causes reticular degeneration (cell membranes intact forming a network pattern)</td>
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<tr>
<td>Bullous pemphigoid</td>
<td>Subepidermal blister with eosinophilic spongiosis (may appear intraepidermal if re-epithelialized)</td>
<td>Autoimmune disruption of the hemidesmosome (impairing attachment of epidermis to dermis)</td>
<td>Elderly; multiple pruritic, tense fluid-filled bullae</td>
<td>Regenerative epithelium at base of blister; eosinophils lined up at BMZ, positive DIF, positive ELISA</td>
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</table>

Abbreviations: BMZ, basement membrane zone; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay.
Figure 5. A biopsy of Hailey-Hailey disease shows (A) acantholysis creating focal suprabasilar clefting. B, More extensive, full-thickness acantholysis resulting in “dilapidated brick wall” appearance (hematoxylin-eosin, original magnification ×10).

Figure 6. Allergic contact dermatitis featuring (A) vesicular spongiotic dermatitis. B, Closer magnification with intraepidermal blister, adjacent spongiosis (arrowhead), and eosinophils (arrows) (hematoxylin-eosin, original magnifications ×10 [A] and ×20 [B]).

Figure 7. A biopsy of an older lesion of bullous pemphigoid reveals (A) a subepidermal bulla containing numerous eosinophils and fibrin, with focal re-epithelialization providing the appearance of an intraepidermal bulla. B, Closer magnification highlights the same features. Immunofluorescence studies were confirmatory (hematoxylin-eosin, original magnifications ×10 [A] and ×20 [B]).
within areas of spongiosis. In early ACD, both stratum corneum and epidermal thickness are normal (Figure 9).

Differentiating between these 2 conditions histologically is difficult in the absence of a DEJ split, but the characteristics described above (reticular degeneration in ACD) may be helpful in determining a diagnosis. The diagnosis of non-bullous BP usually requires high clinical suspicion as well as confirmatory DIF and IIF on salt-split skin when possible. Clinically, nonbullous BP is more common in the elderly, whereas patients with ACD will be younger on average and often have a history of atopy. Patients with ACD often have had exposure to an allergen in the past 12 to 72 hours, and lesions may appear in geometric or linear shapes, indicating areas of skin contact with the allergen.

DERMATITIS HERPETIFORMIS MIMICKED BY LINEAR IgA BULLOUS DERMATOSIS AND BULLOUS SYSTEMIC LUPUS ERYTHEMATOSUS

Dermatitis herpetiformis (DH) is an autoimmune-derived disease characterized by intensely pruritic, small papules and clear fluid-filled vesicles symmetrically distributed on the dorsal surfaces (extremities, scalp, and sacrum). In DH, ingestion of gluten is believed to initiate formation of IgA antibodies to tissue transglutaminase in the gastrointestinal tract, producing a gluten-sensitive enteropathy (celiac disease). These antibodies may also recognize epidermal transglutaminase (TG-3) in the skin, which can activate the complement cascade with subsequent chemotaxis of neutrophils into the papillary dermis. It is not clear why some patients have only celiac disease, whereas others show only DH, and yet others show both phenotypes. Dermatitis herpetiformis is also associated with an increased incidence of other autoimmune diseases, most commonly autoimmune thyroid disease, type 1 diabetes mellitus, and pernicious anemia.

On H&E, DH is characterized by a prominent neutrophilic infiltrate focused within dermal papillae associated with papillary dermal edema and subepidermal vesiculation (Figure 10). There is relative sparing of the rete tips between each dermal papilla. Eosinophils, lymphocytes, and histiocytes migrate into the skin as lesions of DH evolve. Direct immunofluorescence can provide confirmation of the diagnosis, showing granular deposits of IgA alone or in combination with C3 at tips of dermal papillae. There is no staining for IgM and IgG.

