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

T Baltazard[1] MD, F Dhaille[1] MD, S Duvert-Lehembre[2] MD, C Lok[1] MD PhD, G Chaby[1] MD

Affiliations: [1]Department of Dermatology, Hôpital Nord, University of Amiens, Amiens, France, [2]Department of Dermatology, CH Dunkerque, Dunkerque, France

Corresponding Author: Thomas Baltazard, Department of Dermatology, CHU AMIENS, Place Victor Pauchet, 80000 – AMIENS, France, Email: thomas.baltazard@gmail.com

Abstract

Background: Linear IgA bullous dermatosis (LABD) is an autoimmune blistering skin disorder characterized by linear IgA deposits along the dermoepidermal 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

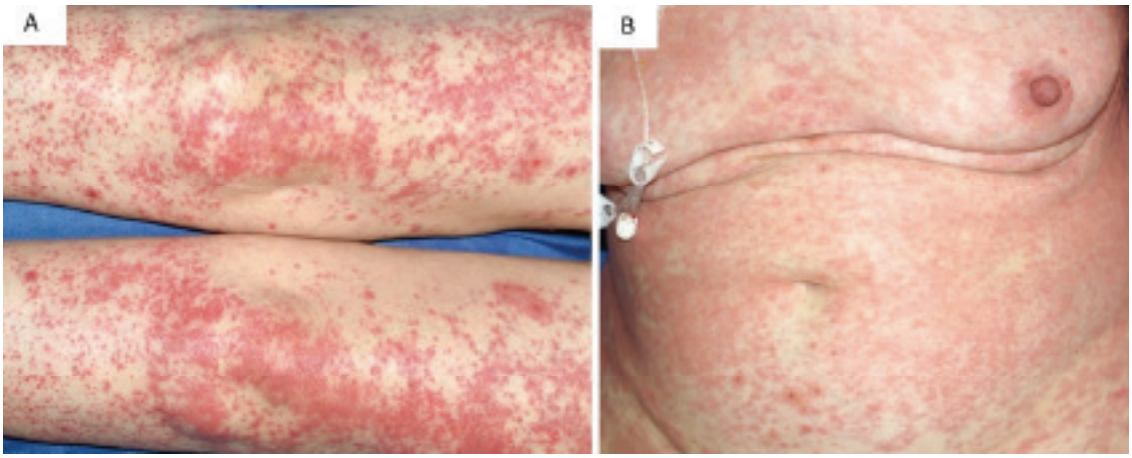

Figure 1. *A) and B) Generalized maculopapular rash after 5 days of trimethoprim-sulfamethoxazole.*

