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Educational Case

Educational Case: Bullous pemphigoid

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.academicpathologyjournal.org/pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Skin, Immune-related disorders, Blistering disorders, Bullous pemphigoid

Primary objective

Objective: SK3.3: Inflammatory blistering disorders. Compare and contrast the pathogenesis, clinical findings, and pathologic features for the cutaneous blistering disorders pemphigus, bullous pemphigoid, and dermatitis herpetiformis.

Competency 2: Organ system pathology; Topic: Skin (SK); Learning Goal 3: Immune-related disorders of the skin.

Patient presentation

A 65-year-old man presents to the dermatologist with several blisters that have become open wounds on his back and chest. This has been occurring for the past month. Before the eruptions occur, his skin becomes extremely itchy. He works as an indoor accountant and notes recent sun exposure resulting in a sunburn. He tried using over-the-counter hydrocortisone cream on the rash for 10 days, but this has not provided relief. His past medical history includes hypertension and type 2 diabetes in the past. His only medication is amlodipine for his hypertension. The patient's wife also notes that he has shown mild cognitive decline over the past year, citing instances of forgetting recent conversations and the location of objects, such as his wallet and keys.

Diagnostic findings, Part 1

On physical examination, the vital signs are as follows: blood pressure 145/90 mmHg, heart rate of 90 beats per minute, respiratory rate of 18 breaths per minute, and temperature of 98 °F. Physical examination reveals a man with Fitzpatrick skin type V (olive to dark brown skin) and green eyes. Extensive lesions are present, including diffuse hypopigmented and violaceous circular macules and patches (2.2–4.5 cm diameter) along with central erosions (5.9–7.2 cm diameter) over the inferior neck, chest, back, and legs (Fig. 1). The dorsal arms are covered with more extensive erosions (9.2–10.5 cm). A few large, tense bullae (1.5 cm in size) filled with clear fluid are present on his superior neck and back. Active urticarial erythema or plaques are present on the forearms bilaterally. There is no ocular or mucous membrane involvement.

Head and neck examination shows no signs of icterus, infection, and no lymphadenopathy of the anterior or posterior cervical lymph node chains or thyromegaly. Cardiac examination reveals normal S1 and S2 sounds and regular rate and rhythm. His lungs are clear on auscultation, with no wheezing, rhonchi, or rales. The abdomen is soft and non-tender with no palpable abdominal mass. Bowel sounds are present. Cranial nerves II-XII are intact. Mini-mental state exam score is 23/30.

Question/discussion points, Part 1

What is the differential diagnosis based on the clinical presentation?

Bullae and vesicles correspond to blistering fluid-filled spaces in the epidermis and/or dermis that differ in clinical size. Common causes include skin damage from injury (e.g., trauma, friction, environmental agents and heat/burns) and environmental agents (e.g., radiation,

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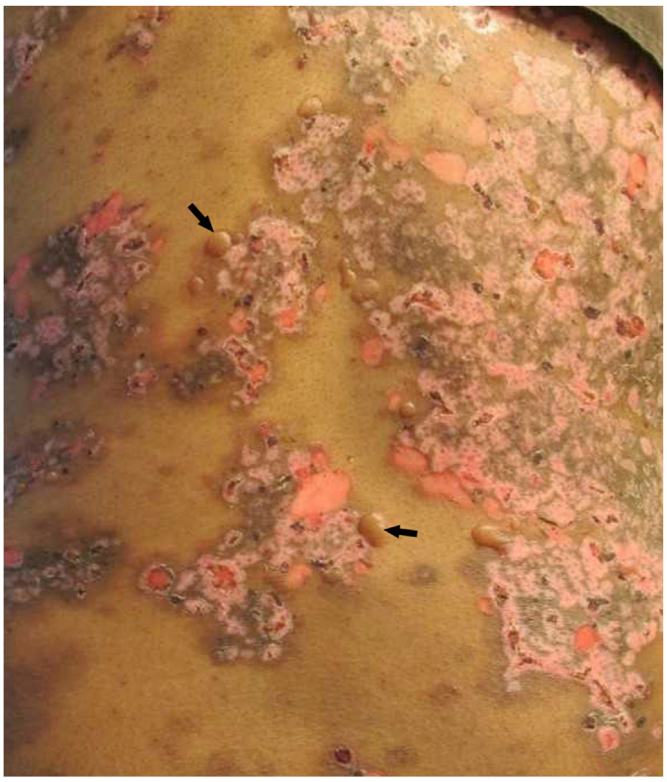

