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Flame figures in linear IgA bullous dermatosis: a novel histopathologic finding

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Abstract

Background: Linear IgA bullous dermatosis (LABD) is an autoimmune subepidermal blistering disease usually with a neutrophil rich inflammatory infiltrate, and characterized by linear IgA deposition at the basement membrane zone (BMZ), and neutrophil predominant dermal inflammation. We report a case of LABD with numerous eosinophils and flame figure formation, a unique histopathologic finding not previously reported. A 69-year-old woman presented with a rapidly progressive, intensely pruritic rash over forearms, breasts, axillae, hips, and thighs. The lesions were comprised of annular vesicles and bullae with hemorrhagic crusts and erosions. The clinical differential diagnosis included bullous pemphigoid (BP), LABD, and epidermolysis bullosa acquisita (EBA). **Results:** A biopsy from a bullous plaque on the wrist revealed a subepidermal blister with neutrophils and numerous eosinophils with flame figure formation. Direct immunofluorescent (DIF) microscopy revealed linear deposition of IgA at the BMZ. **Conclusions:** Although unusual, the combined findings supported a diagnosis of LABD. Increased eosinophils may be associated with drug-induced LABD and may explain the numerous eosinophils in our case. It is important to be aware of this finding as the pathology may easily be misdiagnosed as BP, or possibly bullous Wells syndrome. This case emphasizes that combined clinical, pathologic, and DIF findings are essential in the diagnosis of bullous dermatoses.

Keywords: flame figures, linear IgA bullous dermatosis

Introduction

Linear IgA bullous dermatosis (LABD) is an autoimmune disease characterized by subepidermal blistering, linear IgA deposition along the epidermal basement membrane zone, and usually a neutrophil predominant dermal infiltrate. Multiple different antigenic target sites have been identified and implicated in disease pathogenesis, paralleling substantial diversity in age of onset and clinical symptoms [1, 2]. Cutaneous presentations may range from classic vesicles arranged in a “cluster of jewels” pattern to an erythema multiforme-like picture [3-5]. Not surprisingly, there is considerable overlap with other vesiculobullous diseases, both with regard to antigenic target sites and histopathologic features. This can hinder diagnosis, especially in the absence of DIF studies.

Flame figures were first described by George Wells in 1971 in a group of patients with recurrent granulomatous dermatitis with eosinophilia (Wells syndrome [6]), and have since been described in a number of other eosinophil-rich dermatitides including bullous pemphigoid, herpes gestationis, eczema, arthropod bite, and even tinea pedis [7-8]. Histopathologically, they consist of amorphous foci of granular eosinophilic material encrusted on collagen bundles. MALDI Tof/MS, SEM, and IHC studies further demonstrate that they are composed of discharged eosinophilic granule major basic protein and nuclear debris encrusting intact collagen fibers [9-11].

Case Synopsis

A 69-year-old woman with a history of obesity, hypertension, and hyperlipidemia presented with



Figure 1. Volar wrist; characteristic annular arrangement of vesicles ("cluster of jewels") with hemorrhagic crusts and erosions.

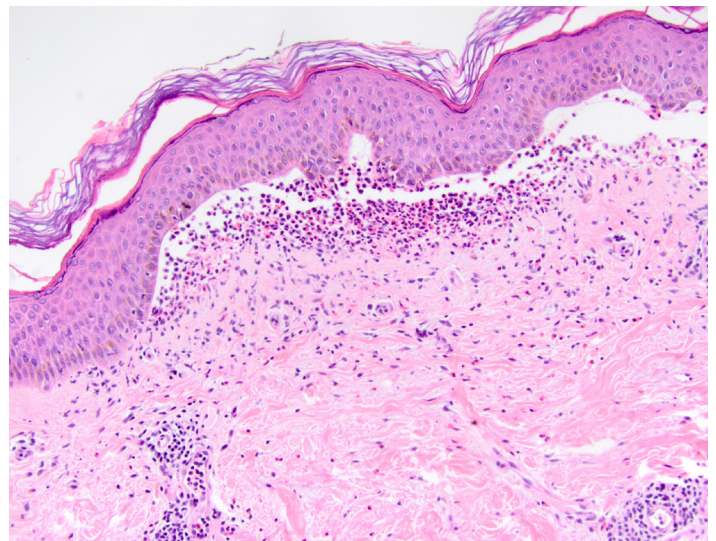


Figure 2. Subepidermal blister with prominent eosinophils, some neutrophils, and lymphocytes. H&E, 200%.