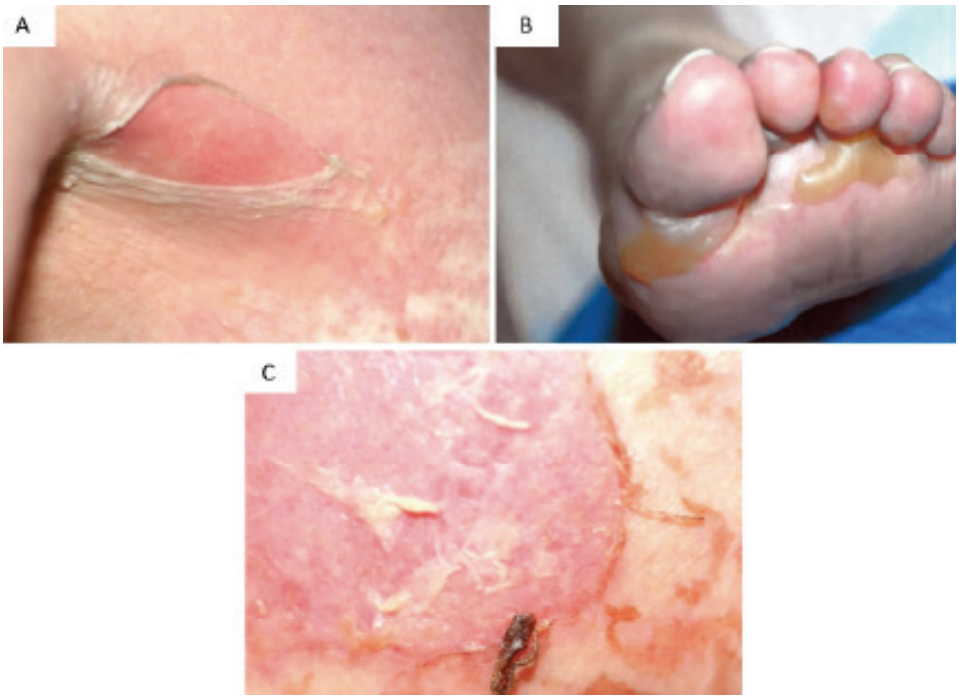

Figure 2. *A) Tense bullae localized on the left foot. B and C) Skin sloughing in the axillary area and the trunk.*

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 (1,300 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

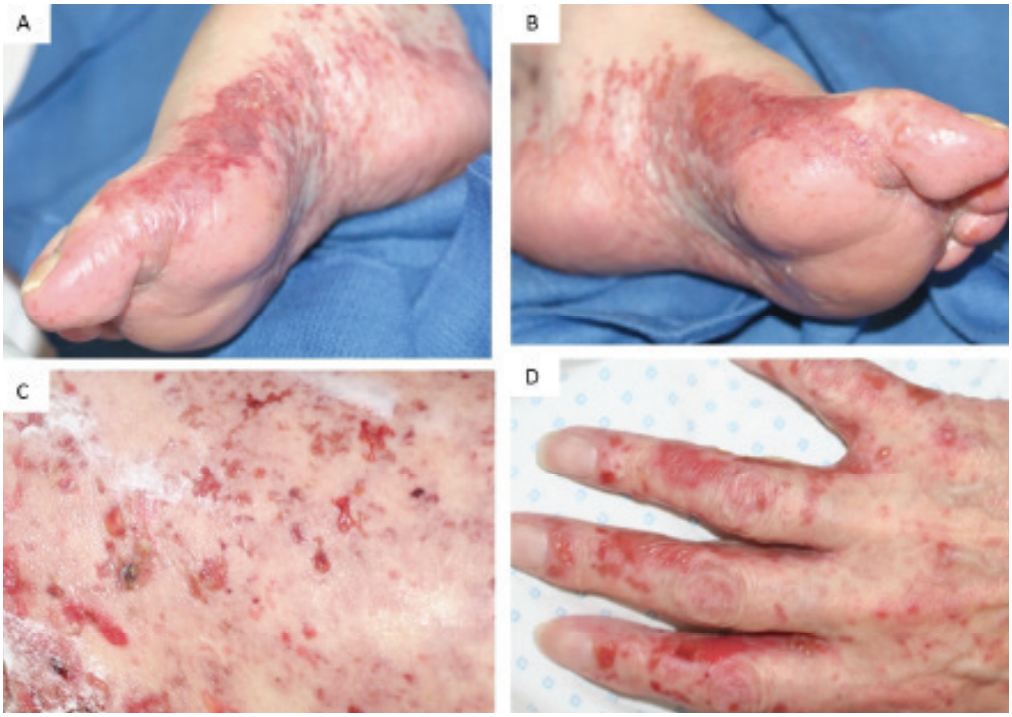

Figure 3. *Polymorphic lesions with herpetiform and rosette-like lesions (feet, thigh and the right hand).*

