CAS CLINIQUE / CASE REPORT

DRUG-INDUCED LINEAR IgA BULLOUS DERMATOSIS SIMULATING TOXIC EPIDERMAL NECROLYSIS

http://www.lebanesemedicaljournal.org/articles/62-3/case3.pdf

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Nasr J, Ammoury A, Chouairy C, Mégarbané H, El Habr C. Drug-induced linear IgA bullous dermatosis simulating toxic epidermal necrolysis. J Med Liban 2014 ; 62 (3) : 176-179.

ABSTRACT: Linear IgA bullous dermatosis (LAD) is an autoimmune subepidermal blistering disorder. LAD may be either idiopathic or drug related; the most common drug being vancomycin. The clinical presentations of both idiopathic and drug-related LAD are variable and may mimic other blistering disorders. We report a case of a 76-year-old man known to have a renal cell carcinoma who presented a vancomycin-induced LAD that clinically mimicked toxic epidermal necrolysis (TEN).

Keywords : IgA bullous dermatosis, drug-induced linear IgA, vancomycin, toxic epidermal necrolysis

Nasr J, Ammoury A, Chouairy C, Mégarbané H, El Habr C. Dermatose bulleuse à IgA linéaire induite par vancomycine simulant une nécrolyse épidermique toxique. J Med Liban 2014 ; 62 (3) : 176-179.

RÉSUMÉ : La dermatose bulleuse à IgA linéaire (DAL) est une maladie bulleuse auto-immune le plus souvent idiopathique. Elle peut être induite par des médicaments avec comme chef de file, la vancomycine. Sur le plan clinique, elle se caractérise par une clinique polymorphe mimant les autres maladies bulleuses, notamment la pemphigoïde bulleuse, l'érythème polymorphe, l'herpès gestationis et plus rarement le syndrome de Lyell. Nous rapportons le cas d'un homme de soixante-seize ans, connu pour avoir un carcinome rénal à cellules claires, qui s'est présenté avec une DAL induite par vancomycine, cliniquement imitant la maladie de Lyell (TEN).

Mots-clés : dermatose bulleuse à IgA, IgA linéaire induite, vancomycine, nécrolyse épidermique toxique

INTRODUCTION

Linear IgA bullous dermatosis (LAD) is an autoimmune subepidermal blistering disorder charaterized by the presence of a linear deposit of IgA at the dermal-epidermal junction (DEJ) [1]. LAD may be either idiopathic, or drug-related [2-3]. Many drugs have been reported to cause drug-induced LAD, among others is vancomycin [3]. We hereby report an interesting case of a 76-year-old male patient known to have renal cell carcinoma who presented a vancomycin-induced LAD that clinically mimicked toxic epidermal necrolysis (TEN).

CASE REPORT

A 76-year-old man presented for a generalized bullous eruption. His past medical history included a renal cell carcinoma (RCC) (clear cell type) that was diagnosed and treated with right nephrectomy two weeks prior to presentation.

His treatment upon admission included the following: omeprazole, aspirin, atorvastatin and bisoprolol [introduced several months ago]. Patient denied any drug allergy. Hospital course was complicated by a pneumonia treated with intravenous vancomycin and piperacillin/tazobactam. Eight days later, he developed a tense, non pruritic, bullous eruption on the trunk, palms, soles and mucous membranes (oral and genital areas). On physical exam he had yellow, tense bullae over an erythematous base (Fig. 1 & 2). There was also edema over the palms and soles. Few superficial skin erosions were noted. The ocular mucosa was spared. The patient didn't complain of itching or tenderness of the skin. The next day the bullae became hemorrhagic, some of them had ruptured, leaving erosions with hemorrhagic and serous crusting