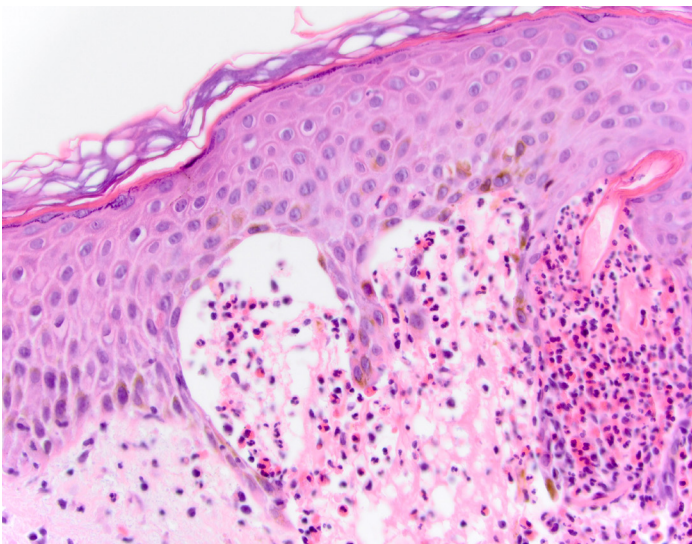


Figure 3. Dermal papillae filled with eosinophils and neutrophils. H&E 400%.

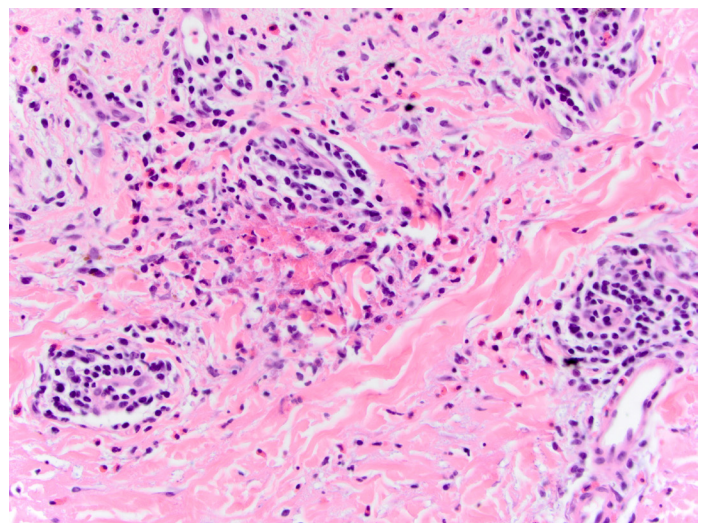


Figure 4. Mid-dermal flame figure with associated eosinophil-rich inflammation, H&E 400%.