Fig. 1. Hypopigmented and violaceous circular macules and patches with central erosions involving the patient's entire back. A few large, tense bulla (arrows) filled with clear fluid are also present. Figure reprinted with permission from Robert J. Smith, Eastern Virginia Medical School, Norfolk, VA.

chemicals such as cosmetics, jewelry and insect bites). Blisters are also seen in infectious disorders (e.g., impetigo and herpes infections) and in immune disorders. Finally, blisters may be drug-induced (e.g., penicillamine and captopril) and may be seen as a paraneoplastic phenomenon.

Given the patient's pruritic skin prior to blister development, and their lack of sun exposure, trauma, exposure to environmental agents, or evidence of infection, an autoimmune blistering disorder is suspected. The clinical differential diagnosis would include but not be limited to pemphigus vulgaris (PV), bullous pemphigoid (BP), dermatitis herpetiformis (DH), and pemphigus foliaceus (PF). However, clinical manifestations alone are insufficient to render a diagnosis. Histopathologic features and autoantibody detection are required for diagnosis.[2–4]

How do pemphigus vulgaris, pemphigus foliaceus, and dermatitis herpetiformis differ from bullous pemphigoid?

Predominantly a disease of elderly patients, BP usually begins with a pruritic stage, appearing similarly to eczematous plaques.[2] Tense bullae, containing clear fluid and measuring 1–3 cm, then form at anatomical locations such as flexor surfaces of the upper and lower extremities in addition to the lower trunk.[2] When blisters rupture, erosions, crusting and hyperpigmented or hypopigmented lesions are left behind.[2,3] Only 10–25 % of BP patients have bulla involving the mucosa, such as the oral cavity.[2,3]

In contrast, PV affects a wide ranges of age groups and typically first presents as an ulcer of the oral mucosa.[4,5] Cutaneous PV without mucosal involvement is rare.[5] PV patients also have a lower incidence of pruritis than seen in BP patients, often complaining of painful lesions.[4] After the formation of mucosal ulcers, fragile blisters associated with PV appear, resulting in raw erosions and crusting. These lesions develop in a "shawl-like" distribution, forming on the upper chest and can involve the face, scalp, and mucosal membranes.[4]

PF develops in a similar anatomical pattern to PV while lacking mucosal involvement.[4] However, since superficial blisters burst more easily than PV, erythematous, scaly patches are observed, which may be misdiagnosed as atopic dermatitis or seborrheic dermatitis.[4] Epidermal peeling is visible on the outer edge of PF erosions.[4]

DH has a variety of clinical presentations, such as grouped vesicles or urticarial plaques that typically itch, resulting in excoriations and erosions.[6] The extensor areas of the elbows and knees are commonly affected. Pruritus can occur prior to blister development. Other clinical presentations for DH include diarrhea and abdominal pain, due to its association with celiac disease.[6]

Diagnostic findings, Part 2

A skin biopsy is performed on perilesional skin. Histological features of the cutaneous biopsy are shown in Figs. 2 and 3. Direct immunofluorescence is performed as well, as outlined below.

Question/discussion points, Part 2

Describe the histological features observed in the biopsy

Bullous disorders are classified, histologically, by whether the blister occurs in an intraepidermal (subcorneal, suprabasal) or a subepidermal

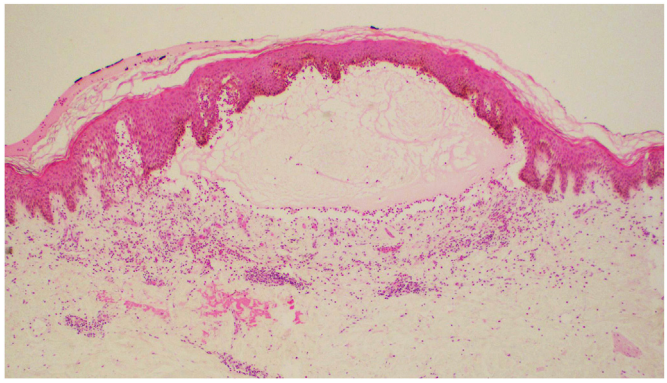

Fig. 2. Bullous pemphigoid. This section of skin shows a prominent subepidermal nonacantholytic blister with dermal inflammatory infiltrate. (H&E, low magnification).