The H&E findings of linear IgA bullous dermatosis (LABD) can be identical to those seen in DH, but the immunologic pathogenesis, DIF, and clinical history of the 2 diseases are quite different (Table 5). The antigens in the 2 diseases are both integral to the attachment of the epidermis to the dermis. In LABD antibodies are directed against

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**Table 4. Allergic Contact Dermatitis Mimicked by Eczematous Pemphigoid (Confusing Feature: Both Can Show Spongiotic Dermatitis With Eosinophils)**

<table>
<thead>
<tr>
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</tr>
</thead>
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</tr>
</tbody>
</table>

**Table 5. Dermatitis Herpetiformis Mimicked by Linear Immunoglobulin (Ig) A Bullous Dermatosis and Bullous Systemic Lupus Erythematosus (Confusing Feature: Subepidermal Blister With Papillary Dermal Edema and Neutrophilic Infiltrate)**

<table>
<thead>
<tr>
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<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Subepidermal vesiculation; papillary dermal edema with “stuffing” of the dermal papillae with neutrophils</td>
<td>IgA antibodies to epidermal transglutaminase</td>
<td>Dorsal surfaces; grouped, excoriated papules and vesicles; history of gluten-sensitive enteropathy; severe pruritus</td>
</tr>
<tr>
<td>Linear IgA bullous dermatosis</td>
<td>Papillary dermal edema with dermal-epidermal blistering. In some cases, collections of neutrophils “stuffing” the dermal papillae</td>
<td>IgA antibodies to BP230 (of hemidesmosome)</td>
<td>Annular, “string of pearls” pruritic vesicles and bullae peripherally surrounding a wheal, particularly involving groin or genital; drug history (especially vancomycin)</td>
</tr>
<tr>
<td>Bullous lupus erythematosus</td>
<td>Subepidermal blister; superficial, sparse lichenoid and perivascular mononuclear or neutrophilic infiltrate in some cases with neutrophils “stuffing” the dermal papillae</td>
<td>Various autoantibodies to components of the BMZ or type VII collagen</td>
<td>Tense vesiculobullous lesions on sun-exposed skin</td>
</tr>
</tbody>
</table>

Abbreviations: BMZ, basement membrane zone; DIF, direct immunofluorescence; ELISA, enzyme-linked immunosorbent assay.
Figure 8. A biopsy of the eczematous phase of bullous pemphigoid shows (A) features of spongiotic dermatitis. B, A perivascular and interstitial inflammatory infiltrate includes numerous eosinophils. Immunofluorescence studies were confirmatory (hematoxylin-eosin, original magnifications ×10 [A] and ×20 [B]).

Figure 9. A biopsy of allergic contact dermatitis with features of (A) spongiosis with eosinophils within the epidermis (eosinophilic spongiosis) and the superficial perivascular and interstitial inflammatory infiltrate. B, Eosinophilic spongiosis (hematoxylin-eosin, original magnifications ×10 [A] and ×20 [B]).

Figure 10. Dermatitis herpetiformis with (A) neutrophils within the dermal papillae (neutrophilic microabscesses). B, A closer view shows a subtle subepidermal split. Immunofluorescence studies were confirmatory (hematoxylin-eosin, original magnifications ×10 [A] and ×20 [B]).
Stevens-Johnson Syndrome is in the same disease spectrum as toxic epidermal necrolysis (TEN), usually precedes the appearance of cutaneous lesions. Ocular (oral, nasal, genital) are present in most cases, and a flulike prodrome eventuates in flaccid bullae and subsequent epidermal sloughing. Mucosal erosions/ulceration (buccal, genital, neck).31 Similarly to DH and LABD, dapsone often produces a dramatic clinical response.32

Both DH and LABD respond clinically to brief courses of systemic steroids and more prolonged suppression with dapsone. The latter presumably acts by suppressing neutrophils. Discontinuation of the offending drug in LABD and avoidance of gluten in DH are also required.

There are 2 histologic patterns seen in bullous systemic lupus erythematosus (SLE): 1) predominantly characterized by mononuclear cells, and 1 characterized predominantly by neutrophils.30 This latter type closely simulates the findings of DH and LABD, with papillary microabscesses of neutrophils “stuffing” the papillae and overlying dermal-epidermal blistering (Table 5). Nuclear dust in the upper dermis and surrounding blood vessels can also be seen. On DIF, there is usually a mix of linear and granular IgG deposition at the BMZ; IgA and IgM deposits may also be present. These immunoreactants are below the lamina densa (on the dermal side of salt-split skin). Some of these patients have autoantibodies to various components of the BMZ or to collagen VII.

Bullous SLE is considered a variant of SLE and requires a clinical diagnosis of SLE. Like SLE, it mainly affects young women in their second to fourth decades and often presents acutely with tense vesicles and bullae (overlying either normal skin or preexisting SLE patches). Another clinically differentiating factor of bullous SLE is its predilection for photo-distributed regions (trunk, upper extremities, face and neck).31 Similarly to DH and LABD, dapsone often produces a dramatic clinical response.32

**TOXIC EPIDERMAL NECROLYSIS MIMicked BY PEMPHIGOID WITH EPIDERMAL NECROSIS AND METHOTREXATE TOXICITY**

Most clinicians are familiar with toxic epidermal necrolysis (TEN), a rapidly progressing dermatologic emergency associated with high mortality (25% to 50%).33 Timely diagnosis of TEN is critical and often requires histopathologic confirmation.

