



Case Report

An array of unusual clinical features in a woman with amlodipine-induced linear immunoglobulin A disease[☆]Pallavi Ailawadi, Isha Narang^{*}, Vijay K. Garg

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ABSTRACT

Linear immunoglobulin A disease (LAD) is a rare, autoimmune, vesicular-bullous disease that is either idiopathic or drug-induced, most commonly by vancomycin and in rare instances by amlodipine. In drug-induced LAD, certain uncommon and atypical clinical features can occur. In our patient, a 49-year-old woman with amlodipine-induced LAD, atypical features such as koebnerization and palmo-plantar involvement occurred. She presented with tense, clear fluid-filled vesicles, bullae, and erosions all over her body, especially on the palms and soles, with some lesions showing a string-of-pearls appearance. The lesions were preceded by pruritus, and the patient had changed her anti-hypertensive medication from telmisartan to telmisartan-amlodipine for previous 10 days. Skin biopsy and direct immunofluorescence testing confirmed LAD. During the hospital stay, along with new crops of lesions, a few vesicles were present along the lines where she had scratched and the band of tight elastic sleeves of the sterile gown she wore, which is suggestive of koebnerization. Knowing the atypical manifestations of drug-induced LAD may aid clinicians in determining an early diagnosis, and LAD should be an important consideration in the differential diagnosis of vesiculobullous disease with palmar-plantar involvement. Amlodipine is a commonly used anti-hypertensive drug, so knowledge of its potential to cause this disease is important. Furthermore, knowing the potential for koebnerization, avoidance of trauma and the gentle handling of these patients can lead to early recovery from this self-limiting disease.

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Introduction

Linear immunoglobulin A (IgA) disease (LAD) is a rare autoimmune, sub-epidermal vesicular-bullous disease. Patients may exhibit widely scattered muco-cutaneous lesions or expanding annular plaques arranged in a cluster-of-jewels pattern (Cauza et al., 2004). LAD is either spontaneous or drug-induced (Gottlieb et al., 2017). Among the drug-induced cases, vancomycin (VCM) has been the most frequently reported as the culprit drug (Whitworth et al., 1996), but amlodipine has also been identified in rare instances (Low et al., 2012). Drug-related LAD has been associated with rapid onset, significantly more atypical and severe forms, with koebnerization, palmoplantar involvement, positive Nikolskiy sign, and erosions that mimic toxic epidermal necrolysis (Chanal et al., 2013). We present a case of a patient with rare and atypical clinical features in drug-induced LAD.

Case synopsis

A 49-year-old woman presented with complaints of multiple fluid-filled lesions for 5 to 6 days, which were preceded by mild pruritus, and appeared first on the back and progressed to involve the entire body over next 3 to 4 days. The patient had a history of intake of telmisartan for hypertension for 1 year, and a recent change to telmisartan-amlodipine for the previous 10 days. There was no other drug intake or positive history.

A physical examination revealed tense, clear, fluid-filled vesicles, bullae, and erosions distributed over the face, trunk, buttocks, and bilateral upper and lower limbs. Similar lesions were also seen on the palms and soles (Fig. 1). Multiple polycyclic lesions with central crusting and a marginal rim of vesicles were observed, forming a classic string-of-pearls appearance (Fig. 2). Similar lesions with marginal activity were also present on the vermilion border of the lips and the periorbital region. These were present either on normal-looking or erythematous skin. There was no mucosal involvement.

During the hospital stay, the patient developed crops of new lesions. Interestingly, few of these vesicles were present in a linear

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Fig. 1. Typical lesions on the palms and sole.

pattern on the arms along lines of scratching, as well as along the band of tight elastic sleeves of the sterile gown worn by the patient, which was highly suggestive of koebnerization (Fig. 3).

A skin biopsy was performed, and the histopathology test results of the lesion showed a typical subepidermal blister with predominant neutrophilic infiltrate and few eosinophils, but perilesional direct immunofluorescence showed linear deposition of IgA at the basement membrane zone. Thus, a diagnosis of LAD was made. Indirect immunofluorescence was not performed, because this was a limited-resource, government-run setting, but could have helped rule out a relatively rare entity, such as IgA epidermolysis bullosa acquisita. All other investigations tested normal, and the infection and malignancy screening results were negative.

Due to the temporal correlation and absence of any other trigger, the onset of LAD was attributed to the introduction of the new drug, amlodipine. The medication was stopped immediately, and oral prednisolone (1 mg/kg) with dapsone (100 mg/day) was started, which led to a rapid resolution of the lesions within a week. Also, the patient was advised to wear loose clothing and avoid scratching, after which no new bullae developed over the next 2 weeks.