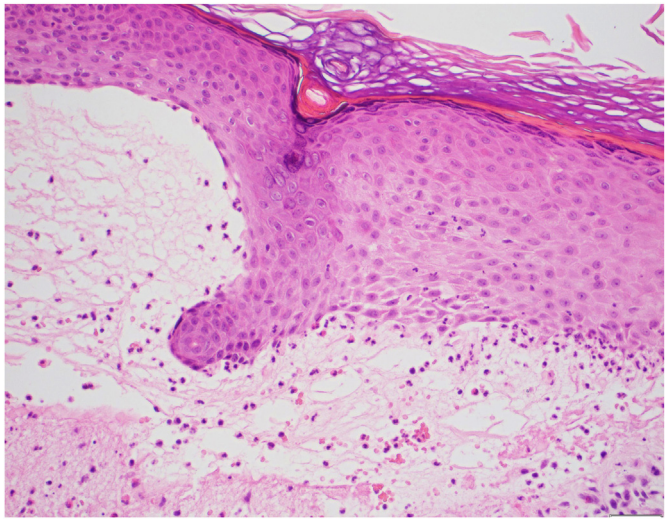

Fig. 3. Higher magnification of the subepidemal blister in bullous pemphigoid. The infiltrate is composed predominantly of esosinophils, neutrophils and lymphocytes (H&E, intermediate magnification).

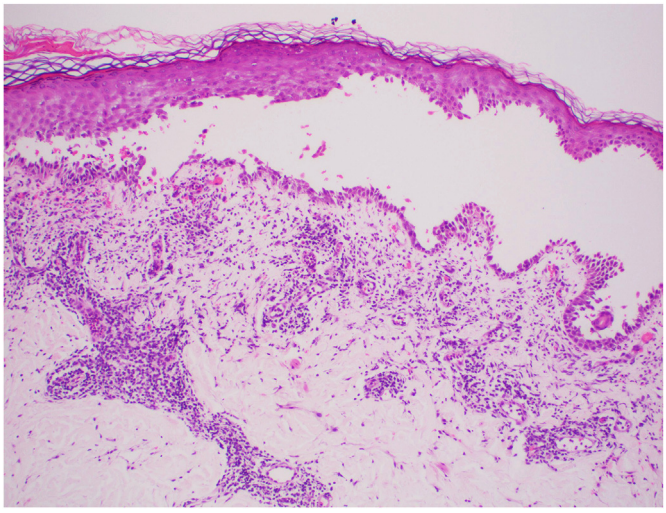

Fig. 4. Pemphigus vulgaris. A ruptured suprabasal blister is seen and a single layer of intact basal cells remains. (H&E, low magnification).

location. The biopsy shows a subepidermal bulla with a mixed inflammatory infiltrate. Cells included in this infiltrate are predominantly lymphocytes, eosinophils and neutrophils.

Based on the biopsy findings, what is the diagnosis?

Biopsy findings are consistent with a diagnosis of BP. BP is the most common autoimmune blistering disorder in the USA, and its incidence is increasing, particularly in the elderly population.[2,7]

How do pemphigus vulgaris, pemphigus foliaceus, and dermatitis herpetiformis differ from bullous pemphigoid histologically?