Toxic epidermal necrolysis is almost always associated with a causative drug that must be promptly identified and discontinued (most commonly implicated are sulfonamides, anticonvulsants, allopurinol, and NSAIDs).34 Clinically, TEN is defined by painful sloughing of the skin involving more than 30% of the body surface area. As it evolves, dusky or purpuric macules coalesce into patches and plaques that eventuate in flaccid bullae and subsequent epidermal sloughing. Mucosal erosions/ulceration (buccal, genital, ocular) are present in most cases, and a flulike prodrome usually precedes the appearance of cutaneous lesions. Stevens-Johnson Syndrome is in the same disease spectrum as Stevens-Johnson Syndrome/TEN overlap.

The distinctive histologic finding of TEN is full-thickness epidermal necrosis (although the absence of this finding does not preclude a diagnosis of TEN; Figure 11). In other cutaneous diseases, if keratinocyte cell death occurs, it is often confined to the basal layer. In TEN, on the other hand, keratinocyte apoptosis is characteristically present within all layers of the epidermis, taking the form of confluent necrosis.11 Established lesions of TEN are characterized by a subepidermal blister, full-thickness necrosis of the epidermal roof, and a notably absent or sparse inflammatory infiltrate (“cell-poor”).11 It is postulated that epidermal necrosis is mediated by cytokines from drug-specific cytotoxic T lymphocytes, although apoptosis of keratinocytes also occurs.35 The action of cytokines may explain the apparent discrepancy between the extent of epidermal damage and the paucity of the dermal infiltrate.11

The characteristic histologic findings of TEN—subepidermal cleaving and full-thickness epidermal necrosis—are also observed in the more common condition of BP (Table 6). In BP, tense blistering occurs at the DEJ. Full-thickness necrosis occurs in blisters that persist for weeks because the epidermis is separated from the dermal blood supply (Figure 12). Because this phenomenon occurs in older lesions of BP, it is generally recommended that only blisters less than 48 hours old be sampled.23

Histologically, the most apparent factor differentiating BP from TEN is the more prominent inflammatory infiltrate and presence of eosinophils in the former condition.11,36 Additional differentiating factors favoring BP include the following: (1) absence of dyskeratosis and necrosis in adjacent nonblistered skin, (2) re-epithelialization of the dermal-epidermal blister correlating with the age of the blister, and (3) sampling of younger blisters showing dermal-epidermal separation without dyskeratosis or necrosis.23 Although DIF sometimes shows diffuse deposition of immunoreactants in the midepidermis in TEN, it is usually negative.34 Direct immunofluorescence is a highly sensitive test for BP, with demonstration of linear IgG and C3 staining at the DEJ.37,38 Indirect immunofluorescence is a more specific test for BP; antibody binding to the epidermal side of split (roof) will be present in 60% to 80% of cases of BP, with a specificity of 95% to 100%.39 Clinical clues to a diagnosis of BP include a history of tense, markedly pruritic blisters, and a negative Nikolsky sign, whereas TEN shows flaccid painful bullae with a positive Nikolsky sign.33 Although many of the same drugs are associated with BP and TEN, BP is more commonly caused by furosemide, captopril, and NSAIDs.

Clinical manifestations of methotrexate (MTX)-induced cutaneous toxicity are very similar to those of TEN, with histology that also mimics that of TEN (Table 6). Although clinically variable, in its most severe form, MTX-induced toxicity is characterized by widespread erythematous or dusky macules, blistering, and desquamation.39 Frequent mucosal involvement (mucositis, stomatitis) often leads clinicians to consider TEN.40 Methotrexate toxicity is usually seen in patients with renal failure, or those given a concomitant medication that causes renal dysfunction or impairs folic acid absorption, especially trimethoprim-sulfamethoxazole. Without appropriate adjustment of MTX dosage, this leads to toxic levels of systemic MTX. The mechanism of pathogenesis may include...
Figure 11. A biopsy of toxic epidermal necrolysis demonstrates (A) epidermal dyskeratosis and confluent necrosis with basket-weave stratum corneum and sparse underlying inflammation. B, Closer magnification reveals focal dermal-epidermal separation and re-epithelialization (hematoxylin-eosin, original magnifications 4X [A] and 10X [B]).

