Milia within resolving bullous pemphigoid lesions

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ABSTRACT

Bullous pemphigoid (BP) is a blistering dermatosis characterized by an autoimmune response to two hemidesmosomal proteins, BP180 and BP230. We describe a case of an 80-year-old man diagnosed with BP by clinical features, histopathology, and immunosorbent assay who developed milia within resolving BP lesions. Milia formation during recovery is common in cases of mucous membrane pemphigoid and epidermolysis bullosa acquisita but has rarely been reported in cases of BP.

KEYWORDS Bullous pemphigoid; milium formation; postbullous milia

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease. Risk factors for BP include older age, neurologic diseases, and medications such as loop diuretics, spironolactone, and neuroleptics. Clinically, the disease may present with a nonspecific, nonbullous phase with eczematous, papular, or urticarial lesions before presenting with the bullous phase, characterized by the formation of tense, pruritic vesicles and bullae on the extremities and trunk. The diagnosis of BP relies on immunopathologic findings such as direct and indirect immunofluorescence microscopy, as well as anti-BP180 and anti-BP230 enzyme-linked immunosorbent assay (ELISA). BP is characterized by the formation of autoantibodies to hemidesmosomal components BP180 and BP230, which are involved in dermal-epidermal cohesion. The mainstay of treatment for BP is high-potency topical and oral steroids. Second-line therapies include immunosuppressive agents, such as azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamide.¹ In addition, both rituximab and intravenous immunoglobulin have been shown to be effective in recalcitrant cases of BP.^{2–4} Postrecovery milia formation is a common feature of epidermolysis bullosa acquisita (EBA) and mucous membrane pemphigoid (MMP) but is rare in BP.⁵ We report a unique case of BP with postrecovery milia formation.

CASE PRESENTATION

An 80-year-old white man presented with a 2-week history of painful blisters over his entire body shortly after

starting furosemide. Physical exam revealed vesicles and tense bullae involving his face, trunk, and upper and lower extremities. Mucous membranes were uninvolved. Complete blood count revealed leukocytosis of 12,700/ μ L with increased eosinophils of 15%. HIV and hepatitis A, B, and C serologies were negative. A punch biopsy of a lesion from the left shoulder revealed a subepidermal bulla with underlying chronic inflammation and numerous eosinophils (*Figure 1a*). Direct immunofluorescence of a punch biopsy from the same lesion showed linear deposits of C3 and immunoglobulin G at the dermal epidermal junction (*Figures 1b, 1c*). ELISA revealed an elevated BP180 antibody level; BP230 antibody was negative. The patient's clinical presentation, biopsies, and serologies were consistent with a diagnosis of BP.

The patient had a difficult and prolonged hospital course. Despite stopping the presumed causative agent, furosemide, and starting high doses of prednisone (1 mg/kg) along with mycophenolate mofetil, the patient continued to develop new, large bullae. Due to the recalcitrant nature of his condition, the patient was given a 4-day course of intravenous immunoglobulin (2 g/kg), and dapsone was started. Over the next 8 weeks, while remaining on mycophenolate mofetil, dapsone, and prednisone taper, the patient's condition stabilized. However, he began to note crops of asymptomatic pinpoint white papules within his resolving bullae (*Figure 2a*). A 4-mm punch biopsy specimen was obtained for histopathologic examination of a representative lesion on the left upper arm. Histologic examination of the specimen from the

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Figure 1. (a) Punch biopsy of the lesion revealing a subepidermal bulla with underlying chronic inflammation and numerous eosinophils, consistent with bullous pemphigoid (hematoxylin-eosin, original magnification $\times 100$). Direct immunofluorescence biopsy showed linear deposits of (b) C3 ($\times 400$) and (c) immunoglobulin G ($\times 400$) at the dermal-epidermal junction.

Figure 2. (a) Pinpoint white papules in grouped and annular distribution along the periphery of resolving bullous pemphigoid lesions noted on the thighs (shown), trunk, and arms. (b) Histology of a 4-mm punch biopsy specimen of a lesion on the left upper arm showing a dermal unilocular cyst lined by stratified squamous epithelium with a granular cell layer and basket-woven keratin debris (hematoxylin-eosin, original magnification $\times 40$).

left upper arm showed a dermal unilocular cyst lined by stratified squamous epithelium with a granular cell layer (Figure 2b). The cyst contents included basket-woven keratin debris. The clinicopathologic findings were suggestive of milia arising within resolving BP lesions.

The patient was reassured of the benign nature of the lesions and no further treatment was pursued for the milia. The patient was successfully tapered off prednisone, while remaining on mycophenolate mofetil and dapsone. At 6-month follow-up, his BP remained stable and no new vesicles or bullae were noted.

DISCUSSION

Postrecovery milia formation is a common feature of EBA and MMP but is rare in BP.⁵ In one study, Prost et al observed that almost half of patients with EBA and MMP had milia but none of the 15 BP patients showed milia formation.⁶ The clinical and histopathologic findings of BP closely resemble those of EBA and MMP. Therefore, additional tests such as ELISA and indirect immunofluorescence performed using a salt split technique are required to differentiate BP from EBA and MMP. In our patient, serologic testing for BP180 antibody was positive, which favors a diagnosis of BP over EBA and MMP.

There have been few case studies that describe milium formation in BP patients with antibodies against BP180 and BP230 antigens. Uchida et al⁵ and Tsuruta et al⁷ reported BP cases with milium formation in patients who had immunoglobulin G autoantibodies to BP180. Venning et al reported that milium formation was detected in two of nine patients reacting only with BP230 antigen, in one of six patients reacting only with BP180 antigen, and in 3 of 15 patients without autoantigen detection.⁸ Furthermore, some individuals may be immunologically predisposed to postbullous milia formation. Banfield et al reported that the presence of milia in patients with BP was linked with a specific human leukocyte antigen DQ6 in both men and women.⁹

The pathophysiologic mechanism of postbullous milia is not clear. Milia secondary to blisters are thought to develop in the process of regenerating sweat glands or hair follicles damaged in the blistering and are therefore expected to be temporary.¹⁰ In a patient with BP, the formation of milia has also been postulated to be due to aberrant interactions between the hemidesmosomes and the extracellular matrix components beneath the hemidesmosomes.⁵

There is no specific treatment for postbullous milia.¹¹ Our patient was closely followed to ensure that there was no

exacerbation of the underlying BP, but no additional treatment was sought for his milia. This case highlights the importance of considering the diagnosis of postrecovery milia in a patient with BP.

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