

## LINEAR IGA BULLOUS DISEASE WITH POSSIBLE IMMUNOREACTIVITY TO THE BASEMENT MEMBRANE ZONE AND DERMAL BLOOD VESSELS

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### Abstract

**Introduction:** Linear IgA bullous dermatosis (LAD) is an immunobullous disorder, in which IgA antibodies are deposited along the basement membrane zone (BMZ) of the skin in a linear pattern. The cause of this disease is unknown, but the eruption may occur more commonly in association with certain medications.

**Case report:** A 61 year old woman presented with blisters in the axillae and legs, with pain, itching and swelling. She was taking many medications for other conditions such diabetes and obesity. Tense blisters were seen, primarily on the legs and accompanied by some ankle swelling.

**Methods:** Skin biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF), and immunohistochemistry (IHC) studies were performed.

**Results:** The H&E examination revealed a subepidermal blister, with small numbers of lymphocytes, neutrophils and eosinophils noted within the blister lumen. The dermis also displayed a mild, superficial, perivascular infiltrate of lymphocytes and histiocytes; eosinophils and neutrophils were also noted. DIF and IHC studies confirmed the diagnosis of linear IgA (LAD) at the BMZ. However, in addition to immunoglobulin A, we also observed deposits of IgA, IgM, IgG, IgD, Kappa, Lambda, Complement/C3c, C1q, fibrinogen and albumin around upper dermal blood vessels.

**Conclusions:** LAD has been most commonly associated with medication intake; the most common DIF immune response is the presence of linear IgA at the BMZ. However, here we found additional reactivity to against dermal blood vessels. Because the patient is affected by diabetes mellitus, it is difficult to know if the observed vascular reactivity was associated with the diabetes or solely an immune reaction to the vessels. Based on our findings, we encourage searching for vascular reactivity in cases of LAD.

**Key words:** Linear IgA bullous dermatosis; drugs; vessels; autoreactivity

**Abbreviations:** Linear IgA bullous dermatosis (LAD), basement membrane zone (BMZ), direct immunofluorescence (DIF), hematoxylin and eosin stain (H&E), idiopathic linear IgA blistering disease (LABD).

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### Introduction

Drug-induced linear IgA (LAD) is a self-limited eruption, characterized by linear deposition of IgA without IgG at the basement membrane zone (BMZ) of the dermal/epidermal junction of the skin. Most patients described with this condition seem to lack circulating antibodies. The distribution of lesions and the course of the disease differ from those of the idiopathic form of linear IgA blistering disease (LABD). LABD is extremely rare, and thus not as well characterized as LAD [1-5].

### Case Report

An obese patient presented with inflamed, large blisters on the legs and smaller ones surrounding the large blisters. In addition, the patient presented with edema and some pitting edema, primarily in the legs. The patient was unable to correlate the appearance of these lesions with any specific medication, since she was taking multiple medications simultaneously. The blisters were tender to palpation, and had been present for a week. The patient's medications included agents therapeutic for diabetes, arthritis, obesity, venous stasis and vulvovaginal Candidiasis.

The patient had a history of hepatitis B. Specifically, she was taking daily hydrochlorothiazide, (diuretic), Metformin® (antidiabetic; helps reduce LDL cholesterol and triglyceride levels), Symlin® (pramlintide acetate; diabetes treatment, A1c lowering and insulin reducing), Lantus® (insulin glargine subQ), Novolog® subQ (Insulin aspartate) and 1% fluconazole (topical antimycotic). A skin biopsy for histologic studies was obtained, as well as a biopsy for direct immunofluorescence (DIF). After the biopsy, the patient was also prescribed 1) triamcinolone acetonide. 0.1% topical cream twice a day for 30 days, as well as 2) hydrocortisone 2.5%. Because the patient was taking many medications, she was sent to the internist to attempt to consolidate her prescriptions.

## Methods

Processing of the H & E biopsy as well as the DIF and immunohistochemistry workups were performed as previously described. For DIF, multiple frozen section sets were cut at four micron thicknesses each, and DIF was performed utilizing antibodies to IgG, IgA, IgM, IgD, IgE, Complement/C1q, Complement/C3, Complement/C4, Kappa light chains, Lambda light chains, albumin and fibrinogen [6-8].