Figure 12. A biopsy of bullous pemphigoid with (A) necrosis of the blister roof. B, Closer magnification highlights re-epithelialization of the base. Immunofluorescence studies were confirmatory (hematoxylin-eosin, original magnifications 4X [A] and 10X [B]).

Figure 13. Full-thickness epidermal necrosis leading to dermal-epidermal separation with sparse underlying inflammation. Patient had renal failure and was incorrectly dosing methotrexate at 3 times the prescribed amount. Improvement was quickly noted after a rescue dose of leucovorin (hematoxylin-eosin, original magnification 10X).
Table 6. Toxic Epidermal Necrolysis Mimicked by Bullous Pemphigoid With Epidermal Necrosis and by Methotrexate (MTX)–Induced Toxicity (Confusing Feature: Both Can Show Full-Thickness Epidermal Necrosis Overlying a Dermal-Epidermal Split)

<table>
<thead>
<tr>
<th>Blistering Disease</th>
<th>Common Histopathologic Findings</th>
<th>Pathophysiology</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic epidermal necrosis</td>
<td>Subepidermal blister with overlying confluent full-thickness epidermal necrosis; sparse or absent lymphocytic infiltrate</td>
<td>Release of cytokines from drug-specific T lymphocytes, causing epidermal necrosis</td>
<td>Cell-poor; negative DIF</td>
</tr>
<tr>
<td>Bullous pemphigoid with epidermal necrosis</td>
<td>Subepidermal blister with a necrotic (often full-thickness) epidermal roof; eosinophils “lined up” at the DEJ; lymphocytes and neutrophils in papillary dermis</td>
<td>Autoantibodies to components of the hemidesmosomes (BP180 or BP230)</td>
<td>Initially pruritic and tense; biopsy of &lt;48 h old shows no epidermal necrosis</td>
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<td>MTX-induced cutaneous toxicity</td>
<td>Focal subepidermal separation with keratinocyte dystrophy and full-thickness epidermal necrosis; mixed inflammatory infiltrate with eosinophils</td>
<td>Dose-dependent drug-induced toxicity, direct cell toxicity and potential allergic reaction component</td>
<td>Widespread blistering progressing to desquamation; significant mucositis, renal insufficiency, and cytopenias</td>
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Abbreviations: BSA, body surface area; C3, complement 3; DEJ, dermal-epidermal junction; DIF, direct immunofluorescence; IgG, immunoglobulin G; IIF, indirect immunofluorescence.

an allergic as well as a dose-dependent toxicity reaction. Although the cutaneous findings are not life-threatening, they may herald pancytopenia, which can be fatal.

On H&E, focal dermal-epidermal clefting and variable degrees of keratinocyte dystrophy (including full-thickness epidermal necrosis) are seen (Figure 13). A background of interface dermatitis and a mixed dermal inflammatory infiltrate with eosinophils may be present, which in some cases may be abundant. Epidermal dysmaturation, nuclear pleomorphism, and atypical mitotic figures have also been reported.

Helpful features favoring MTX toxicity versus TEN include especially severe mucositis (including involvement of the gastrointestinal tract with symptoms such as dysphagia and diarrhea), concomitant cytopenia(s), and acute renal insufficiency. Neutropenic fever may be seen but typically follows the onset of cutaneous manifestations, whereas the flulike prodrome of TEN precedes the rash. Histologically, epidermal necrosis may be less prominent than that seen in TEN, with a heavier inflammatory infiltrate that includes eosinophils.

Monitoring serum levels of MTX, particularly in patients with impaired hepatic or renal function, avoiding medications that interfere with MTX metabolism (eg, trimethoprim-sulfamethoxazole, sulfonamides, NSAIDs), and quickly initiating leucovorin rescue can help prevent and treat MTX toxicity.

**SUMMARY**

It is not possible to include all possible blistering disease mimics in an article of this type. Rather, our goal was to highlight common situations that have confused us initially or led us to a misdiagnosis. A systematic, “top-down” histopathologic approach can help simplify the evaluation of blistering diseases. Special attention to biopsy technique, the clinical stage of disease, the age of the biopsied blister, and immunofluorescence findings are important for both clinician and pathologist. Effective communication between clinician and pathologist to ensure that appropriate biopsy technique and media are used is critical for accurate diagnosis.

**References**


*Mimickers of Blistering Skin Disease—Tintle et al*


