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Journal
Dermatology Online Journal, 23(8)

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Publication Date
2017-01-01

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Trimethoprim-sulfamethoxazole-induced linear IgA bullous disease presenting as toxic epidermal necrolysis

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Abstract

Background: Linear IgA bullous dermatosis (LABD) is an autoimmune blistering skin disorder characterized by linear IgA deposits along the dermo-epidermal junction. Usually idiopathic, LABD can be drug-induced.

Objective: To report the atypical characteristics of a case of trimethoprim-sulfamethoxazole-induced LABD presenting as toxic epidermal necrolysis (TEN).

Methods: A 63-year-old woman treated with trimethoprim-sulfamethoxazole for Pneumocystis jirovecii infection developed a generalized maculopapular rash with herpetiform lesions, rosette-like lesions, and tense bullae with Nikolsky sign.

Results: Anti-basement membrane zone antibodies were negative, but immunoblot revealed a 160 kDa band corresponding to subepidermal class IgA desmoglein 1. Skin biopsy specimens revealed a subepidermal bulla and direct immunofluorescence showed linear IgA deposition along the basement membrane zone. A diagnosis of toxic epidermal necrolysis was excluded and replaced by trimethoprim-sulfamethoxazole-induced LABD.

Conclusion: We report a case of trimethoprim-sulfamethoxazole-induced LABD with a 160 kDa IgA desmoglein 1 found by immunoblotting analysis, probably by epitope spreading.

Keywords: trimethoprim-sulfamethoxazole, drug-induced, IgA dermatosis, LABD, toxic epidermal necrolysis

Introduction

Linear IgA bullous dermatosis (LABD) is a rare autoimmune blistering skin disorder characterized by linear IgA deposits along the dermo-epidermal junction. Antibodies targeting various autoantigens have been identified for the immune response. Although usually idiopathic, many drugs have been reported to cause LABD (vancomycin being the most commonly involved). The clinical features of LABD are heterogeneous and polymorphic, with atypical forms resembling other bullous dermatosis such as bullous pemphigoid or dermatitis herpetiformis, cicatricial pemphigoid, erythema multiforme, and toxic epidermal necrolysis (TEN).

We report a patient with trimethoprim-sulfamethoxazole-induced LABD mimicking toxic epidermal necrolysis with evidence of IgA antibodies to the 160-kDa desmoglein 1.

Case Synopsis

A 63-year-old woman with a history of angioimmunoblastic T-cell lymphoma was treated with trimethoprim-sulfamethoxazole for Pneumocystis jirovecii infection recently diagnosed on chest CT scan. After 5 days of treatment, she developed a generalized maculopapular rash (Figure 1) rapidly associated with herpetiform lesions, rosette-like lesions, and tense bullae, predominantly localized on the proximal parts of the thighs and arms, trunk, and skinfolds (Figures 2, 3). Buccal mucosa erosions were noted but she had no conjunctival or genital mucosa lesions.

Nikolsky sign was positive with skin detachment involving approximately 50% of her body surface area. She also developed extensive desquamation.
of the skin associated with marked general malaise. No treatments other than trimethoprim-sulfamethoxazole were prescribed before onset of the rash. Laboratory work-up showed inflammation (CRP = 34.4 mg/L), leukocytosis (20.8 x 109/L) and eosinophilia (1300 eosinophils), and positive antinuclear antibodies (1/320). In view of the extensive skin detachment, the large number of bullous lesions, and her general malaise, a diagnosis of toxic epidermal necrolysis was initially suspected.

A punch biopsy from a bulla revealed a subepidermal blister with eosinophil and neutrophil infiltration and some necrotic keratinocytes. Direct immunofluorescence showed linear IgA deposition as well as complement and C3 deposition along the basement membrane zone, corresponding to the distribution of neutrophils (Figure 4). In blood samples, anti-basement membrane zone antibodies were negative, but immunoblotting with epidermal and dermal extracts of normal human skin revealed antibodies bound to an antigen of molecular weight 160-kDa corresponding to subepidermal class IgA desmoglein 1. The diagnosis of toxic epidermal necrolysis was excluded and replaced by trimethoprim-sulfamethoxazole-induced LABD.

Because of the severity and rapid progression of the lesions, bolus methylprednisolone treatment was initially administrated to stop tissue damage. Trimethoprim-sulfamethoxazole was rapidly discontinued, moisturizing ointment and topical betamethasone were applied. No new lesions developed and complete resolution of skin lesions was observed at 6 weeks with no recurrence and no sequelae.

