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Linear IgA bullous dermatosis associated with ulcerative proctitis: treatment challenge

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Abstract

Linear IgA bullous dermatosis is a rare bullous disease in children and adults that can be associated with autoimmune conditions, malignancies, infections, or medication exposure. The definitive diagnosis relies on the biopsy. A 58-year-old man presented to our clinic with a pruritic vesicular and bullous eruption. Histology showed the classic findings of a subepidermal blister with neutrophilic infiltrate and linear IgA deposition along the dermal-epidermal junction. Upon further evaluation, he was diagnosed with ulcerative proctitis. His therapy was complicated owing to side effects and lack of response to the standard treatment options. Dapsone, a first-line therapy, caused symptomatic methemoglobinemia whereas niacinamide with doxycycline were not effective. He required intravenous and oral steroids to reach improvement followed by transitioning to methotrexate.

Keywords: linear IgA bullous dermatosis, ulcerative proctitis, autoimmune bullous dermatosis

Introduction

Linear IgA bullous dermatosis is a rare autoimmune bullous disease with childhood and adult variants. Vesicular eruption can be variable and definitive diagnosis is made with a biopsy. IgA antibodies are found against cleaved products of BPAg 2, a hemidesmosome transmembrane protein, with characteristic subepidermal blister with neutrophils and linear IgA deposition along the basement membrane on direct immunofluorescence. Etiology is idiopathic in the majority of cases but can include drugs, infection, malignancy, or autoimmune conditions.

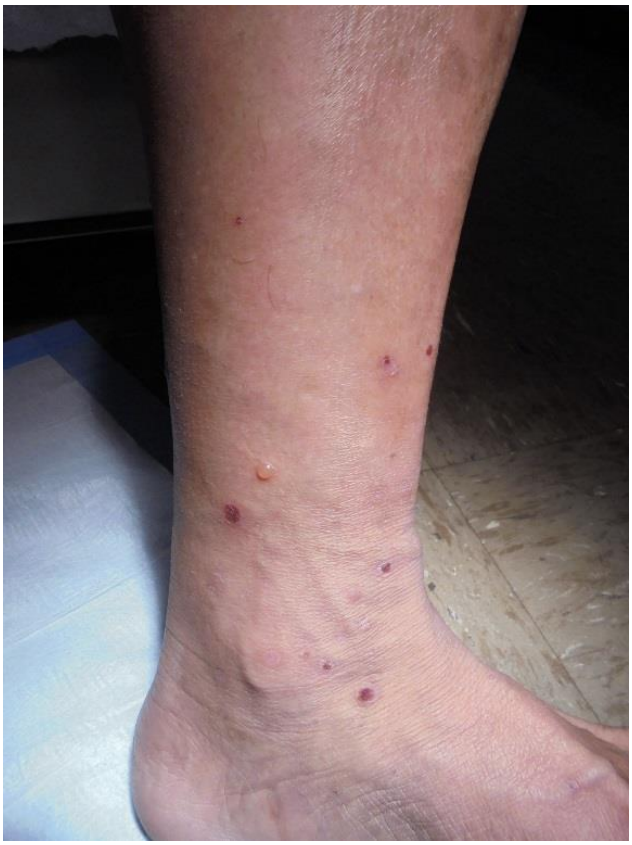

Figure 1. *Small vesicles on distal extremity during initial presentation.*

Case Synopsis

A 58-year-old Fitzpatrick skin type 4 otherwise asymptomatic male presented with a 6-month history of intensely pruritic vesicles and bullae on the trunk, bilateral extremities, and occiput. He denied any mucosal or genital lesions and reported no

