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Drug-induced linear IgA bullous dermatosis after discontinuation of cefuroxime axetil treatment

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Abstract

Background: Linear immunoglobulin A (IgA) bullous dermatosis (LABD) is a rare autoimmune blistering disorder. The disease may be either idiopathic or drug-induced. Over the past 30 years, approximately one hundred LABD cases have been described as induced by a wide range of drugs, chiefly antibiotics.

Main observations: We report the case of 37-year-old woman who developed pruritic bullous lesions spread all over the body three weeks after her last dose of cefuroxime axetil. Antibiotic therapy was started due to rhino-sinusitis.

Conclusions: In most reported cases of drug-induced LABD, skin lesions occur within the time of drug administration. However, the onset of disease may be even after discontinuation of treatment. It seems that in such cases, other clinical conditions (like infection) act, as cofactors of immunologic response. (*J Dermatol Case Rep*. 2012; 6(4): 117-119)

Introduction

Linear IgA bullous dermatosis (LABD) is a rare autoimmune subepidermal blistering disorder, characterized by continuous linear IgA deposits along basement membrane zone (BMZ) when visualized with direct immunofluorescent microscopy (DIF). The disease may be idiopathic — subdivided into adult and childhood syndromes, or drug-induced. Drug-induced LABD clinically and histologically resembles classic LABD; however, most cases of drug-induced LABD occur soon after the treatment initiation and disappear even without any treatment after the drug is discontinued.[1] Over the past 30 years, approximately one hundred LABD cases have been described as induced by a wide range of drugs, chiefly intravenous administered vancomycin. However, other antibiotics, such as trimethoprim-sulfamethoxazole, ampicillin/sulbactam and amoxicillin-clavulanic acid have also been reported.[2] As far as we know, cefuroxime has been reported only once in a case of LABD.[3] Herein, we described a case of drug-induced LABD three weeks after cefuroxime axetil termination.

Case Report

A 37-year-old woman was referred to the Department of Dermatology, with a one week history of bullous lesions spread all over the body and accompanied by intense itching. The patient experienced rhino-sinusitis five weeks before the onset of skin lesions. She was treated by her GP with cefuroxime axetil (500 mg p.o., b.i.d) for 10 days. The patient has not been treated before with cefuroxime axetil. She did not suffer from any other disease. She denied taking any drugs due to other reasons. There was also no family history of blistering diseases and other autoimmune disorders.

On the admission, the patient had no symptoms and signs of upper respiratory tract infection. She has not been taking any medications since three weeks. She had no preceding history of drug allergy.

Physical examination revealed numerous tense blisters — the biggest one up to 2.5 cm in diameter — filled with clear fluid. They were found: on the face, symmetrically on extensor surface of both arms and on the trunk (Fig. 1). Some blisters

were on the erythematous and oedematous background. Some of them were on ground of the apparently intact skin. In some areas, bullous lesions clustered around resolving lesion, showing shape, referred to as "cluster of jewels".[1] Some of lesions appeared as grouped papulovesicles as seen in dermatitis herpetiformis (i.e. herpetiform pattern) (Fig. 2). Nikolsky's sign was negative. The oral, ocular and genital mucosa were not involved.

Basic laboratory examination revealed no abnormalities. Skin biopsy taken from a single site showed a subepidermal bulla and an intense neutrophilic infiltrate. Direct immunofluorescence assay (DIF) of the perilesional skin demonstrated positive linear IgA and weak C3 at the epithelial basement membrane zone. Deposition of IgG and IgM was not found. Indirect immunofluorescence (IIF) studies were reproducibly negative. Serum levels of all immunoglobulins were within normal range. No antigliadin (IgG or IgA), antiendomysium (IgA) or anti-tissue transglutaminase antibodies were detected in the serum.

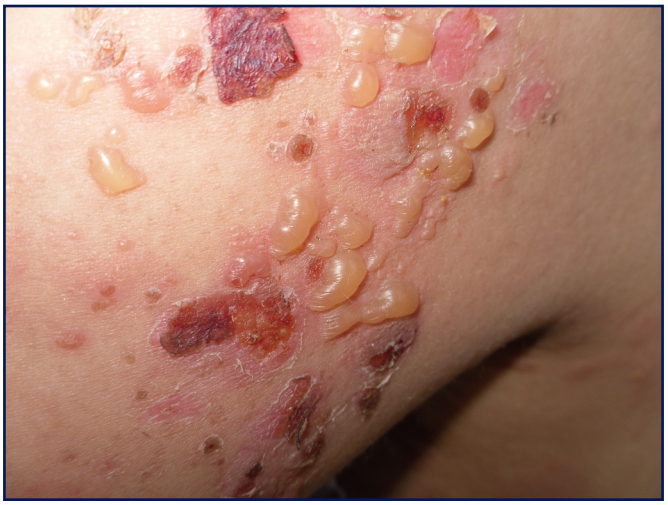

Figure 1
Tense blisters and erosions (side of the left arm).