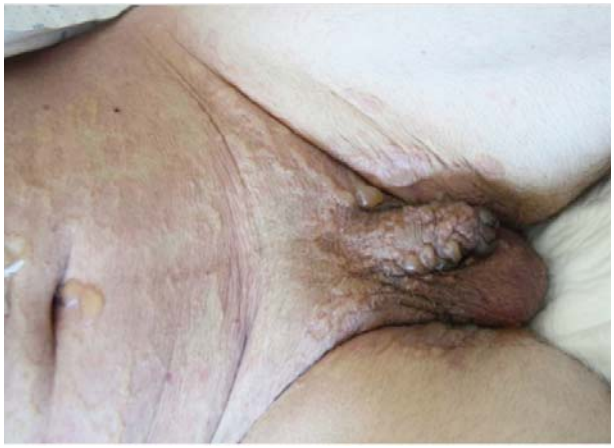

FIGURE 1. Tense bullae over an erythematous base. Note the involvement of the genital area.

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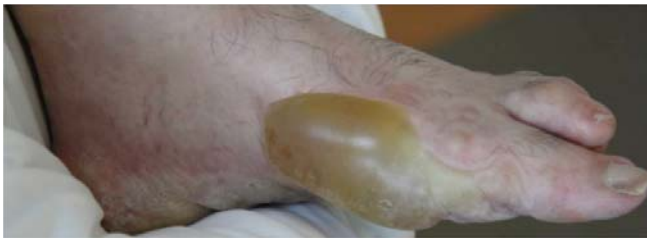

Figure 2. Tense bullae involving the medial side of the foot.

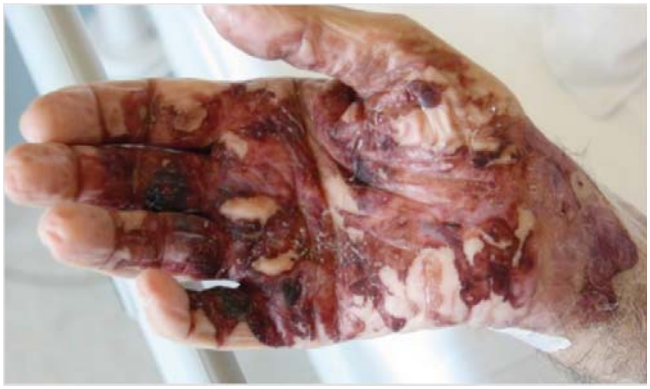

Figure 3. Skin erosions with haemorrhage and crusting of the palms.

(Fig. 3). His lips were crusted but his oral mucosa was clear. No lymphadenopathies, no edema of the face, no pustules, no purpuric lesions and no flexural reinforcement of the lesions.

The result of blood profile upon admission showed elevated white blood cells count at 17400 cells/mm^3 with 15138 neutrophils/mm^3, lymphopenia at 1218 cells/mm^3 but no eosinophilia, and no atypical lymphocytes. Liver function tests were normal. Bacterial culture of the skin showed a heavy growth of methicillin-resistant *Staphylococcus aureus* (MRSA). A skin biopsy was performed and showed a sub-epidermal blister with perivascular and interstitial infiltrate of neutrophils with abundant neutrophilic nuclear "dust" in the papillary dermis (Fig. 4a, 4b, 4c). Direct immunofluorescence revealed a linear strong deposit of IgA antibodies with a faint C3 linear deposit along the basement membrane. This was compatible with the diagnosis of drug-induced linear IgA bullous dermatosis. All antibiotics were promptly discontinued. No new blisters were noted and the lesions were completely healed within two months despite the evolution of the renal carcinoma with multiple metastases leading to his death few months later.

