Recurrent Oral and Gluteal Cleft Erosions

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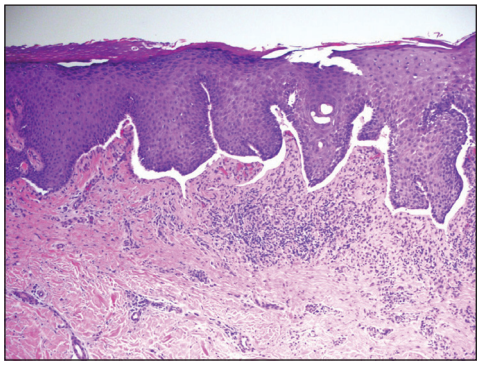

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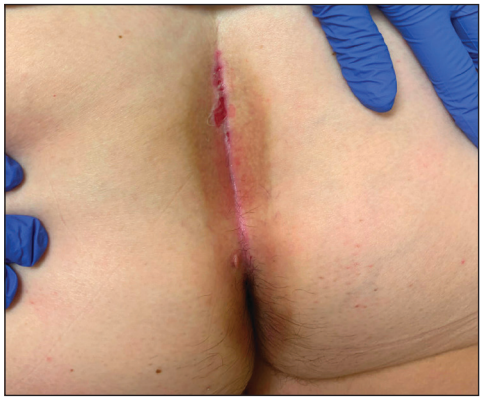

Erythematous eroded plaque of the gluteal cleft.

A 71-year-old woman with no relevant medical history presented with recurrent painful erosions on the gingivae and gluteal cleft of 1 year's duration. She previously was diagnosed by her periodontist with erosive lichen planus and was prescribed topical and oral steroids with minimal improvement. She denied fever, chills, weakness, fatigue, vision changes, eye pain, and sore throat. Dermatologic examination revealed edematous and erythematous upper and lower gingivae with mild erosions, as well as thin, eroded, erythematous plaques within the gluteal cleft. Indirect immunofluorescence revealed IgG with epidermal localization in a human split-skin substrate, and an enzyme-linked immunosorbent assay revealed positive IgG to bullous pemphigoid (BP) 180 and negative IgG to BP230. A 4-mm punch biopsy of the gluteal cleft was performed.

THE BEST **DIAGNOSIS IS:**

a. bullous lichen planus
b. bullous pemphigoid
c. classic lichen planus
d. lichen planus pemphigoides
e. paraneoplastic pemphigus

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doi:10.12788/cutis.0749

THE **DIAGNOSIS:** Lichen Planus Pemphigoides

Lichen planus pemphigoides (LPP) is a rare acquired autoimmune blistering disorder with an estimated worldwide prevalence of approximately 1 in 1,000,000 individuals.[1] It often manifests with overlapping features of both LP and bullous pemphigoid (BP). The condition usually presents in the fifth decade of life and has a slight female predominance.[2] Although primarily idiopathic, it has been associated with certain medications and treatments, such as angiotensin-converting enzyme inhibitors, programmed cell death protein 1 inhibitors, programmed cell death ligand 1 inhibitors, labetalol, narrowband UVB, and psoralen plus UVA.[3,4]

Patients initially present with lesions of classic lichen planus (LP) with pink-purple, flat-topped, pruritic, polygonal papules and plaques.[5] After weeks to months, tense vesicles and bullae usually develop on the sites of LP as well as on uninvolved skin. One study found a mean lag time of about 8.3 months for blistering to present after LP,[5] but concurrent presentations of both have been reported.[1] In addition, oral mucosal involvement has been seen in 36% of cases. The most commonly affected sites are the extremities; however, involvement can be widespread.[2]

The pathogenesis of LPP currently is unknown. It has been proposed that in LP, injury of basal keratinocytes exposes hidden basement membrane and hemidesmosome antigens including BP180, a 180 kDa transmembrane protein of the basement membrane zone (BMZ),[6] which triggers an immune response where T cells recognize the extracellular portion of BP180 and antibodies are formed against the likely autoantigen.[1] One study has suggested that the autoantigen in LPP is the MCW-4 epitope within the C-terminal end of the NC16A domain of BP180.[7]

Histopathology of LPP reveals characteristics of both LP as well as BP. Typical features of LP on hematoxylin and eosin (H&E) staining include lichenoid lymphocytic interface dermatitis, sawtooth rete ridges, wedge-shaped hypergranulosis, and colloid bodies, as demonstrated from the biopsy of our patient's gluteal cleft lesion (quiz image 1), while the predominant feature of BP on H&E staining includes a subepidermal bulla with eosinophils.[2] Typically, direct immunofluorescence (DIF) shows linear deposits of IgG and/or C3 along the BMZ. Indirect immunofluorescence (IIF) often reveals IgG against the roof of the BMZ in a human split-skin substrate.[1] Antibodies against BP180 or uncommonly BP230 often are detected on enzyme-linked immunosorbent assay (ELISA). For our patient, IIF and ELISA tests were positive. Given the clinical presentation with recurrent oral and gluteal cleft erosions, histologic findings, and the results of our patient's immunological testing, the diagnosis of LPP was made.

