Clinical History:
A 74-year-old man with a history of type 2 diabetes mellitus and colon cancer status post resection presented with a blistering rash that healed with scarring and involved the bilateral hands, arms, abdomen, bilateral thighs, and oral mucosa. Focal areas on the dorsal hands showed milia formation. Two biopsies of the left wrist were performed, one submitted for routine histopathologic evaluation, the other for direct immunofluorescence.
74-year-old man with a blistering rash involving the oral mucosa

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History

• 74M, history of type 2 diabetes mellitus and colon cancer, presents with a 1 year history of a blistering rash

• Per report, prior outside skin biopsy consistent with bullous pemphigoid (managed with topical betamethasone, oral steroid taper for flare)
Left wrist
Left wrist
Direct immunofluorescence

Patient bx

Antigen

Complement

Ig (G, A, E, M)
Direct immunofluorescence

- Patient bx
- Antigen
- Complement
- Anti-IgG, A, E, M
- Anti-complement
- FITC
Left wrist
DIF, IgG
Left wrist
DIF, C3
1M NaCl
Left wrist
Salt-split
DIF, C3
Left wrist Salt-split DIF, IgG
Data

• Serology:
  • BP 180: <9 U
  • BP 230: <9U
  • DSG1: <18U
  • DSG2: <19U

• Indirect immunofluorescence:
  • Cell surface AB IgG: Negative
  • Basement membrane IgG: BMZ positive titer 1:80
  • Monkey esophagus IgG: Positive
  • Human split skin IgG: Positive; dermal pattern
Epidermolysis bullosa acquisita

- Autoantibodies directed against type VII collagen (below the lamina lucida)
- Classic type resembles hereditary dystrophic epidermolysis bullosa
- Can be a paraneoplastic phenomenon, also associated with IBD, SLE
- The clinical presentation can be key in making the diagnosis (skin lesions that heal with scarring can be mistaken for MMP)
Classic type

- Flaccid blisters on trauma-prone areas (extensor surfaces)
- Scarring, milia, hyper/hypopigmentation
Inflammatory type

- Resembles linear IgA bullous dermatosis or pemphigoid (BP or MMP)

Classic type

Inflammatory type

Other subepidermal blistering rashes that involve the oral mucosa
Bullous pemphigoid (BP)  
Mucous membrane pemphigoid (MMP)  
Mild oral involvement 10-20%

Bullous pemphigoid

• Most common subepidermal blistering disease
• Elderly patients: 7th decade and older
• 10-40% have mild oral lesions
• Abdomen, groin, flexor surface of arms and legs
• Tense bullae on normal or erythematous skin
• Severe pruritus
• Prebullous stage
Bullous pemphigoid (BP)  Mucous membrane pemphigoid
Mild oral involvement 10-20% dominant mucosal involvement

Mucous membrane pemphigoid

- Mucosal blisters are rare due to fragility - typically erosions
- Skin lesions heal with scarring
- Histologically and clinically can mimic the inflammatory type of EBA
- Can involve conjunctiva and lead to loss of vision
- Involvement of other mucosal sites common (esophagus, anogenital, pharynx, larynx, etc.)
Oral 85%
Conjunctivae 30%
Nasal cavity 30%
Anogenital 20%
Pharynx 20%
Larynx 5-10%
Esophagus 10%

Skin lesions in ~25%

Linear IgA Bullous Dermatosis

- Chronic Bullous Disease of Childhood:
  - Large, tense bullae arising during the 1st decade
  - Predilection for perioral and genital regions
  - Usually benign course
Varo et al., BMJ Case Rep. bcr2016218315 (2017)
Linear IgA Bullous Dermatosis

- Adult Linear IgA Bullous Dermatosis
  - Varied presentations
  - Common association with drugs (vancomycin, NSAIDs)
  - Mucosal involvement more common
Oral lichen planus

- Can be mistaken clinically and even histologically for MMP or PV
- Oral reticulation (Wickham’s striae) very specific for OLP, even when there is desquamative gingivitis (erosion and erythema)
- ‘Max Joseph space’ – subepithelial separation often seen in OLP
Key questions when evaluating blistering diseases in general

- Where is the split (intraepidermal vs. subepidermal)
- Are there inflammatory cells present, and what type?
- Any helpful clinical clues?
- What is the pattern of DIF if available?
- Serologic studies? IIF?
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CASE 10

DIAGNOSIS: Epidermolysis bullosa acquisita (EBA), classic type

CASE HISTORY: A 74-year-old man with a history of type 2 diabetes mellitus and colon cancer status post resection presented with a blistering rash that healed with scarring and involved the bilateral hands, arms, abdomen, bilateral thighs, and oral mucosa. Focal areas on the dorsal hands showed milia formation. Two biopsies of the left wrist were performed, one submitted for routine histopathologic evaluation, the other for direct immunofluorescence.