The defining characteristic of PV histology is suprabasal acantholysis (loss of adherence of the epidermal layers), due to decreased adhesion among the keratinocytes (Fig. 4). Given this prominent split in the epidermis, the remaining basal cells e seen lining up along the basement membrane and are described as having a "tombstone appearance."[8,9] Eosinophilic spongiosis and eosinophils along the dermal-epidermal junction are commonly seen in intact skin adjacent to the bulla, similar to that seen in BP (Fig. 5).[2,3]

In contrast to the subepidermal blister of BP, the defining characteristic of PF is an intraepidermal split, usually subcorneal or within the stratum granulosum (Fig. 6).[8,9] A dermal inflammatory infiltrate is also seen.[8] In contrast, DH primarily involves the dermal papillae, with the presence of neutrophils and eosinophils. Microabscesses originate in the dermal papillae and can lead subepidermal clefting and the development of vesicles (Fig. 7A and B).[8]

How does the pathogenesis of bullous pemphigoid differ from other autoimmune blistering disorders?

In the epidermis, hemidesmosomes are responsible for connecting the basal layer of epithelial cells to the basement membranes.[10] These anchoring complexes are made up of multiple proteins, including dystonin-e (BP230 or BPAg1) and collagen XVII (BP180 or BPAg2).[2] BP patients develop IgG autoantibodies against these protein components of the hemidesmosomes, inhibiting their anchoring function. The attachment of these circulating antibodies also induces complement and attracts inflammatory cells, thus contributing to epidermal-dermal separation and subepidermal bulla formation.[2,11] The most common target of IgG antibodies is BP180, likely due to its transmembrane structure (Fig. 8).[11]

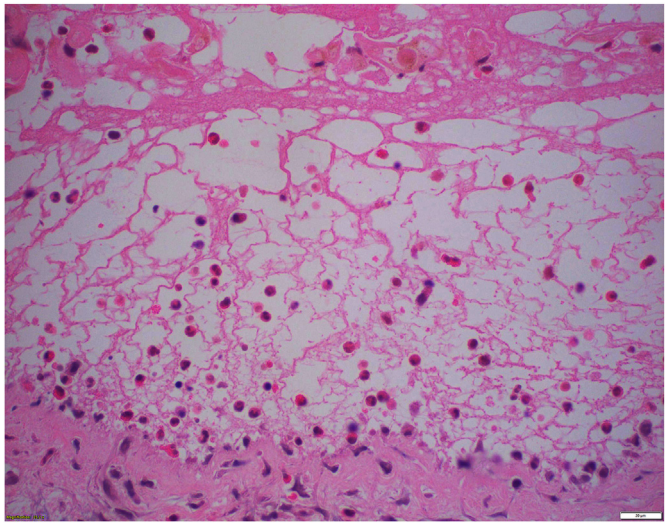

Fig. 5. Higher magnification of bullous pemphigoid from a different patient showing numerous eosinophils within the blister. (H&E, intermediate magnification).

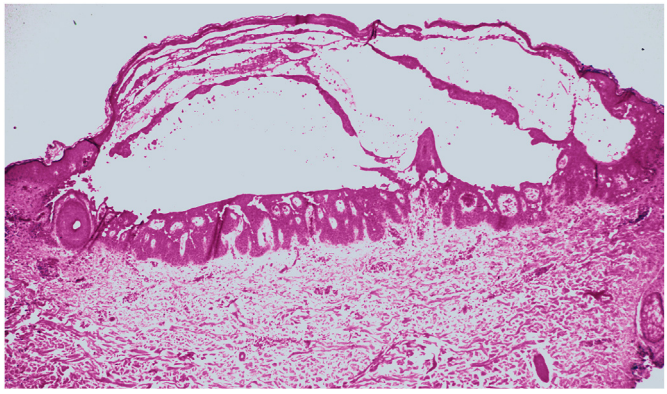

Fig. 6. Pemphigus foliaceus. This biospy shows a prominent subcorneal blister at the level of the stratum granulosum. (H&E, low magnification).

When comparing BP to PV, PV also utilizes antibodies to inhibit proteins in the epidermis; however, a different type of cell to cell adhesion complex is targeted than seen in BP.