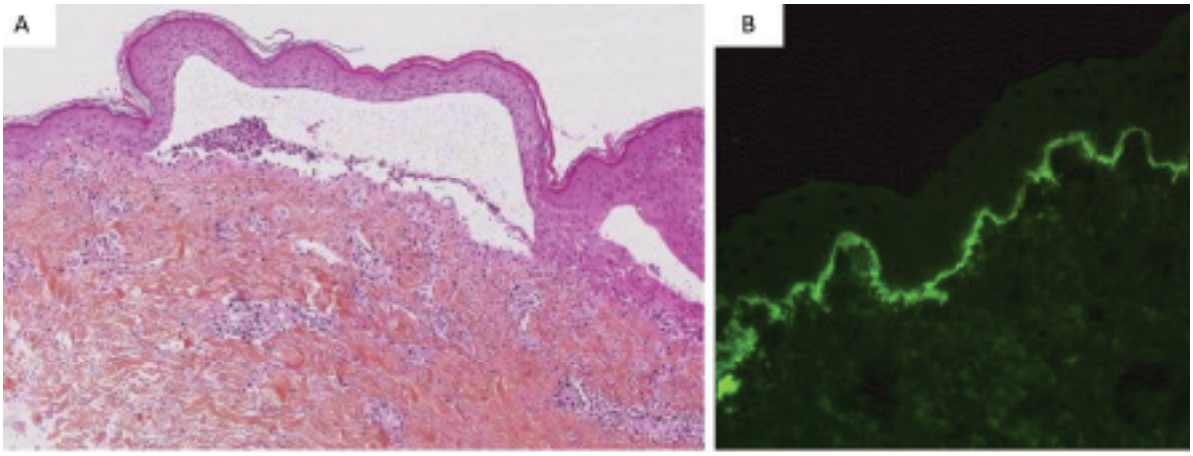

Figure 4. *A) Punch biopsy, H&E, 10x. Subepidermal bulla, some necrotic keratinocytes and neutrophilic infiltration. B) Direct immunofluorescence with linear IgA deposition along the basement membrane zone (10x).*

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].

Drug-induced linear IgA bullous dermatosis has been reported in association with many drugs; **Table 2** gives a nonexhaustive list of drugs found in the literature. The medications most commonly implicated are vancomycin and phenytoin, but vancomycin is the most consistently found [2, 4, 5]. As in our case, four cases of drug-induced LABD with trimethoprim-sulfamethoxazole have been reported [6-9].

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.

Reference	Age, sex	Implicated medication(s)
Paul et al.[7] 1997	71 years, female	Diclofenac
Wetterwald et al.[17] 1999	70 years, female	**Vancomycin**, gentamycin
Schneck et al.[18] 1999	73 years, female	Uncertain, modenol, aspirin
Waldman et al.[19] 1999	77 years, male	Vancomycin
Mofid et al.[20] 2000	87 years, female	**Vancomycin**, phenytoin
Hughes et al.[21] 2001	77 years, male	**Vancomycin**, phenytoin, enalapril
Tran et al.[22] 2003	60 years, female	Phenytoin
Dellavalle et al.[23] 2003	74 years, male	**Vancomycin**, piperacillin, tazobactam, ciprofloxacin
Coelho et al.[24] 2006	67 years, female	Vancomycin
Cummings et al.[25] 2007	54 years, male	Azithromycin, zanamivir, rimantadine
Khan et al.[11] 2009	57 years, female	Phenytoin, **vancomycin**, furosemide, amiodarone
Trufant et al.[26] 2010	49 years, male	Piperacillin-tazobactam, sulfamethoxazole-trimethoprim
Schroeder et al.[27] 2011	91 years, female	Verapamil
Jheng-Wei et al.[28] 2011	41 years, female	**Vancomycin**, ceftriaxone
Kakar et al.[3] 2013	91 years, female	**Vancomycin**, piperacillin-tazobactam, ceftazidime, ampicillin/sulbactam, augmentin
Nasr et al.[29] 2014	76 years, male	Vancomycin
Current patient. 2016	63 years, female	Sulfamethoxazole-trimethoprim

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].

Table 2: non exhaustive list of drugs for linear IgA bullous dermatosis in the literature [2].

Vancomycin
Captopril
Trimethoprim-sulfamethoxazole
Phenytoin
Diclofenac
Amiodarone
Piroxicam
Naproxen
Acetaminophen
Ceftriaxon
Amoxicillin/ampicillin
Atorvastatin
Lithium carbonate
Gemcitabine
Furosemide
Penicillin
Verapamil
Vigabatrin
Imipenem
Ketoprofen
Piroxicam [30]
Intereron γ/interleukin-2
Infliximab [31]
Moxifloxacin [10]
Ustekinumab [32]

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.

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Table 3. Results of immunoblotting in drug-induced LABD.

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

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