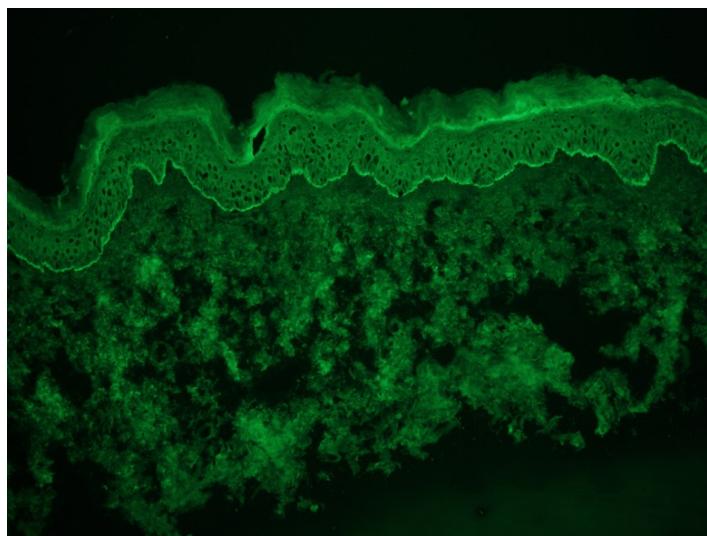


Figure 5. DIF for IgA demonstrating linear IgA deposition at the BMZ, 40%. DIF for IgG, IgM, C3 and fibrinogen were negative.

few, scattered, severely pruritic vesicles which rapidly progressed over three weeks to involve her forearms, breasts, axillae, hips, and thighs. The lesions were comprised of annular vesicles and bullae with hemorrhagic crusts and deep erosions (**Figure 1**). There was no mucosal involvement. Several days after presentation, the patient had a modest peripheral eosinophilia (absolute eosinophil count 336/ μ L), but otherwise unremarkable CBC, liver transaminases, alkaline phosphatase, total bilirubin, and G6PD. Active medications at the time of presentation included amlodipine, simvastatin, aspirin, and metoprolol. The clinical differential diagnosis included BP, LABD, and EBA.

A shave biopsy from a bullous plaque on the left wrist revealed a subepidermal blister with associated mixed inflammatory cell infiltrate comprised of numerous eosinophils, neutrophils, and lymphocytes (Figures 2, 3). The inflammatory infiltrate also extended into the superficial and mid-dermis, predominantly in a perivascular distribution. There was mild effacement of the rete with moderate superficial dermal edema. Flame figures were present in the mid-dermis (**Figure 4**), which consisted of amorphous aggregates of eosinophilic granular material encrusted on dermal collagen fibers. A second peri-lesional shave biopsy for DIF staining revealed linear deposition of IgA at the BMZ (**Figure 5**). There was a lack of C3, IgG, IgM or significant fibrinogen staining. Salt split skin and serum studies for circulating anti-basement membrane zone IgA were not performed. Although the predominant eosinophils and finding of a flame figure are not expected findings in LABD, the positive DIF with IgA staining confirmed the diagnosis of LABD.

Within two weeks of initiating dapsone monotherapy, her lesions cleared. She underwent a slow taper and dapsone was successfully discontinued eight months later. Preceding the onset of her eruption, she had an upper respiratory infection as well as the death of a close family member. As LABD is often drug-induced, her amlodipine and simvastatin were also considered possible culprits [12-13]. Her simvastatin was therefore discontinued. She still continues to take amlodipine.

Case Discussion

The usual algorithm when approaching subepidermal blistering dermatoses uses inflammatory cell type as a dividing point. Whereas some vesicles and/or bullae may be predominantly neutrophilic or predominantly eosinophilic, there appears to be more overlap than originally appreciated as exhibited in this case.

LABD is a rare, spontaneous or drug-induced autoimmune disease characterized by linear deposition of IgA at the DEJ. Numerous antigenic targets have been described [3]. There are two clinical variants, chronic bullous dermatosis of childhood and adult linear IgA bullous dermatosis. The clinical presentation is variable. Polycyclic clusters of bullae with central crusting (the "cluster of jewels") on the trunk or limbs are a classic finding in the childhood form. Although this pattern may be observed in adult LABD, clinical lesions in adults can include DH and BP-like lesions. Some cases show early lesions of urticarial papules and vesicles but lack bullae; these are termed linear IgA dermatosis. Pruritus, skin burning, and mucosal involvement are common. The drug-induced form of the disease may be especially severe and may produce larger erosions or even mimic toxic epidermal necrolysis. Vancomycin is the most commonly implicated drug [3-5], of which there are many, including amiodarone, acetaminophen, non-steroidal anti-inflammatory drugs, and ampicillin. Simvastatin, the drug possibly implicated in this case, has not been previously associated with LABD.