The pathogenesis of PV involves desmosomes, protein complexes responsible for adhering adjacent keratinocytes together in the epidermis.[4] In PV, IgG antibodies target Desmoglein 1 (Dsg1) and Desmoglein 3 (Dsg3), resulting in the failure of these protein complexes and thus, subsequent suprabasal blistering. Similarly, the IgG antibodies associated with PF only target Dsg1, but do not target Dsg3 (Fig. 8).[4]

For DH, tissue transglutaminase targeted by IgA in gastrointestinal tract has been shown to have 64 % similarity with epidermal tissue transglutaminase. For DH, the pathogenesis is linked to IgA antibodies attacking the epidermal tissue transglutaminase, resulting in IgA deposition at the dermal papillae and subsequent lesions. HLA DQ2 has been linked with a strong susceptibility for DH and celiac disease onset.[6]

In regards to BP, most factors that predispose patients to develop BP are still unknown.[2] However, certain drugs with a sulfhydryl group, such as captopril, furosemide, cephalexin and penicillamine, have been associated with the onset of BP.[2,12] The mechanism for how certain drugs induce autoantibody formation is still unclear, but some hypothesized theories include molecular mimicry and drugs functioning as antigenic haptens that modify proteins associated with hemidesmosomes.[12]

BP is not a hereditary disorder, but certain genetic factors can predispose patients to this disease. For example, specific human leukocyte

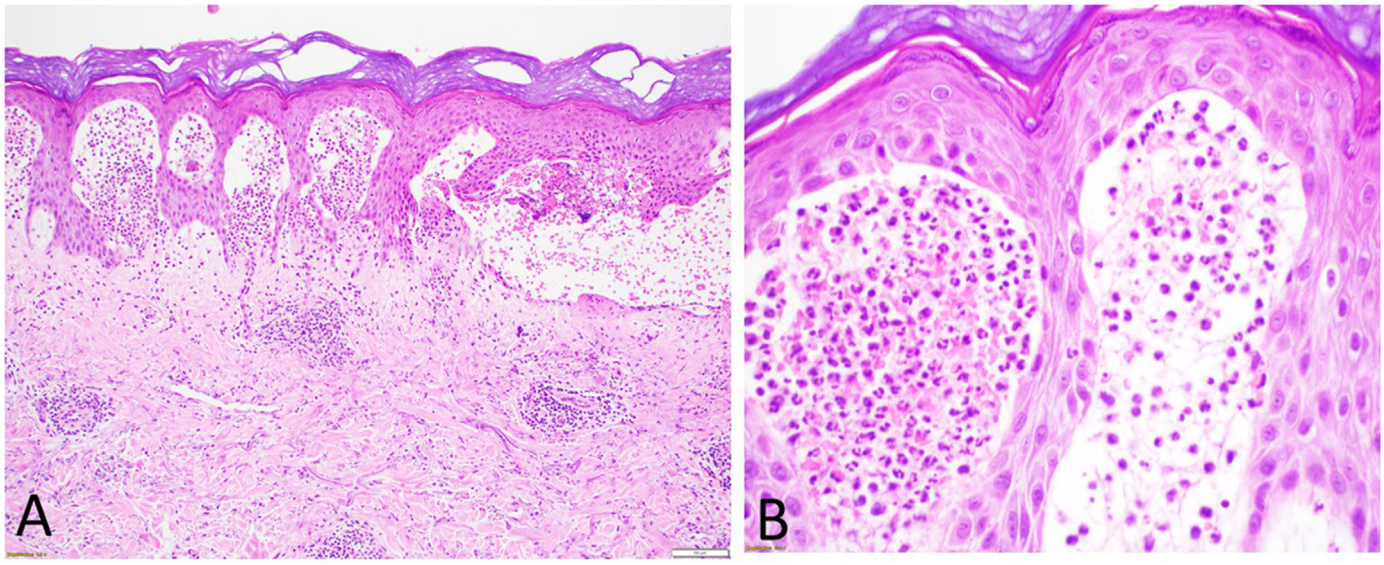

Fig. 7. Dermatitis herpetiformis. A, Small microabcesses are present at the dermal papillae tips. B, Higher magnification shows separation of the dermal epidermal junction. Neutrophils and strands of fibrin are present in the microabcesses. (H&E, A. low magnification, B. intermediate magnification).