DISCUSSION

LAD is defined by the presence of linear deposits of IgA at the dermal-epidermal basement membrane [1]. Most linear IgA bullous dermatosis cases are idiopathic, but some are associated with the use of certain drugs, infections, lymphoproliferative disorders, internal malignancies, autoimmune disorders, collagen diseases or, very rarely, other skin diseases, including autoimmune bullous

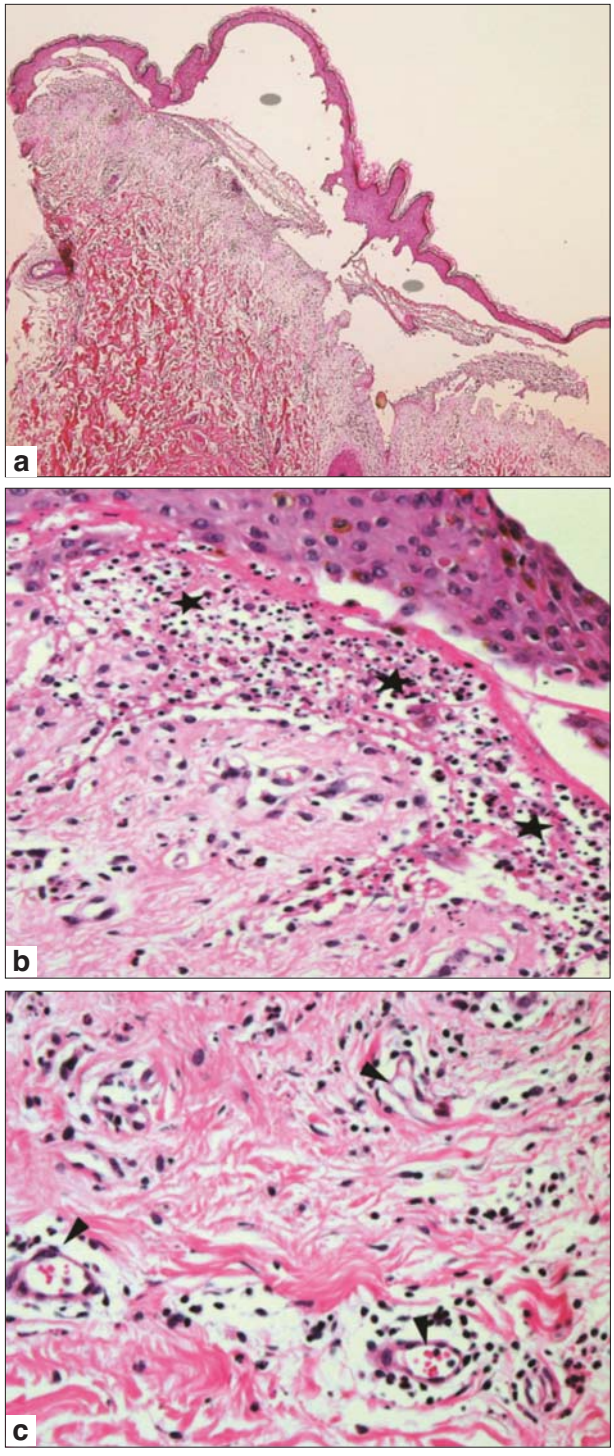

Figure 4

(**a**) Skin biopsy showing a subepidermal vesicle (gray ellipse shapes). Epidermis is normal. (haematoxylin and eosin, original magnification x40).

(**b**) Abundant karryorectic debris of neutrophils in the papillary dermis (black stars), with a band like distribution (haematoxylin and eosin, original magnification x400).

(**c**) The capillaries are patent and show no features of fibrinoid necrosis (black arrowheads). Extravasated erythrocytes are absent (haematoxylin and eosin, original magnification x400).

diseases. The main drugs implicated include vancomycin followed by ß-lactam antibiotics, captopril, non-steroidal anti-inflammatory drugs, phenytoin, rifampin, sulfonamides, amiodarone, furosemide and lithium [4]. In contrast to idiopathic LAD, drug-induced LAD develops within 1-15 days of the first dose of the inducing medication [5]. In our patient, the blistering eruption occurred eight days following the first dose. Cutaneous findings in both forms are quite variable and include bullous, urticarial, erythematous, and targetoid erythema multiforme-like lesions often favoring the trunk, extremities, palms, soles, and sparing the head and neck [6]. Histologically, LAD shows subepidermal blisters with an infiltrate consisting of neutrophils. Direct immunofluorescence of perilesional skin usually shows deposition of IgA along the basement membrane zone (BMZ) usually in a homogenous linear pattern although granular rather than linear deposition of IgA along the dermal-epidermal junction has also been described [4,7].