## Results

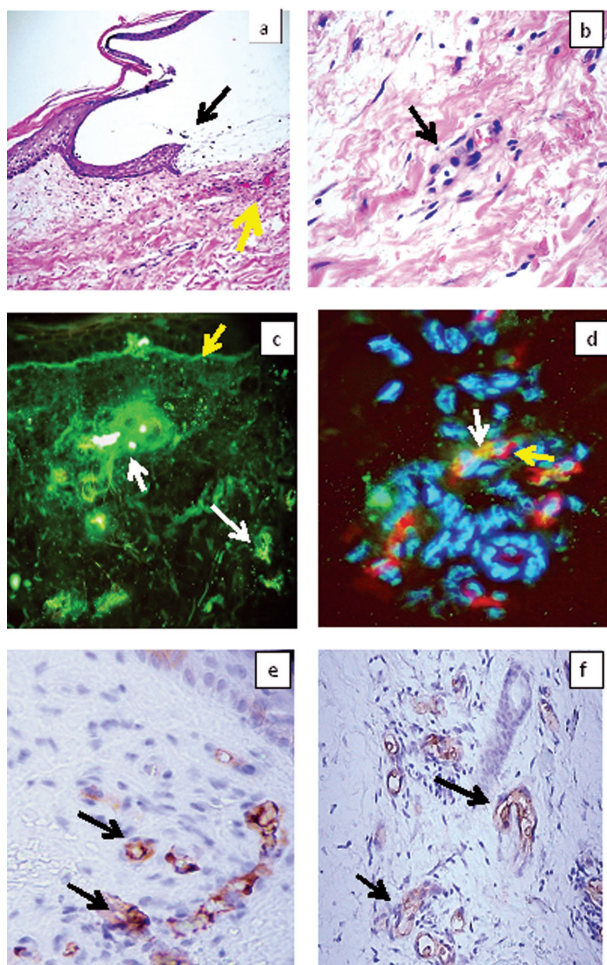
### Microscopic Description and DIF findings

Examination of the H&E tissue sections demonstrated diffuse, moderate epidermal spongiosis present. Significant superficial

papillary dermal edema was noted (Fig. 1). A subepidermal blister was seen, with small numbers of lymphocytes and eosinophils noted within the blister lumen (Fig. 1). The dermis also displayed a mild, superficial, perivascular infiltrate of lymphocytes and histiocytes; eosinophils and neutrophils that were rare. No definitive vasculitis was present but some inflammation and edema around the upper vessels was observed. DIF and IHC demonstrates the following results: IgG (+, focal dermal perivascular); IgA (+, focal dermal perivascular and faint linear BMZ stain); IgM (+, focal dermal perivascular and focal epidermal anti-cytokeratin); IgD (+, focal dermal perivascular); IgE (-); Complement/C1q (+, focal dermal perivascular); Complement/C3(+, focal dermal perivascular and focal epidermal anti-cytokeratin); Complement/C4 (-); kappa light chains (+, focal dermal perivascular); Lambda light chains (+, focal dermal perivascular and focal epidermal anti-cytokeratin); albumin (+, focal punctate dot epidermal stratum corneum) and fibrinogen(+++, focal dermal perivascular, perieccrine and faint linear BMZ). (Fig. 1, 2). The patient was free of lesions within 5 weeks after consolidation of some medicines and the use of topical steroids.