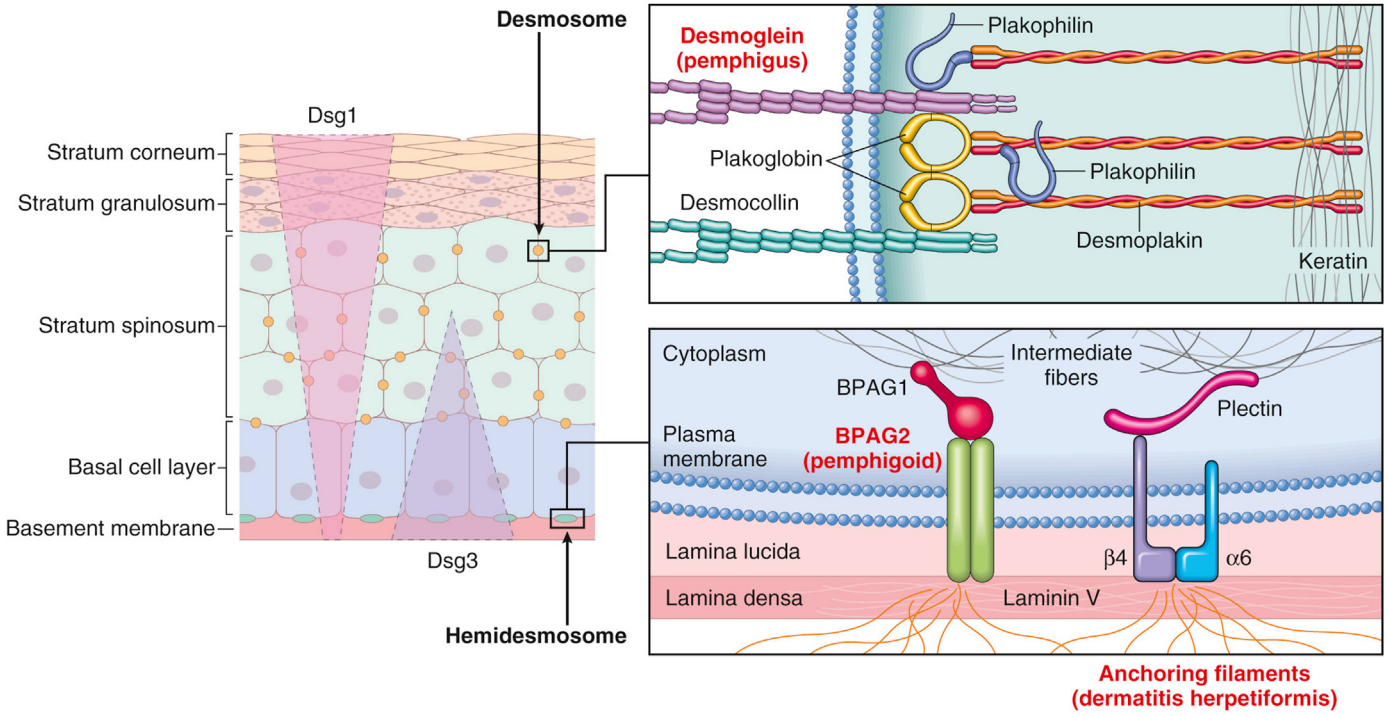

Fig. 8. Illustration of Structural Components Involved in Pathogenesis of Blistering Diseases. Desmoglein is a cellular adhesion protein apart of the desmosome complex that links surrounding keratinocytes together. Antibodies targeting Dsg1 and/or Dsg3 results in PV while solely targeting Dsg 1 results in PF. BPAG2 is the hemidesmosome protein that links the basal cell layer of the epidermis to the basement membrane and is targeted by antibodies in BP. Antibodies that target the anchoring filaments present in the lamina densa are responsible for the pathogenesis of DH.
Figure 25–28 from Lazar AJ. The Skin, In: Kumar V, Abbas A, Aster JC, Turner JR, eds. *Robbins and Cotran Pathologic Basis of Disease*. 10th ed. Elsevier; 2021:1160. Reprinted with permission.