Topical steroids often are used to treat localized disease of LPP.[8] Oral prednisone also may be given for widespread or unresponsive disease.[9] Other treatments include azathioprine, mycophenolate mofetil, hydroxychloroquine, dapsone, tetracycline in combination with nicotinamide, acitretin, ustekinumab, baricitinib, and rituximab with intravenous immunoglobulin.[3,8,10-12] Any potential medication culprits should be discontinued.[9] Patients with oral involvement may require a soft diet to avoid further mucosal insult.[10] Additionally, providers should consider dentistry, ophthalmology, and/or otolaryngology referrals depending on disease severity.

Bullous pemphigoid, the most common autoimmune blistering disease, has an estimated incidence of 10 to 43 per million individuals per year.[2] Classically, it presents with tense bullae on the skin of the lower abdomen, thighs, groin, forearms, and axillae. Circulating antibodies against 2 BMZ proteins—BP180 and BP230—are important factors in BP pathogenesis.[2] Diagnosis of BP is based on clinical features, histologic findings, and immunological studies including DIF, IIF, and ELISA. An eosinophil-rich subepidermal split typically is seen on H&E staining (Figure 1).

Direct immunofluorescence displays linear IgG and/or C3 staining at the BMZ. Indirect immunofluorescence on a human salt-split skin substrate commonly shows linear BMZ deposition on the roof of the blister.[2] Indirect immunofluorescence for IgG deposition on monkey esophagus substrate shows linear BMZ deposition. Antibodies against the NC16A domain of BP180 (NC16A-BP180) are dominant, but BP230 antibodies against BP230 also are detected with ELISA.[2] Further

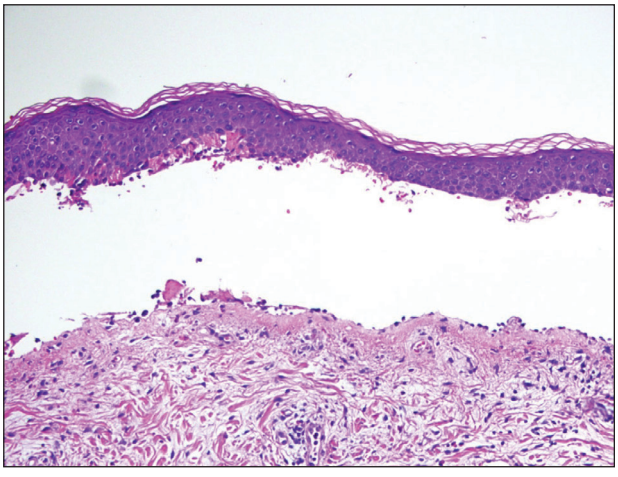

FIGURE 1. Bullous pemphigoid. An eosinophil-rich subepidermal blister is present (H&E, original magnification ×200).

studies have indicated that the NC16A epitopes of BP180 that are targeted in BP are MCW-0-3,[2] different from the autoantigen MCW-4 that is targeted in LPP.[7]

Paraneoplastic pemphigus (PNP) is another diagnosis to consider. Patients with PNP initially present with oral findings—most commonly chronic, erosive, and painful mucositis—followed by cutaneous involvement, which varies from the development of bullae to the formation of plaques similar to those of LP.[13] The latter, in combination with oral erosions, may appear clinically similar to LPP. The results of DIF in conjugation with IIF and ELISA may help to further differentiate these disorders. Direct immunofluorescence in PNP typically reveals positive intercellular and/or BMZ IgG and C3, while DIF in LPP reveals depositions along the BMZ alone. Indirect immunofluorescence performed on rat bladder epithelium is particularly useful, as binding of IgG to rat bladder epithelium is characteristic of PNP and not seen in other disorders.[14] Lastly, patients with PNP may develop IgG antibodies to various antigens such as desmoplakin I, desmoplakin II, envoplakin, periplakin, BP230, desmoglein 1, and desmoglein 3, which would not be expected in LPP patients.[15] Hematoxylin and eosin staining differs from LPP, primarily with the location of the blister being intraepidermal. Acantholysis with hemorrhagic bullae can be seen (Figure 2).