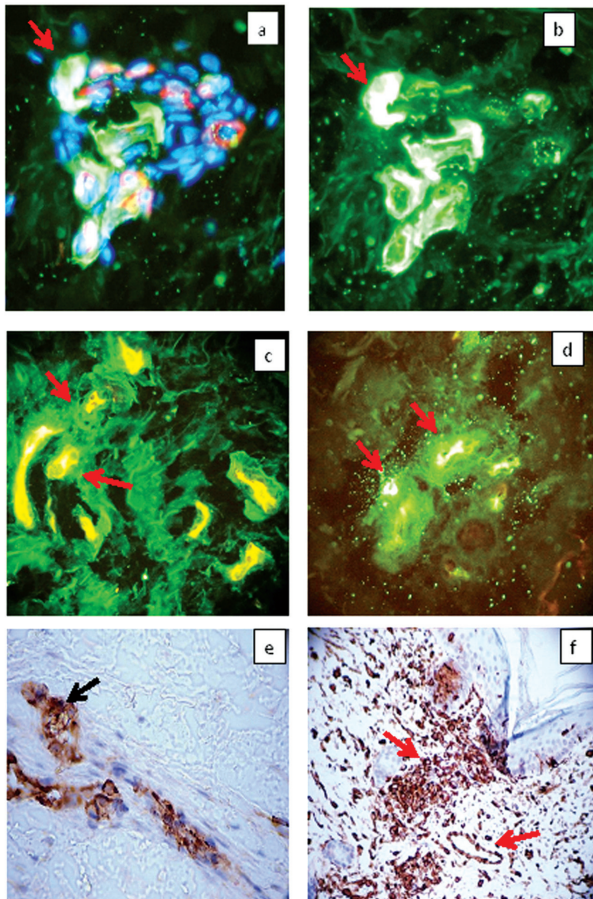
## Discussion

LAD is an immunobullous disorder in which IgA antibodies are deposited within the BMZ in a linear pattern. The cause of the disease is unknown, but the eruption has been most commonly associated with selected medications [1-5].



**Figure 1.** a. H&E section, demonstrating a subepidermal blister with focal re-epithelialization of the blister base (black arrow). Please note the presence of possible erythrocytic rouleaux and pink fibrinous material in the upper dermal blood vessels under the blister (yellow arrow) (100x). b. H&E section, demonstrating mild perivascular inflammation around an upper dermal blood vessel (black arrow; 200x). c. DIF, utilizing FITC conjugated anti-human IgA and showing positive linear IgA deposits at the BMZ (green staining; yellow arrow), as well simultaneous deposits of IgA on upper dermal blood vessels (green/white staining; white arrows). d. DIF, again highlighting FITC conjugated IgA positivity on dermal blood vessels (green/yellow staining; white arrow). Note that the IgA staining colocalizes with a vascular marker, Rhodamine conjugated Ulex europaeus agglutinin I (Vector Labs, Burlingame, California, USA; red staining; yellow arrow). e. Positive IHC staining for IgA to upper dermal blood vessels (brown staining; black arrows; 200x); note the IHC colocalization with a von Willebrand factor vascular marker (red staining; black arrows). f. IHC staining, showing positive staining for vimentin around inflamed dermal blood vessels and around eccrine sweat duct supply vessels (brown staining; black arrows, 200x).





**Figure 2.** a. DIF, demonstrating FITC conjugated IgA positive staining on upper and intermediate dermal blood vessels (green staining; red arrow). Note the IgA positive reactivity in the vessels colocalizes with Cy5 conjugated ICAM-1/CD54 antibodies (white staining) and Rhodamine conjugated Ulex europaeus agglutinin I antibodies (red staining). The nuclei of endothelial cells were counterstained with Dapi (blue). b. Similar to a, but utilizing only FITC conjugated IgA. c. DIF, demonstrating positive staining with FITC conjugated IgD on dermal eccrine glands (yellow/white staining; red arrows). d. DIF, demonstrating positive staining with FITC conjugated IgA on dermal blood vessels (green/white staining; red arrows). e. IHC, demonstrating positive staining for IgA on dermal blood vessels (brown staining; black arrow). f. IHC, demonstrating positive staining for Complement/C3c on dermal blood vessels around the sweat glands (brown staining; red arrows).

As previously suggested by Plunkett, et. al. [1], all the cases we have encountered of LAD were associated with a drug reaction. Thus, LAD cases should be confirmed by DIF; a search should be made for any drug eliciting the disorder. Moreover, the majority of the cases reported in the medical literature seem to be drug induced. In contradistinction, idiopathic LAD is rare, and not well immunologically characterized. We have been working for more than 21 years with autoimmune blistering diseases, and have not encountered a single confirmed case of idiopathic LAD. In many countries, physicians may encounter adults taking 3 or more medications simultaneously. Any new medication can induce a drug-drug interaction [9,10]. Based on our current case and others, we advise dermatopathologists to search not only for deposits of immunoglobulin A at the BMZ, but also around dermal blood vessels and eccrine glands in suspected cases of LAD.

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