Treatment with prednisolone was tapered and stopped in the following 2 months, but dapsone was continued for 6 months. Patient was followed every 6 months for a year after stopping treatment with dapsone, and there was no recurrence of the condition.

Case discussion

Among the various drugs implicated, VCM is the most common. Other drugs include captopril, penicillin, ceftriaxone, sulphonamides, furosemide, lithium, phenytoin, carbamazepine, glibenclamide, atorvastatin, and non-steroidal anti-inflammatory drugs (Chanal et al., 2013; Pastuszczak et al., 2012). The mechanism of drug-induced LAD remains elusive, and two proteins (i.e., 97-kD and 285-kD) in the basement membrane zone are potential antigens. Drugs may elicit an autoimmune response by acting as haptens, complexing or modifying proteins, and breaking self-tolerance to these antigens (Fortuna et al., 2012; Paul et al., 1997).

In a study utilizing sera from a typical case of VCM-induced LAD, co-incubation with VCM resulted in linear IgA deposition at the basement membrane zone by indirect immunofluorescence, which



Fig. 2. String-of-pearls appearance.



Fig. 3. Koebnerization at the (A) initial stage and (B) after evolution.

indicates that COL7 is a target autoantigen in VCM-induced LAD, and VCM mediates IgA autoreactivity against COL7 (Yamagami et al., 2018). The lesions in drug-induced LAD can occur as rapidly as within 24 hours to 780 days after initiation of medication (Fortuna et al., 2012).

In our patient, LAD occurred with amlodipine, and a rash appeared 10 days after starting the drug. A similar pathomechanism can also be attributed to amlodipine. Amlodipine is a very rare cause of such an eruption, and there has been only a single case report of amlodipine-induced LAD in the literature where the rash began after 7 days (Low et al., 2012). Other amlodipine-induced presentations include bullous pemphigoid, erythematous multiforme, alopecia, peripheral edema, and angio-edema (Low et al., 2012).

Irrespective of etiology, LAD has a predilection for the trunk, and only a few patients have presented with involvement of the palmar-plantar surfaces. These patients had either a generalized eruption with prominent palmar-plantar or sole involvement (Cauza et al., 2004; Norris et al., 2015; Walsh et al., 2009). The majority of these patients had drug-induced LAD, which substantiates the observation that such atypical clinical features are common in this subtype. Of note, LAD should be an important consideration in the differential diagnosis of vesiculobullous disease with palmar-plantar involvement.

The Koebner phenomenon is the development of isomorphic pathologic lesions in traumatized uninvolved skin (Kuner et al., 2003). Our patient developed linear lesions at the sites of the tight sleeves of the sterile gowns she wore, as well as along the lines of where she scratched her arms. This has been seldom seen in LAD. Document VCM-induced LAD cases show occurrences of koebnerization at sites of adhesive placement on the skin (McDonald et al., 2010) and scar sites of cardiac surgery on the abdomen (Mori and Yamamoto, 2013), but metronidazole and hyoscine-N-butylbromide-induced LAD had evidence of koebnerization as reported in one case (Rashid Dar and Raza, 2008).

Our findings are consistent with those of previously reported cases in the literature, and strengthen this association. Among various hypotheses, one is that traumatized epidermis may express antigens or expose new epitopes (Mori and Yamamoto, 2013). Another hypothesis is that the development of new lesions could be due to increased blood flow in areas of scratching due to trauma and friction, thus bringing in more auto-antibodies to the site (Rashid Dar and Raza, 2008). Moreover, since our patient had palmoplantar involvement, the koebnerization phenomena can be speculated to have led to the development of blisters in acral areas as well.

Drug-induced LAD is usually expected to rapidly resolve after withdrawal from the offending agent, but additional systemic therapy such as corticosteroid or other immunosuppressive drugs may be required. Furthermore, care should also be taken for gentle skin handling, loose clothing, or avoiding the use of tapes and adhesives, when possible, to avoid koebnerization.

The atypical features in our case can be substantiated by the fact that in one series, in comparison with spontaneous LAD, drug-induced LAD was characterized by a significantly more atypical and severe form (Chanal et al., 2013). This knowledge of atypical manifestations may aid clinicians with an early diagnosis and intervention when suspecting such disorders. Also, amlodipine is a commonly used hypertensive agent, and knowing its potential to cause this vesiculo-bullous disease is important. Furthermore, the significance of koebnerization in drug-induced LAD implies that an avoidance of trauma and the gentle handling of these patients can lead to an early recovery from this self-limiting disease.

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