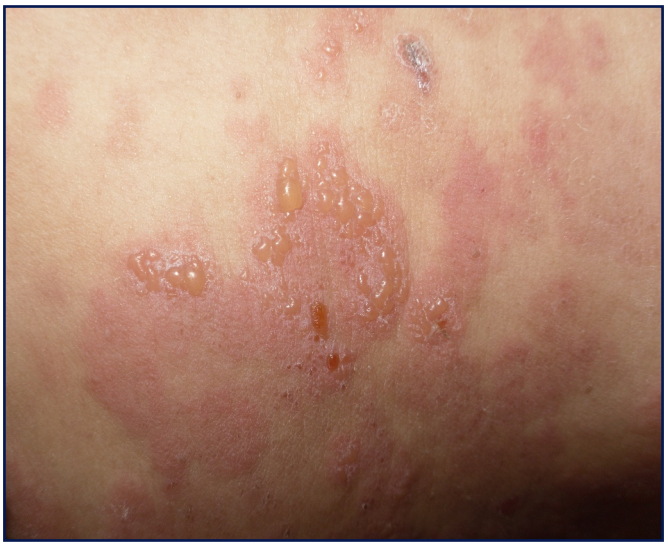

Figure 2
Vesicles with herpetiform pattern (abdominal skin).

The therapy with dapsone (100 mg p.o. q.d.) and prednisone (20 mg p.o. q.d.) was started. The complete remission was noted within 10 weeks of therapy. The treatment with dapsone and prednisone was discontinued. Six-month follow-up revealed no signs of recurrence.

Discussion

Linear IgA bullous dermatosis is a rare acquired subepidermal blistering disease. Cutaneous findings in LABD are heterogeneous and may mimic other bullous diseases. Lesions may appear as tense arciform bullae in a "cluster of jewels" configuration, developing de novo or on an urticarial base as seen in bullous pemphigoid. Less commonly, the clinical features of LABD may resemble those of dermatitis herpetiformis with a primarily pruritic papulovesicles.[1]

Cases of drug-induced LABD are significantly less common than idiopathic subtype. Autoantibodies in patients with drug-induced LABD are directed to the same heterogeneous group of proteins as in the idiopathic form.[4] Until now, there have not been identified typical clinical, histologic or immunologic features of drug-induced variant of this disease. However some studies have reported that when compared to idiopathic subtype in drug-induced LABD: (1) only a minority of patients have circulating antibodies, (2) mucous membranes are affected less frequently (40% vs. 80%), and (3) almost one-third cases show additional linear deposition of C3 at BMZ.[3,5] All these features were compatible with the clinical and laboratory findings of our patient.

The most important characteristic of drug-induced LABD, distinguishing it from the idiopathic subtype, is the onset within the time of drug administration. The recent review of the previously reported cases of drug-induced LABD showed that the onset of cutaneous manifestations upon administration of the suspected drug ranged from 1 to 780 days.[2] On the other hand, similarly to our patient, there was a case report of drug-induced type of the disease which occurred two weeks after discontinuance of the treatment with the offending drug.[6]

The mechanism of drug-induced LABD remains unclear. Two proteins (a 97-kD and a 285-kD) localized in the lamina lucida and sublamina densa have been implicated as potential antigens. Some authors suggest that drugs involved may elicit an autoimmune response by acting as haptens complexing or modifying protein molecules. It may cause breaking the self-tolerance to these native antigens.[4,7]

Recent study, that reviewed all reported cases of drug-induced LABD till December 2010 showed, that although in the majority of cases the suspected offending drug was withdrawn, spontaneous resolution with any additional systemic therapy was reached in less than 50% of cases. Thus it is likely that an amplification of the immunological signal occurred in some cases of drug-induced LABD, resulting in a self-maintaining immune response.[2]

Usually first exposure to the drug induces primary asymptomatic autoimmune response. However some authors have suggested that clinical conditions such as infections (for example upper respiratory tract infections) may act as

cofactors of immunologic response in the pathogenesis of drug induced LABD. Then triggering event such as: infection and subsequent treatment, may be required to initiate an immunologic response, even in patients who were not previously sensitized to the drug.[6,8,9] In our patient the blistering eruption occurred three weeks after the last dose of the cefuroxime axetil. The disease occurred probably because of two factors — drug and infection together. The delay in skin eruption might have been due to the lack of previous exposure to the drug.

The majority of previous LABD cases, reported many concurrent medications. Confident distinction was not always possible. Some cases were confirmed with the dechallenge-rechallenge procedure.[2] Our patient denied taking any another drugs. For ethical reasons, we did not rechallenge the patient.

Unlike what was previously thought, up to 50% of drug-induced LABD cases require additional treatment.[2] In contrast to idiopathic LABD, long-term therapy is not necessary in drug-induced variant.[1,2] Dapsone is considered to be the first-line therapy. Its efficiency has been proven in monotherapy or in combination with other drugs, such as: corticosteroids, nicotinamide and antibiotics. Systemic therapy is required until patients enter complete clinical remission; then a maintenance dosage of medication should be scheduled as determined by the clinical appearance of the mucocutaneous lesions.[1] For the first two weeks our patient was receiving dapsone at the dose 100 mg q.d. and prednisone 20 mg q.d. During that time we did not observe any new lesions formation. The dose of dapsone was tapered to 50 mg q.d. This dose was entered for the next 9 weeks. The gradual resolution was observed.

Conclusion

LABD secondary to antibiotics is an uncommon disease and may clinically resemble other blistering disorders. In the presented case of LABD it is not possible to ascertain confidently the association between the blistering disorder and cefuroxime axetil. However, in previous report it has been suggested that drug-induced LABD may appear even after the drug discontinuance.[6] However in such cases other clinical conditions (i.e. infection) serving as cofactors may be required. Then rechalange with the suspected offending drug may not be sufficient to induce skin lesions. The exact pathogenesis of drug-induced LABD remains obscure. Further studies are needed to rule out a role of drugs and cofactors in its pathogenesis.

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