Histopathologic findings classically involve subepidermal blistering with a dermal inflammatory infiltrate dominated by neutrophils, with or without a generally smaller subset of eosinophils. As in this case, linear epidermal BMZ immunofluorescent IgA staining is diagnostic. Although not performed in our case, IgA staining may localize to either the dermal side, epidermal side, or both sides of salt-split skin, and concomitant staining with IgG, IgM, C3 or fibrinogen is common [3-5].

On H&E stained sections, this histopathologic picture may be identical to that of dermatitis herpetiformis (DH). Whereas soft features favoring DH may include focal acantholysis (owing to increased neutrophils) and fibrin at the tips of dermal papillae, these differences are non-specific and the two entities may

be impossible to differentiate without DIF and clinical context. In contrast to LABD, DIF of DH often shows granular deposits of IgA in dermal papillae and/or at the DEJ. Rare cases of DH with an absence of IgA deposition have been reported and consequently clinical presentation, including association with gluten-sensitivity and serologic markers of gluten-sensitive disease, remain important for diagnosis [14-15]. Although typically a neutrophil-predominant entity, DH with prominent eosinophils and flame figures has been previously reported [16], paralleling the significance of our case of eosinophil-predominant LABD with flame figures. In cases with subepidermal blisters and an eosinophil-rich dermal inflammatory infiltrate, traditionally neutrophil-predominant entities should remain in the differential diagnosis until DIF studies are performed to rule them out.

Owing to the predominant eosinophils, the main histopathologic condition in the differential diagnosis in this case is BP. As mentioned previously, LABD may in some cases, mimic BP clinically; BP was in the clinical differential diagnosis in this case. BP typically shows a subepidermal blister with numerous eosinophils and cases with flame figures have been reported. Tagging of eosinophils at the BMZ adjacent to the vesicle might favor BP. However, our case of LABD showed this finding as well. DIF was necessary to exclude BP and make the diagnosis of LABD. DIF in BP should demonstrate deposition of IgG and C3 at the DEJ that localizes to the epidermal side of salt split skin [14-17]. Similar to the aforementioned typically neutrophil-predominant subepidermal blistering lesions that may present with a preponderance of eosinophils, BP has been reported to display neutrophil-rich infiltrates, or neutrophils tagging at the DEJ [15, 18, 19].

Flame figures are characteristically associated with Wells syndrome (WS), which shows associated superficial and deep perivascular lympho-eosinophilic inflammation, neutrophils in early stages, and dermal edema. In some cases of WS, the marked papillary dermal edema may lead to subepidermal blister formation. Therefore, WS is considered in the pathologic differential diagnosis of our case. However, clinically, the process in our patient was not a recurrent cellulitic picture usually observed with WS, and negative DIF studies helped

to exclude WS [8, 20, 21]. Although flame figures are characteristically associated with WS, they are found in a number of eosinophil-rich processes. As the eosinophilic infiltrate evolves, eosinophils degranulate to form flame figures. Therefore, this is not an unexpected finding in an eosinophil-rich dermatitis.

Lastly, inflammatory EBA, while not as likely, would enter the pathologic differential diagnosis and was considered clinically. The common form of EBA is classified as a cell-poor subepidermal blister. The inflammatory variant usually shows a more prominent neutrophilic component, but eosinophils are noted. To date, there are no published reports of EBA with prominent eosinophils or flame figures.

Conclusion

The presence of flame figures has not been previously reported in LABD. Clinically, the finding of peripheral blood eosinophilia, although mild, parallels the marked presence of eosinophils in the biopsy and may support a drug-induced etiology. Our case of LABD with flame figures and descriptions of DH with flame figures and BP with predominant neutrophils emphasize the considerable histopathologic overlap between cell types in inflammatory dermatoses with subepidermal blisters. This emphasizes the requirement of DIF studies for definitive diagnosis. Our case demonstrates that LABD, despite typically featuring a neutrophil-predominant infiltrate, should be included in the differential diagnosis of lesions with eosinophil-rich subepidermal blisters, possibly with flame figures. This case also highlights the nature of flame figures as expressions of eosinophilic activity.

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