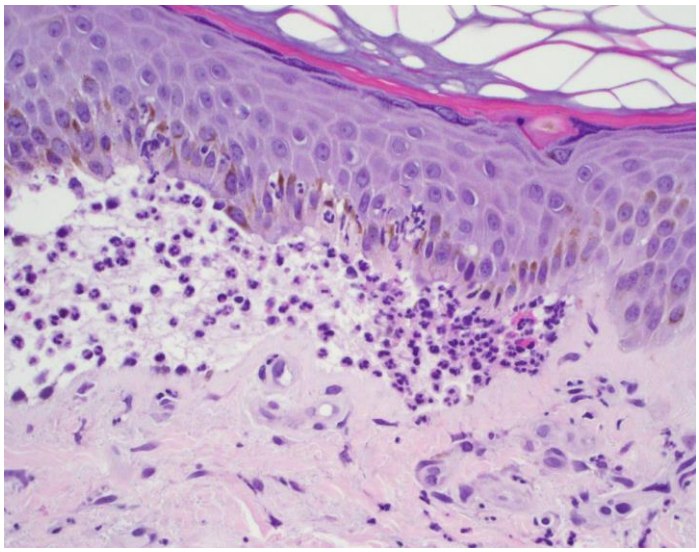

Figure 2. *H&E stain on 400× shows subepidermal blister with neutrophilic infiltrate.*

constitutional symptoms. He was not taking any medications or supplements. Triamcinolone and hydroxyzine prescribed by his primary care provider did not provide any relief.

Small vesicles were present on the chest, back, and distal extremities with mild underlying erythema (**Figure 1**). Two biopsies were obtained at the time of his evaluation in the dermatology clinic.

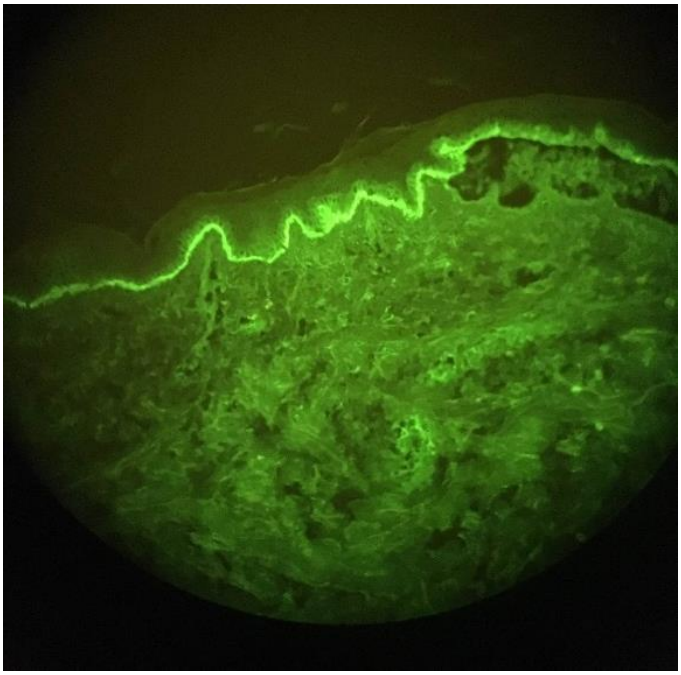

Figure 3. *Direct immunofluorescence on 100× shows homogenous linear deposition of IgA along the basement membrane zone.*

Hematoxylin and eosin staining revealed a subepidermal blister with predominately neutrophils while direct immunofluorescence (DIF) revealed a strong homogenous linear deposition of IgA along the basement membrane zone (**Figures 2, 3**, respectively). Given the biopsy findings, the patient was diagnosed with linear IgA bullous dermatosis (LABD).

The review of systems and lab workup for underlying infection, malignancy, or connective tissue disease were initially negative. He was not taking any medications at the time of symptoms onset. The patient reported a normal colonoscopy 3 years prior. Given the low number of active lesions at presentation, conservative treatment was initiated with topical clobetasol ointment. However, it was not sufficient to control the symptoms; in fact, the patient developed a topical steroid-induced widespread acneiform eruption. Dapsone was initiated and titrated to 150mg per day. The lesions responded rapidly to the medication. Unfortunately, the patient developed symptomatic methemoglobinemia reaching a level of 5.8% and, subsequently, dapsone was discontinued because of significant fatigue. His methemoglobinemia symptoms resolved but the LABD lesions rapidly returned (**Figure 4**). He was transitioned to 3 months of niacinamide 500mg twice daily with doxycycline 100mg twice daily but developed larger, more pruritic, and more widespread bullae (**Figures 5, 6**).