antigen (HLA) genes, which are essential for identifying self-antigens versus foreign antigens, have been linked to BP.[13] Moreover, individuals with HLA-DQB1*0301 alleles, especially those who are Brazilian, Chinese, White, and Iranian, have a higher genetic susceptibility for BP if exposed to certain environmental factors (e.g., UV radiation, drugs, trauma).[13]

What additional laboratory testing would be useful to confirm the diagnosis? Describe this technique and the expected lab finding

Direct and indirect immunofluorescence microscopy (DIF, IIF) would be beneficial to confirm the diagnosis of BP. DIF is used to identify where

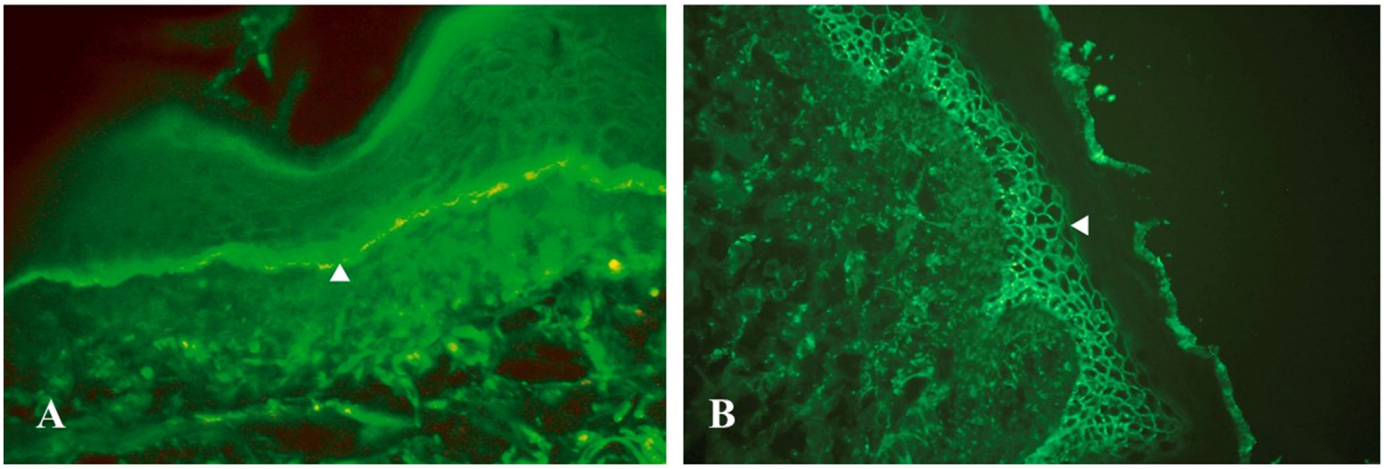

Fig. 9. Immunofluorescence of blistering disorders. A. Bullous pemphigoid. A linear band of IgG is distributed along the basement membrane (arrowhead). B. Pemphigus vulgaris. Antibodies directed against IgG form a netlike pattern (arrowhead). (Direct immunofluorescence for IgG) A. Figure 16.75 and B. Figure 16.72 from Klatt EC. *Robbins and Cotran Atlas of Pathology*. Fourth ed. Philadelphia, PA: Elsevier; 2021. Reprinted with permission.

Table 1
Target antigens, autoantibodies, and immunofluorescence results for blistering diseases.[2,4,6,8,15–17]

Disease	Antigen targeted	Autoantibody	Immunofluorescence results
Bullous pemphigoid	Dystonin-e (BP230 or BPAg1) and collagen XVII (BP180 or BPAg2)	IgG and/or C3	Linear pattern along the epidermal side of the basement membrane
Pemphigus vulgaris	Desmoglein 1 (Dsg1) and Desmoglein 3 (Dsg3)	IgG and C3	"Net like or honey comb like" pattern, prominent in the suprabasal intercellular spaces
Pemphigus foliaceus	Desmoglein 1 (Dsg1)	IgG and/or C3	"Net like or honey comb like" pattern, prominent in the subcorneal intercellular spaces
Dermatitis herpetiformis	Tissue transglutaminase (tTG)	IgA	Pattern consistent with the tips of the dermal papillae

the autoantibodies have deposited in the epidermis and dermis, while IIF detects the specific autoantibodies circulating in a patient's serum.[8,14] These methods utilized a primary or secondary fluorescent antibody that tags its desired target. Biopsy of perilesional skin is critical to have best yield of positive results in DIF testing of BP.[8,14]