Although the clinical, histological and immunofluorescence features of drug-induced LAD are the same as the idiopathic form, the history and course of drug-induced LAD help to distinguish them. Regarding the etiology, a heterogeneous group of antigens has been elucidated as targets in the idiopathic form of the disease. These antigenic targets are localized to the BMZ. The 97kDectodomain of the 180kD bullous pemphigoid antigen and type-VII collagen, are two of the most commonly identified antigens, and may play a pathogenic role [4]. The target antigens involved in the drug-induced subset are the 230kD antigen, the 97kD antigen, and type-VII collagen in non-vancomycin drug-induced LAD [4]. On the other hand, one study described two patients with vancomycin-induced LAD with autoantibodies directed against BP180 and LAD 285 [8].

The frequency of mucosal involvement is as high as 45 percent of cases of drug-induced LAD and include oral and genital erosions and blisters [8-9]. In our case, there was a severe mucosal involvement with striking hemorrhagic blisters, crusting and erosions on the genital area. Unlike the prolonged course of idiopathic LAD, all patients with the drug-induced disease have spontaneous remission after withdrawal of the drug; new lesions cease to form 24-72 hours after discontinuation of the responsible agent and remaining lesions resolve within 2-7 weeks [4]. In our case, we noted complete resolution of lesions within 2 months but the disease became inactive promptly upon discontinuation of vancomycin. There have been eight cases of drug-induced LAD that have clinically mimicked TEN [10-16]. *Similar to our patient*, three of these patients had hemorrhagic blisters [10], one of them had targetoid lesions on the palms and soles [13], one of them presented crusted lips [10], and one had widespread bullae and erosions [16]. Five of these cases were induced by vancomycin, two of them were induced by phenytoin and one case was induced by diclofenac [10]. Complete healing was noted within three weeks except for two cases with a prolonged course after discontinuation of the offending drug, up to several months [15]. Like in our case, all of the patients cleared upon withdrawal of possible offending drugs *without any other treatment* [10]. In the current case, what initially made us think of TEN was the extensive hemorrhagic blistering, the significant genital involvement with widespread erosions and the crusting of the lips. The diagnosis of LAD was confirmed on the identification of a homogenous linear band of IgA at the basement zone on direct immunofluorescence. Association between LAD and malignancy has been described. Tumors that have been reported in patients with LAD include: B-cell lymphoma, chronic lymphocytic leukemia and carcinoma of the bladder, thyroid and esophagus; single case reports of ocular melanoma [17-21] and renal cell carcinoma [22-23] have also been described. Van der Waal *et al*. reported a case of a patient with a metastasized renal cell carcinoma who developed an extensive blistering eruption similar to our case. The lesions showed immunopathological findings characteristic of LAD. The patient showed a fair response to prednisolone and dapsone. Treatment to control the LAD was no longer required when interferon-α was started as palliative therapy for the metastasized renal cell carcinoma [23].

In our case, although the patient was suffering from a metastasized renal cell carcinoma, his eruption was more linked to drug intake than to his current carcinoma because of the clinical course and the spontaneous prompt resolution of lesions upon withdrawal of the offending drug despite a progression of the underlying renal cell carcinoma. It was difficult to judge which drug was involved in this reaction (vancomycin, piperacillin or tazobactam) as all drugs were introduced and withdrawn concomitantly.

Our case report points to two important conclusions. First it emphasizes the value of direct immunofluorescence study in all cases of suspected drug-induced LAD in order to confirm the diagnosis because this entity can mimic other bullous disorders like TEN. Second, it illustrates the importance of the clinical evolution after drug withdrawal in order to relate the blistering reaction to drug intake.

DECLARATION OF COMPETING INTERESTS: None to declare.

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