Bullous Pemphigoid with Milia: An Uncommon Clinical Manifestation

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ABSTRACT:
Bullous pemphigoid (BP) is the most prevalent autoimmune disorder characterized by subepidermal blistering, primarily affecting older adults. While BP primarily presents with tense bullae on the extremities and trunk, milia formation during recovery is a rare but notable occurrence. We report an 86-year-old Thai male diagnosed with BP who developed milia on the trunk and extremities during the recovery phase. Diagnosis was confirmed by clinical findings, histopathology, and immunological studies, which showed subepidermal blistering, elevated anti-BP180 levels, and epidermal-side IgG deposition. Treatment included prednisolone, doxycycline, nicotinamide, and topical clobetasol, with lesion improvement observed.
Key words: Bullous pemphigoid, Milia formation, Postbullous milia, Secondary milia, Autoimmune blistering disease

Introduction

Bullous pemphigoid (BP) is the most frequent autoimmune disease causing subepidermal blistering, predominantly seen in older adults[1]. BP usually manifests as pruritic, tense bullae on the trunk and extremities, often following a non-bullous phase characterized by eczematous or urticarial lesions[2]. Diagnosis of BP involves histopathologic findings of subepidermal blistering with eosinophilic infiltration and immunopathologic identification of IgG and C3 deposits along the basement membrane zone (BMZ). Autoantibodies targeting BP180 and BP230, essential proteins for dermal-epidermal cohesion, are identified through techniques like direct immunofluorescence, ELISA, and immunoblotting. The standard treatment includes high-potency corticosteroids and immunosuppressants in recalcitrant cases[3].

Post-recovery milia formation, though rare in BP, has been observed in some cases, contrasting with its more frequent occurrence in other subepidermal blistering diseases, such as epidermolysis bullosa acquisita (EBA)[4]. Milia commonly develop in areas of prior blistering and are histologically composed of stratified squamous epithelium with a granular cell layer. They are categorized as primary, arising spontaneously, or secondary, occurring due to trauma, underlying disease, or medication use[5]. Here, we present the case of an older male with bullous pemphigoid who developed milia formation.

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Case report

An 86-year-old Thai male presented with multiple tense bullous lesions and erosions affecting the trunk and extremities, without mucosal involvement persisting for two years. The patient had a medical history of Parkinson's disease and irritable bowel syndrome. His current medications included quetiapine, tolvaptan, prucalopride, domperidone, levodopa/benserazide, clonazepam, and itopride. A skin biopsy revealed subepidermal separation with dense eosinophilic infiltration. Indirect immunofluorescences revealed negative IgG antibodies against the basement membrane zone. Based on the clinical presentation of tense bullae, histopathology findings, and serological results, the patient was diagnosed with bullous pemphigoid. Initial treatment of prednisolone 30 mg/kg/day, nicotinamide 600 mg/day, and doxycycline 200 mg/day has been prescribed, along with topical corticosteroids for active lesions. During the two-year follow-up, the prednisolone dose was gradually tapered according to clinical improvement, reaching a maintenance dose of 5 mg/day. The disease remained generally well controlled, with intermittent mild flare-ups managed by adjusting the corticosteroid dose. Laboratory investigations showed stable hematologic and biochemical parameters, and no mucosal involvement or systemic complications were observed during this period.

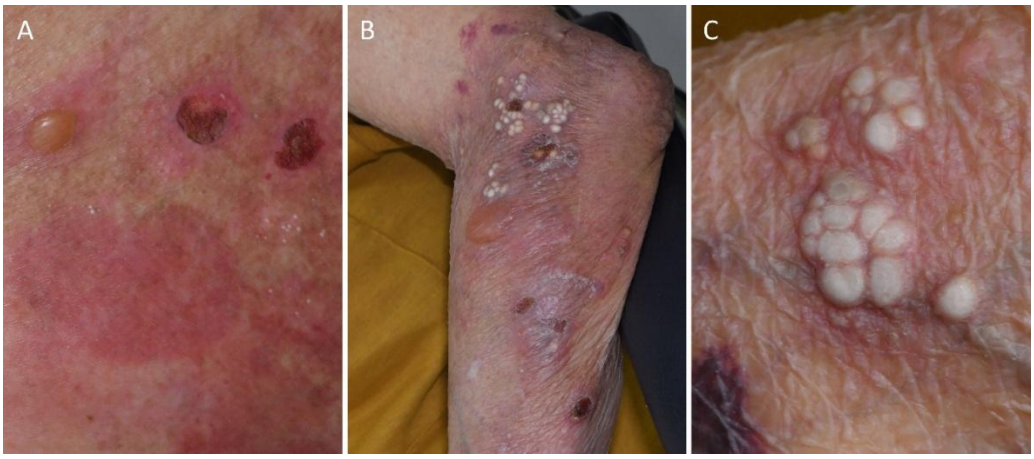

Figure 1 Multiple tense bullous eruptions on an urticarial base with small milia on the back. (A) Tense bullous eruptions with milia formation on the left forearm (B-C)

However, two years after the diagnosis, the patient reported the development of few tense bullae on the trunk and extremities, along with small whitish papules on the extremities (Figure 1), despite good adherence to regular systemic therapy. There was no mucosal involvement. Dermatological examination revealed multiple tense bullae and erosions, along with numerous tiny whitish papules on the trunk and extremities. No oral ulcers or mucosal lesions were observed. Other systemic examinations were otherwise normal. The differential diagnoses for this patient included BP, epidermolysis bullosa acquisita, and bullous systemic lupus erythematosus with milia formation.