In BP, autoantibodies deposit at the epidermal–dermal junction as their target antigens are components of hemidesmosomes. There is linear fluorescence for IgG and C3 along the epidermal side of the basement membrane (Fig. 9).[8] In contrast, IF results for PV consist of a "honeycomb like" pattern present in the suprabasal intercellular spaces while PF has this same pattern but in the subcorneal intercellular spaces. IF for DH shows antibody deposition at the tips of the dermal papillae.[8,14,15] Key features of the blistering diseases discussed are summarized (Table 1).[2,4,6,8,15–17]

What disorders are associated with bullous pemphigoid?

BP has been showed to be associated with several neurological disorders, such as dementia, stroke, and Parkinson's disease.[18,19] Interestingly, proteins, such as BPAg1 and BPAg2, that function to link intermediate filaments to hemidesmosomal proteins are present both in the epidermis and the brain. When the blood brain barrier deteriorates due to neurological diseases, the neuronal isoforms of these BPAg1 and BPAg2 antigens are exposed to immune cells.[18,19] Autoantibodies are then generated against BPAg1 and BPAg2, but these antibodies can then cross react against their epidermal counterpart.[18,19] Thus, BP often occurs in the elderly after the onset of neurological diseases.[18,19] Finally, mortality is six times higher for patients with BP when compared to healthy individuals in the same age cohort.[2,13] Patients with BP who suffer from a stroke had an increased one-year mortality compared to those with a neurological disease.[18]

What are the treatment options for bullous pemphigoid?

There are a number of different treatment options available for BP, including topical and systemic corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, cyclosporine, tacrolimus, tetracyclines, chlorambucil, dapsone, sulfonamides, erythromycin, niacinamide, intravenous immunoglobulins, and plasmapheresis.[20] Treatment regimen include one or a combination of the listed agents.[17] Prednisone is commonly used in a tapered dose to suppresses the inflammatory response associated with severe BP.[17] Topical corticosteroids may be the only treatment needed for mild BP while biologic or immunosuppression therapies may be required for refractory BP. Overall, BP is self-limiting and some cases can resolve on their own within six years.[17]

Teaching points

- Bullous pemphigoid is an autoimmune blistering disease that presents clinically as tense bulla on the flexor surfaces of the upper and lower extremities and the lower trunk, rarely involving mucosa.
- On histology, BP is characterized as a subepidermal bulla with a mixed inflammatory infiltrate containing eosinophils.
- Autoantibodies of IgG against hemidesmosomes proteins dystonin-e (BP230 or BPAg1) and collagen XVII (BP180 or BPAg2) are associated with BP development.
- Other blistering diseases include pemphigus vulgaris (PV), pemphigus foliaceus (PF), and dermatitis herpetiformis (DH).
- PV is associated with fragile blisters with mucosal involvement, due to an antibody targeting Desmoglein 1 (Dsg1) and Desmoglein 3 (Dsg3). PF develops in a similar anatomical pattern while lacking mucosal involvement.

- DH presents typically as grouped vesicles or urticarial plaques resulting in erosions on extensor surfaces. DH pathogenesis is linked to antibodies against tissue transglutaminase.
- Certain drugs, such as captopril, furosemide, cephalexin and penicillamine, have been associated with the onset of BP.
- BP is not a hereditary disorder, but specific Human Leukocyte Antigen (HLA) genes can predispose patients to this disease.
- In regards to immunofluorescence lab results, linear fluorescence along the epidermal side of the basement membrane targeting IgG±C3 is observed for BP.
- Due to the pathogenesis of BP, it has been shown to be associated with several neurological disorders, such as dementia, stroke, and Parkinson's disease.
- Although self-limiting, current treatment options for BP are topical and systemic corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, cyclosporine, tacrolimus, tetracyclines, chlorambucil, dapsone, sulfonamides, erythromycin, niacinamide, intravenous immunoglobulins and plasmapheresis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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