**Case Discussion**

LABD is a rare sub-epidermal blistering disorder diagnosed by the detection of a linear band of IgA along the basement membrane zone [1]. LABD may be either idiopathic or drug induced, as in our patient. In contrast with the idiopathic form, drug-induced LABD appears to be more severe with atypical features mimicking other forms of bullous dermatosis: Chanal et al. reported a significantly higher frequency of Nikolsky sign and more extensive erosions in these forms [2]. Many TEN-like drug-induced LABD have...
been reported previously (Table 1): seventeen cases, including ours', of LABD presenting as TEN have been found in the literature. Patients ranged in age from 41 to 91 years with a mean age of 69 years, and the main medications responsible were vancomycin (n= 11/17, 65%), phenytoin (n= 4/17, 24%), and piperacillin-tazobactam (n = 3/17, 18%). Moreover, cases of LABD mimicking TEN tend to present more severe involvement of the palms and soles and mucous membranes. All of the patients who survived showed resolution of lesions after discontinuation of the implicated medication after 2 or more weeks [3].

Symptoms most commonly appear about two days to 4 weeks after exposure to the drug, and skin lesions resolve over a period of 5 weeks after discontinuation of the drug, with no specific treatment. This clinical course suggests a drug-induced etiology of these LABD [10]. Histological features are similar to those of toxidermic epidermal necrolysis with keratinocyte necrosis associated with tense subepidermal bullae or a polymorphic lymphocytic infiltration. IgG deposits are usually not associated with IgA deposits [11].

The autoantibodies in both variants of LABD are of the IgA class, directed against complex and heterogeneous target antigens within the dermal-epidermal junction, including antigens in the lamina lucida, sub-lamina densa, or both. For drug-induced LABD cases, we found eight reports describing the target antigens (Table 3), including BP180, BP230, the 97 kDa LAD, type VII collagen, LAD285,
Table 1: Reported cases of LABD mimicking TEN.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, sex</th>
<th>Implicated medication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paul et al. [7] 1997</td>
<td>71 years, female</td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Wetterwald et al. [17]  1999</td>
<td>70 years, female</td>
<td>Vancomycin, gentamycin</td>
</tr>
<tr>
<td>Schneck et al. [18] 1999</td>
<td>73 years, female</td>
<td>Uncertain, modenol, aspirin</td>
</tr>
<tr>
<td>Waldman et al. [19] 1999</td>
<td>77 years, male</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Mofid et al. [20] 2000</td>
<td>87 years, female</td>
<td>Vancomycin, phenytoin</td>
</tr>
<tr>
<td>Hughes et al. [21] 2001</td>
<td>77 years, male</td>
<td>Vancomycin, phenytoin, enalapril</td>
</tr>
<tr>
<td>Tran et al. [22] 2003</td>
<td>60 years, female</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Dellavalle et al. [23] 2003</td>
<td>74 years, male</td>
<td>Vancomycin, piperacillin, tazobactam, ciprofloxacin</td>
</tr>
<tr>
<td>Coelho et al. [24] 2006</td>
<td>67 years, female</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Cummings et al. [25] 2007</td>
<td>54 years, male</td>
<td>Azithromycin, zanamivir, rimantadine</td>
</tr>
<tr>
<td>Trufant et al. [26] 2010</td>
<td>49 years, male</td>
<td>Piperacillin-tazobactam, sulfamethoxazole-trimethoprim</td>
</tr>
<tr>
<td>Schroeder et al. [27] 2011</td>
<td>91 years, female</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Jheng-Wei et al. [28] 2011</td>
<td>41 years, female</td>
<td>Vancomycin, ceftriaxone</td>
</tr>
<tr>
<td>Kakar et al. [3] 2013</td>
<td>91 years, female</td>
<td>Vancomycin, piperacillin-tazobactam, ceftazidime, ampicillin/sulbactam, augmentin</td>
</tr>
<tr>
<td>Nasr et al. [29] 2014</td>
<td>76 years, male</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Current patient. 2016</td>
<td>63 years, female</td>
<td>Sulfamethoxazole-trimethoprim</td>
</tr>
</tbody>
</table>

Undetermined antigens, the 130 kDa desmoglein 3, and the 145-165 kDa α3 unit of laminin 322. BP180 is a major target antigen also seen in bullous and cicatricial pemphigoid, herpes gestationis, and lichen planus pemphigoides. In our case, immunoblotting revealed a 160 kDa IgA protein corresponding to desmoglein 1, which may explain the atypical clinical presentation of our patient. This antigen (160 kDa desmoglein 1 in IgA) has been found in three cases of the literature: herpetiform pemphigus, pemphigus IgA, and pemphigoid nodularis [12-14]. The variety of these target antigens explains the heterogeneous clinical and immunologic features of LABD (as in ours') in IgA pemphigus or paraneoplastic pemphigus, bullous pemphigoid, and dermatitis herpetiformis borderline forms [7, 15].