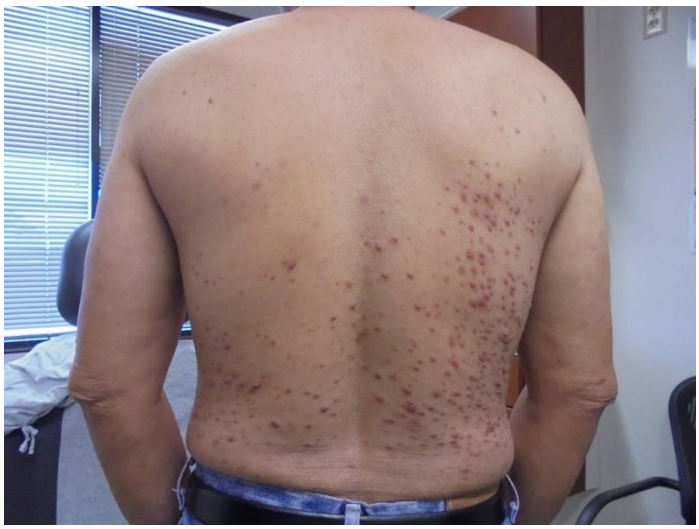

Figure 4. *Small erythematous vesicles on trunk.*

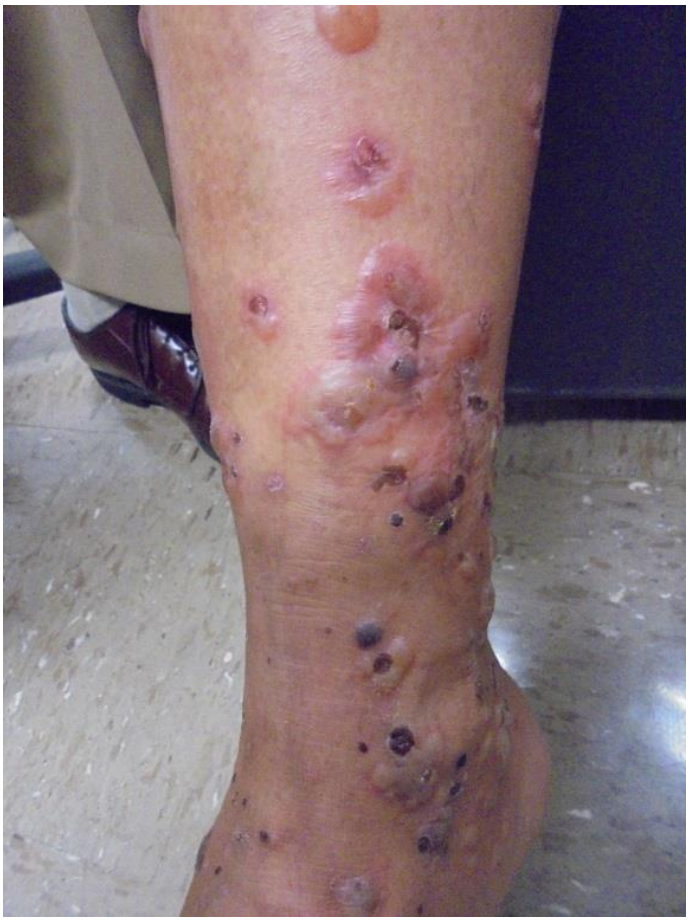

Figure 5. *Large bullae on right distal leg.*

In addition, the patient developed intolerable flushing on this regimen. He was started on high dose prednisone but continued having numerous new lesions. Owing to the significant number of vesicles, large bullae, and associated severe pruritus, the patient was admitted for a three-day course of intravenous methylprednisolone. Associated with the flare, he also reported hematochezia and mild abdominal pain. Review of his previous colonoscopy with biopsy showed evidence of chronic ulcerative proctitis, a limited variant of ulcerative colitis (UC). Further evaluation of the gastroenterology records revealed that the patient was lost to follow up. A gastroenterology consultant evaluated the patient and started mesalamine for his chronic inflammatory condition. Long-term treatment with methotrexate was deemed to be necessary to concomitantly control his LABD and gastrointestinal issues.