Classic LP is an inflammatory disorder that mainly affects adults, with an estimated incidence of less than 1%.[16] The classic form presents with purple, flat-topped, pruritic, polygonal papules and plaques of varying size that often are characterized by Wickham striae. Lichen planus possesses a broad spectrum of subtypes involving different locations, though skin lesions usually are localized to the extremities. Despite an unknown etiology, activated T cells and T helper type 1 cytokines are considered key in keratinocyte injury. Compact orthokeratosis, wedge-shaped hypergranulosis, focal dyskeratosis, and colloid bodies typically are found on H&E staining, along with a dense bandlike lymphohistiocytic infiltrate at the dermoepidermal junction (DEJ)(Figure 3). Direct immunofluorescence typically shows a shaggy band of fibrinogen along the DEJ in addition to colloid bodies that stain with various autoantibodies including IgM, IgG, IgA, and C3.[16]

Bullous LP is a rare variant of LP that commonly develops on the oral mucosa and the legs, with blisters confined on pre-existing LP lesions.[9] The pathogenesis is related to an epidermal inflammatory infiltrate that leads to basal layer destruction followed by dermal-epidermal separations that cause blistering.[17] Bullous LP does not have positive DIF, IIF, or ELISA because the pathophysiology does not involve autoantibody production. Histopathology typically displays an extensive inflammatory infiltrate and degeneration of the basal keratinocytes, resulting in large dermal-epidermal separations called Max-Joseph spaces (Figure 4).[17] Colloid bodies are prominent in bullous LP but rarely are seen in LPP; eosinophils also are much more prominent in LPP compared to

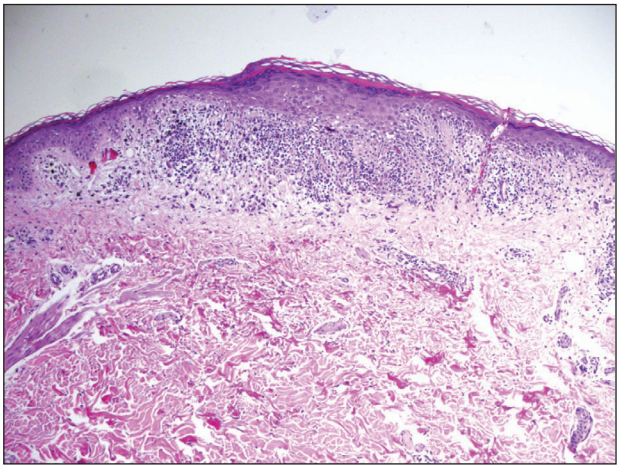

FIGURE 3. Classic lichen planus. Lichenoid interface dermatitis at the dermoepidermal junction (H&E, original magnification ×100).

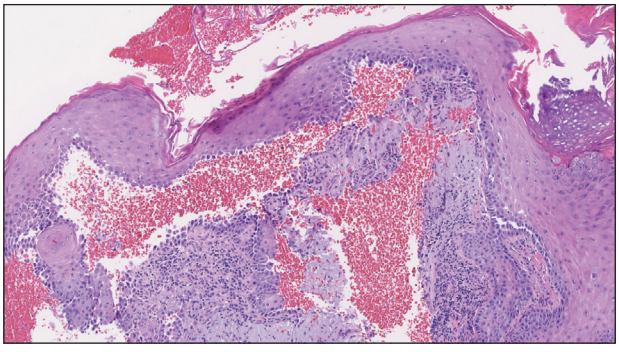

FIGURE 2. Paraneoplastic pemphigus. Acantholysis, hemorrhagic bullae formation, and suprabasilar dyscohesion are present (H&E, original magnification ×100).

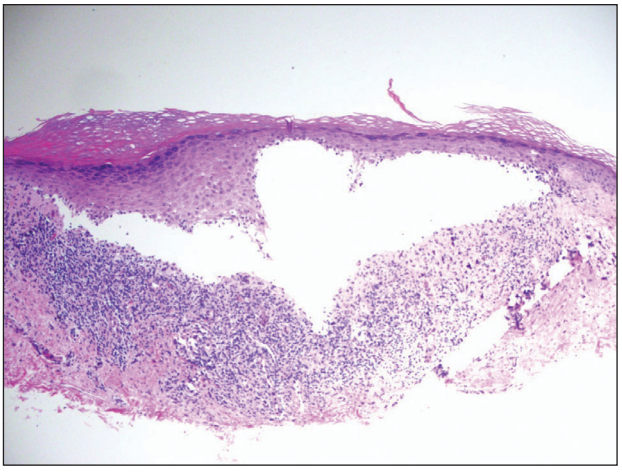

FIGURE 4. Bullous lichen planus. A Max-Joseph space is visible due to a lichenoid infiltrate and degeneration of basal keratinocytes (H&E, original magnification ×100).

bullous LP.[18] Unlike in LPP, DIF usually is negative in bullous LP, though lichenoid lesions may exhibit globular deposition of IgM, IgG, and IgA in the colloid bodies of the lower epidermis and/or papillary dermis. Similar to LP, DIF of the biopsy specimen shows linear or shaggy deposits of fibrinogen at the DEJ.[17]

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