The mechanism by which drugs can stimulate the immune response of a susceptible individual to produce IgA antibodies against the basement membrane in LABD is still unclear. Drugs may induce immunobullous diseases by cross-reaction of target epitopes, by altering the conformation of epitopes, or by exposing previously sequestered antigens to the immune system. The immune responses generated may evolve to target additional epitopes (‘epitope spreading’), [16]. Using immunoblotting techniques, the autoantibodies in drug-induced LABD are found to be directed to the same heterogenous group of antigens as idiopathic LABD. Several authors have suggested that medications may initiate an autoimmune response by acting as a hapten or by modifying structural proteins responsible for skin lesions. Certain cofactors, such as infections (particularly respiratory tract infections) could also be implicated in the immune response of drug-induced LABD [6, 9].
In the present case, the very likely causal relationship with the drug and rapid healing after medication discontinuation excluded a diagnosis of paraneoplastic or IgA pemphigus. To our knowledge, we detected for the first time IgA antibodies to the 160-kDa of desmoglein 1 by immunoblotting analysis associated with a drug-induced trimethoprim-sulfamethoxazole LABD.

References:

14. Fujisawa H, Ishii Y, Tateishi T, Kawachi Y, Otsuka F, Amagai M et al. Pemphigoid nodularis with IgA autoantibodies against the
Table 3. Results of immunoblotting in drug-induced LABD.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, sex</th>
<th>Drug</th>
<th>Clinical features</th>
<th>Mucosal involvement</th>
<th>Target antigen size, kDa (isotype)</th>
<th>Target antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer et al. [15] 1997</td>
<td>75 years, female</td>
<td>Vancomycin</td>
<td>Limbs; urticarial lesions, flaccid bullae</td>
<td>Oro-genital ulceration</td>
<td>180 (IgA, IgG) 285 (IgA)</td>
<td>BP180</td>
</tr>
<tr>
<td>Palmer et al. [15] 1997</td>
<td>86 years, female</td>
<td>Vancomycin</td>
<td>Trunk, proximal limbs; erosions, flaccid bullae</td>
<td>Oral ulceration</td>
<td>180 (IgA, IgG) 285 (IgA)</td>
<td>BP180</td>
</tr>
<tr>
<td>Paul et al. [7] 1997</td>
<td>32 years, male</td>
<td>Vigabatrin</td>
<td>Hands and feet; pruritic papular and bullous eruption</td>
<td>Oro-genital ulceration</td>
<td>97 (IgA)</td>
<td>BP180</td>
</tr>
<tr>
<td>Paul et al. [7] 1997</td>
<td>74 years, male</td>
<td>TMP/SMX</td>
<td>Chest, scalp, trunk and axillae; pruritic papular and bullous eruption</td>
<td>Oro-genital ulceration</td>
<td>230 (IgA)</td>
<td>BP230</td>
</tr>
<tr>
<td>Wakelim et al. [33] 1998</td>
<td>76 years, male</td>
<td>Penicillin</td>
<td>Trunk, limbs, buttocks, thighs, palms, soles; blistering eruption, tense bullae</td>
<td>Oral ulceration</td>
<td>250</td>
<td>Collagen VII</td>
</tr>
<tr>
<td>Armstrong et al. [34] 2004</td>
<td>81 years, male</td>
<td>Vancomycin</td>
<td>Back, palmoplantar; erythema multiform-like</td>
<td>Oral ulceration</td>
<td>210 130 (IgA) 83</td>
<td>Desmoglein 3 (130 kDa)</td>
</tr>
<tr>
<td>Tashima et al. [4] 2013</td>
<td>84 years, male</td>
<td>Vancomycin</td>
<td>Whole body; pruritic annular erythema, herpetiform vesicles</td>
<td>Oral ulceration</td>
<td>180 (IgA)</td>
<td>BP180 (NC16a domain)</td>
</tr>
<tr>
<td>Zenke et al. [5] 2014</td>
<td>62 years, male</td>
<td>Vancomycin</td>
<td>Trunk, thighs, buttocks; erythema, bullae, erosions</td>
<td>No oral ulceration</td>
<td>165-145 α3 unit of laminin 332 (IgA)</td>
<td>BP180</td>
</tr>
<tr>
<td>Current case. 2016</td>
<td>63 years, female</td>
<td>TMP/SMX</td>
<td>Trunk, thighs, arms, skinfolds; rosette-like and herpetiform lesions, tense bullae</td>
<td>Oral ulceration</td>
<td>160 (IgA)</td>
<td>Desmoglein 1</td>
</tr>
</tbody>
</table>