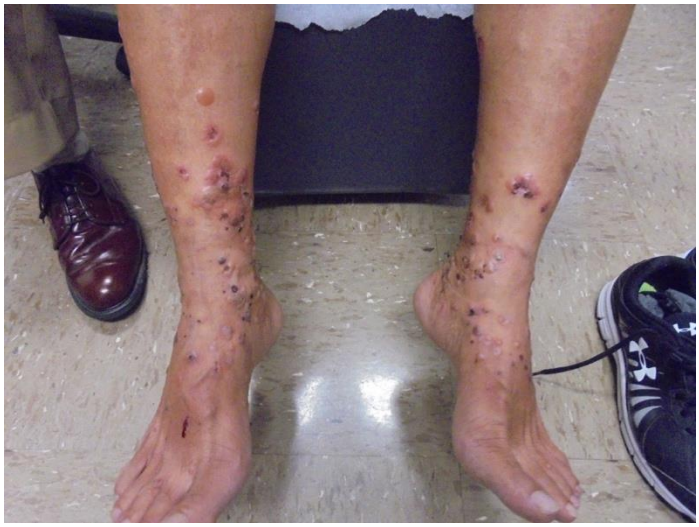

Figure 6. *Large bullae on bilateral distal legs.*

The patient is currently taking 22.5mg of methotrexate weekly and mesalamine with near clearance of the skin lesions. The hematochezia and abdominal pain resolved and occasional small vesicles are managed with topical clobetasol as needed.

Our patient's LABD was most likely driven by the underlying chronic proctitis since his flares and response to treatment were correlated. One challenge of this case was that the skin symptoms had consistently been out of proportion to the gastrointestinal symptoms. The failure of mesalamine monotherapy and outpatient systemic corticosteroid treatment lead the authors to suspect the underlying proctitis was more severe than his symptoms indicated.

Case Discussion

LABD is a rare autoimmune vesiculobullous disease with the classic histologic finding of a subepidermal blister with neutrophilic infiltrate and linear IgA deposition along the dermal-epidermal junction [1]. No definitive genetic, gender, or racial predisposition has been identified [2]. Two somewhat distinct forms exist in children and adults, which are united by their common antigenic determinant. The childhood variant of IgA tends to peak around 2-3 years of age with the more characteristic finding of a "crown of jewels" vesicular eruption on physical exam, whereas the adult variant can present with variable morphological features mimicking dermatitis herpetiformis or bullous pemphigoid most

commonly around the age of 60 [1, 3]. Mucosal involvement is frequent and can be found in up to 60% of the patients [3]. Pathophysiology of LABD involves production of IgA antibodies against 97-kilodalton or 120-kilodalton antigens, which are cleaved products of the collagen XVII (BPAg2, BP180) transmembrane protein localized to a hemidesmosome.

Multiple causes have been reported, including drugs, infections, malignancy (non-Hodgkins lymphoma and chronic lymphocytic leukemia), ultraviolet radiation, and autoimmune conditions like ulcerative colitis and systemic lupus erythematosus [2-5]. The most frequently encountered causative medication is vancomycin but others have been reported as well, such as captopril, phenytoin, amiodarone, naproxen, penicillin, and piroxicam [2]. However, the etiology is often unclear in half of the cases with a more persistent but less severe course [6]. Association of UC and LABD has been increasingly emphasized with the first case of inflammatory bowel disease (IBD) and LABD being reported in 1988 [7]. The incidence of UC is approximately 7% in LABD patients whereas it is only 0.05% in general population [8]. The etiology is unclear but it is postulated that exposure to the autoantigens in the gastrointestinal tract sensitizes the immune system to react to the similar antigens in the skin [8,9]. Another support for the association of UC and LABD comes from the case reports of skin lesions improvement after achieving UC remission with infliximab [4].

Treatment is aimed at improving the underlying condition or withdrawing the offending medication with reports of complete remission of LABD within 3 weeks of discontinuing a causative drug [5]. Additionally, spontaneous resolution of the childhood linear IgA can occur after running its natural course for several years and remitting by adolescence [2]. Unfortunately, if left untreated, morbidity from scarring can be devastating leading to blindness or upper airway stenosis in a worst-case scenario.

Dapsone is considered to be the first-line therapy for LABD along with topical corticosteroids. However, dapsone use is contraindicated in G6PD deficiency or potentially limited because of its side effects, including hemolytic anemia or methemoglobinemia [5, 10]. Case reports of successful treatments with tetracycline and niacinamide, sulfasalazine, and immunosuppressants have been published [3, 11]. A relapse is possible and would require medical therapy to be continued weeks to months beyond the resolution of the lesions.

Conclusion

This patient highlights the variety, relative efficacy, and potential complications of treatments for LABD. Additionally, it is a reminder to reconcile records with patient's reports, as diagnosis and management of our patient's UC ultimately led to clearance of the skin lesions.

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