Histopathological examination of a whitish papule from the left forearm showed subepidermal separation of the epidermis with hyperkeratosis. No inflammatory cells or acantholytic cells were identified in the separated space. The dermis exhibited mild superficial perivascular lymphocytic infiltration with fibrosis, and milia formation

was noted (Figure 2). An ELISA test was conducted, revealing a positive result for anti-BP180 at 223 U/mL (normal < 20 U/mL) and anti-BP230 at 31 U/mL (normal < 20 U/mL), while the collagen VII IgG result was negative. ANA was positive at 1:80 with a speckled and cytoplasmic pattern. Salt-split skin testing revealed IgG deposition on the epidermal side of the split skin.

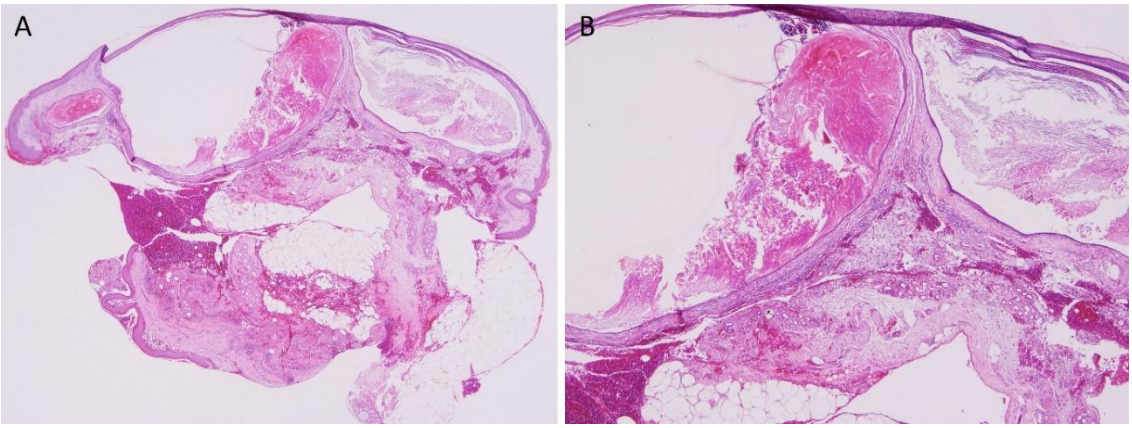

Figure 2 Histopathology reveals subepidermal separation of the epidermis with hyperkeratosis. The dermis shows mild superficial perivascular lymphocytic infiltration with fibrosis and evidence of milia formation (A, H&E, X40; B, H&E, X100)

Based on these findings, the patient was diagnosed with milia associated with bullous pemphigoid. His treatment was adjusted by increasing prednisolone to 30 mg/kg/day while continuing doxycycline, nicotinamide, and topical clobetasol. Two weeks after these adjustments, the tense bullae and milia improved, allowing for tapering of prednisolone.

Discussion

Milia are typically benign keratinous cysts that appear as pearly white, dome-shaped lesions, measuring between 1 and 4 mm in diameter. Milia can be categorized as primary, occurring spontaneously, or secondary, resulting from trauma, burns, dermatologic conditions, or blistering diseases such EBA, mucous membrane pemphigoid (MMP), and occasionally BP[6-7]. Secondary milia are believed to develop from the regeneration of damaged sweat glands or hair follicles during the healing process. In BP, milia formation is rare but has been reported during recovery, often associated with severe or refractory cases[8].

The exact pathogenesis of milia in BP is not fully understood, but it is thought that immunological factors and abnormal interactions between hemidesmosomal proteins (BP180 and BP230) and the extracellular matrix may play a role[9]. Genetic factors, including the presence of HLA-DQ6, have been associated with an increased risk of milia formation in patients with BP[6,10]. Elevated serum IgE levels, which correlate with BP severity, may also play a role in disease progression and milium development[9].

Several studies have highlighted the variability in the prevalence of milia among BP patients, ranging from 7.8% to 31%[2,11]. This discrepancy underscores the importance of careful differentiation between BP with milia and other blistering disorders like EBA, where milia are more commonly observed.

The occurrence of milia in BP, though uncommon, reflects a unique aspect of its recovery phase rather than active disease progression. This distinction is critical to avoid unnecessary escalation of immunosuppressive therapy[12].

There is no standardized treatment for postbullous milia. While spontaneous resolution often occurs within months, patients seeking cosmetic improvement may benefit from procedures such as curettage, excision, electrodessication, or laser therapies[7]. Topical retinoids, such as tretinoin, are effective in promoting keratinocyte turnover and have been successfully used in case reports[12]. However, given the benign nature of milia, interventions are typically pursued only for aesthetic reasons.

In conclusion, we present a case of milia arising in BP, where lesion progression ceased following an adjustment in systemic corticosteroid dosage. This case highlights the significance of identifying milia as a benign consequence of BP, particularly during recovery. Understanding the underlying immunological and genetic factors contributing to milium formation may further aid clinicians in managing these cases and counseling patients.

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