MICROSCOPIC DESCRIPTION: At low magnification, a subepidermal blister is seen. Few inflammatory cells are present within the blister cavity and within the subjacent dermis, and a focal area of dermal fibrosis can be appreciated. Eosinophils are not conspicuous. Looking closer at the epidermis, changes to suggest an interface dermatitis, such as Civatte bodies or vacuolar change, are not seen. By direct immunofluorescence (DIF), linear IgG and C3 deposition was seen along the dermal-epidermal junction, and areas suggestive of a pattern of u-serration were present. Additional DIF studies performed on salt-split skin showed IgG and C3 deposition on the dermal side of the separation. Serologic studies for BP180 and BP230 antigens as well as desmogleins 1 and 3 were negative.

DISCUSSION: Epidermolysis bullosa acquisita (EBA) is a rare autoimmune blistering disorder that affects the skin and mucous membranes. Although cases in children have been reported, the disease predominantly affects adults in the fourth to fifth decade of life. Two types of EBA are recognized, the classic type (also known as non-inflammatory or mechanobullous) and the inflammatory type. The classic type typically presents with blisters and erosions localized at pressure-prone body sites such as extensor surfaces, and closely resembles hereditary dystrophic epidermolysis bullosa acquisita, a disorder caused by germline mutations in the gene encoding collagen VII. These patients typically have a gradual onset of disease and a prolonged clinical course. Skin fragility and scarring with restriction of movement as well as milia formation are typical. The inflammatory type typically clinically resembles linear IgA bullous dermatosis or pemphigoid (bullous pemphigoid or mucous membrane pemphigoid; see below). EBA can occur as a paraneoplastic phenomenon associated with hematologic or solid malignancies or in association with inflammatory bowel disease or systemic lupus erythematosus. Approximately 50% of cases involve mucosal sites. Autoantibodies are typically directed against type VII collagen, located below the level of the lamina lucida (see figure below).

Histopathology of an intact blister of the classic type of EBA shows a subepidermal split with few subjacent inflammatory cells. Fibrosis of the dermis is commonly seen. Lesions of the inflammatory type characteristically show a dense inflammatory infiltrate present both within the blister space and underlying superficial dermis that is
composed of lymphocytes, neutrophils, eosinophils, and histiocytes. DIF of perilesional skin shows linear deposition of IgG and C3 along the basement membrane zone in most cases. Salt-split perilesional skin (skin without an intact blister split at the level of the lamina lucida using a hypertonic salt solution) shows deposition on the dermal side of the split. A u-serrated pattern is present at high magnification, which is specific to EBA and bullous systemic lupus erythematosus, as opposed to the n-serrated pattern that is seen in other autoimmune blistering disorders including bullous pemphigoid (BP), some cases of linear IgA bullous dermatosis, and mucous membrane pemphigoid (MMP). Although often difficult to appreciate in practice, the pattern is diagnostically useful, as anti-laminin 332 MMP (n-serrated) can be distinguished from EBA (u-serrated), as these disorders have an identical staining pattern in salt-split skin.

Several other immunobullous disorders are also characterized by subepithelial blisters. The most common is bullous pemphigoid (BP), which preferentially affects elderly adults in the seventh decade of life or older. Secondary involvement of mucosal sites is seen in a minority of cases (10-40%). Typically, antibodies directed against the BP180 and/or BP230 antigens are present in patients and can be detected with serologic studies. Histopathology of an intact blister often shows a robust lymphocytic infiltrate containing numerous eosinophils and a variable number of neutrophils. Lesions in the prebullous stage show spongiosis with an infiltrate containing numerous eosinophils. Often, “tagging” of the dermal-epidermal junction by eosinophils can be appreciated. DIF of perilesional skin shows linear deposition of C3 (nearly 100% of cases) and/or IgG (90-95% of cases). Deposition of IgM or IgA can rarely be seen. Interestingly, as BP180 and 230 are also expressed in the brain, patients with BP have a 6-fold increased risk of neurologic disorders, including neurodegenerative diseases (Parkinson, Alzheimer, multiple sclerosis, epilepsy, bipolar disorder).

Mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid, is a heterogeneous disease that primarily affects the mucous membranes and can secondarily affect the skin in 25% of cases. Women are preferentially affected, typically in the sixth to seventh decade of life. The most common site of involvement is the oral mucosa (85% of cases) followed by conjunctiva (30%) and sinonasal mucosa (30%). Anogenital, pharynx, larynx, and esophagus are less commonly involved. Skin lesions tend to heal with scarring. As MMP is a heterogeneous disease, antibodies can be directed against several basement membrane antigens, including BP180, BP230, a6 integrin (preferentially expressed in oral mucosa), b4 integrin (preferentially expressed in ocular mucosa), laminin 332 (often seen in paraneoplastic MMP), and collagen VII. Histopathologic sections of intact blisters show a subepithelial split with preservation of basal cells and an associated lymphocytic infiltrate. As opposed to BP, eosinophils are typically not as numerous in cases of MMP, and spongiosis is not a common feature. DIF on perilesional skin shows linear IgG and C3 deposition along the basement membrane zone in 80-100% of cases. Again, although often difficult to
evaluate in practice, an n-serrated pattern is seen at high-power, in contrast to the u-serrated pattern seen in EBA and bullous SLE. The presence of IgA is common and should not be interpreted as linear IgA disease unless the characteristic skin lesions are also present (see below). Salt-split perilesional skin (skin split at the level of the lamina lucida using a hypertonic salt solution) shows an epidermal pattern of staining in 2/3 of cases and a dermal pattern of staining in 1/3 of cases (the latter representing anti-laminin 332 and anti-collagen VII antibodies).

Linear IgA bullous dermatosis (LABD) has two recognized clinical variants, with a subset of cases occurring in young children in the first decade of life (chronic bullous dermatosis of childhood or CBDC) and a second syndrome with a bimodal age distribution with a peak incidence in young adults and again in the sixth decade (adult LABD). Cases of CBDC commonly show involvement of perioral and genital skin, and mucosal involvement is uncommon. The disease can be precipitated by the administration of penicillin, most commonly in the setting of an upper respiratory infection. Adult LABD tends to involve the trunk and extremities and commonly includes mucosal sites (approximately 80% of cases). Adult LABD is also commonly precipitated by medications including vancomycin (most commonly) as well as non-steroidal anti-inflammatory drugs. Both CBDC and adult LABD are characterized by an annular arrangement of bullous lesions that resemble a ‘string of beads’ or ‘cluster of jewels.’ As LABD is a heterogeneous disease, multiple antigens within the basement membrane complex can be targeted, including the bullous pemphigoid antigens BP180 and BP230 as well as several degradation products of these proteins. In sub-lamina densa-type LABD, several other antigens can be targeted, including type VII collagen. Histologic sections of intact vesicles show a subepidermal blister containing fibrin, edema fluid, and numerous neutrophils. Often, adjacent to the blister, neutrophils are observed at the dermal-epidermal junction both in a linear array and as small collections at the dermal papillae, a pattern identical to that seen in dermatitis herpetiformis. DIF shows deposition of IgA in a linear fashion, as opposed to a granular or fibrillar pattern seen in dermatitis herpetiformis.

Oral lichen planus (OLP), which preferentially affects adult females, can often be confused clinically and histologically with an autoimmune bullous disorder, particularly MMP and pemphigus vulgaris. Helpful clinical clues include the presence of oral reticulation (Wickham striae) as well as symmetric involvement of the oral mucosa. Histology typically shows a lichenoid interface dermatitis with Civatte bodies, ‘saw-tooth’ rete ridges, acanthosis or atrophy, and hyperkeratosis. Subepithelial separation is often seen, termed the ‘Max-Joseph space.’ Although a non-specific pattern, DIF often shows deposition of shaggy fibrin at the basement membrane. Cytoid bodies are often seen due the presence of an interface reaction. Rare cases classified as lichen planus pemphigoides show linear deposition of IgG and C3 at the basement membrane zone.
The diagnosis of immunobullous disorders requires an integration of clinical, histologic, and direct immunofluorescence data to achieve accuracy. As no diagnostic modality is perfect in the diagnosis of these disorders, including direct immunofluorescence, integration of clinical, histologic, and adjunct assays is necessary for definitive diagnosis.

REFERENCES:


