

# FUROSEMIDE INDUCED LINEAR IgA BULLOUS DERMATOSIS

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## ABSTRACT

A case of linear IgA bullous dermatosis in a 59-year-old female patient is reported. She developed generalized erythema and bullous eruption few months after starting furosemide treatment for arterial hypertension. Histopathology revealed a subepidermal blister, and direct immunofluorescence disclosed linear IgA deposits along the epidermal basement membrane. To the best of our knowledge, this is the first report of this disease from Jordan.

**Key words:** Linear IgA bullous dermatosis

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## Introduction

Linear IgA bullous dermatosis (LABD) is a rare autoimmune blistering disease that resembles bullous pemphigoid or dermatitis herpetiformis clinically.<sup>(1)</sup> The incidence of the disease in Western Europe is reported at less than 0.5 per million, and around 0.6 per 100,000 adults in the United States.<sup>(1,2)</sup> It usually presents with pruritic urticarial papules, vesicles, or bullae on extensor surfaces, elbows, knees, or buttocks.<sup>(2,3)</sup> The differential diagnosis of LABD includes dermatitis herpetiformis, bullous pemphigoid, cicatricial pemphigoid, erythema multiforme, nodular prurigo, and neurotic excoriations.<sup>(1)</sup>

Histopathologically, features of LABD are usually similar to those found in dermatitis herpetiformis. There are subepidermal bullae with infiltrate of neutrophils along the basement membrane zone (BMZ) and dermal papillae tips. However, the histology may occasionally resemble that seen in bullous pemphigoid or other blistering diseases.<sup>(1-5)</sup> In drug-induced LABD, there is an associated lympho eosinophilic infiltrate as well.<sup>(5)</sup>

The diagnosis of LABD can only be established with direct immunofluorescence (DIF) by demonstrating a linear immunoglobulin A (IgA) band at the BMZ.<sup>(5)</sup> There may also be deposition of IgG, IgM, and C<sub>3</sub>. The autoantibodies are of the IgA class, which is a rather rare event among the autoimmune disorders. LABD target antigens are heterogeneous and complex; epidermal and dermal associated antigens have been identified including hemidesmosome, lamina lucida, lamina densa, sublamina densa and anchoring fibrils (collagen type VII).<sup>(1,2)</sup> Low titers of circulating anti-squamous BMZ IgA antibodies have been identified in 20% to 60% of cases.<sup>(4,5)</sup>

Application of split skin technique has demonstrated that the majority of antibodies bind to the epidermal side of the lamina lucida, whereas the rest adheres to the dermal side of the artificial blister, and a few are of a combined pattern. Two main subsets of IgA antibodies have been identified in LABD. The first one comprises antibodies directed against antigens with molecular weight of 285 kDa as well as the bullous pemphigoid 230 kDa antigen (BP230) and the 97 kDa and 120 kDa,

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which appear to be fragments of extracellular domain of bullous pemphigoid antigen BP180 (type XVII collagen). They bind to the roof of the salt-split skin and are responsible for the development of classic LABD. The second subset comprises antibodies against type VII collagen, which bind to the floor of the salt-split skin and characterize IgA mediated epidermolysis bullosa acquisita (IgA-EBA).<sup>(1,5-8)</sup>

The described immunological heterogeneity could be responsible for variations in the clinical course of LABD.

## Case Report

A 59 years old female presented to the emergency department at Prince Hashem Hospital on October 10<sup>th</sup> 2004, complaining of fever with severe itching and generalized erythematous skin rash. Recent medical history includes treatment with Furosemide, which has been started just few months prior to presentation for mild arterial hypertension.

On physical examination, the patient was generally weak; she had an oral temperature of 39.6 °C and her blood pressure was 105/70. She had generalized diffuse erythematous skin eruptions, with overlying tense vesicles and bullae present mainly over limbs and abdomen (Fig. 1).



**Fig. 1.** Generalized erythema with overlying blisters

Few vesicles and erosions were seen over the buccal mucosa. Ophthalmological examination was normal. There was no peripheral lymphadenopathy and the rest of her physical examination was unremarkable.

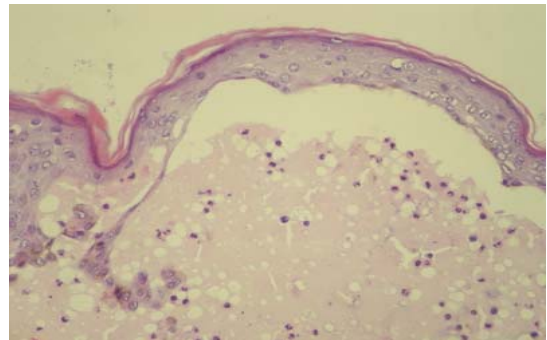
The patient's clinical features were suggestive of an immunobullous disease (mostly bullous pemphigoid). A drug-induced etiology was suggested because the blisters developed only few

weeks after commencing treatment with Furosemide. Therefore, the patient was admitted to hospital and all recent drugs were stopped. Septic work up was done; including blood culture, urine culture, and throat swab culture. Laboratory investigations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antistreptolysin O (ASO) titer, liver function tests, kidney function tests, and fasting blood glucose.

Her ASO titer was negative, but her CRP was positive, and her ESR was 85 mm in the first hour. The white blood cell count was  $12.6 \times 10^9/L$ , and her hemoglobin level was 13.2 mg/dl. The peripheral blood smear revealed normochromic normocytic red blood cells (RBCs), with neutrophilic leucocytosis. Her blood urea nitrogen, serum creatinine, alanine aminotransferase, aspartate aminotransferase, and fasting blood glucose were all within normal limits. The level of glucose-6-phosphate dehydrogenase (G6PD) was 97 mIU/  $10^9$  RBCs.

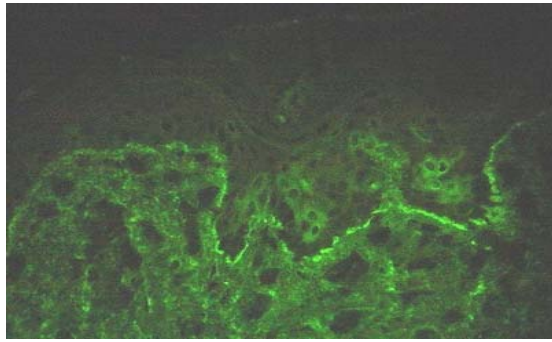
Urine culture revealed *E. coli*  $> 10^5$  sensitive to norfloxacin, gentamycin, ceftriaxone, nalidixic acid and cephalothin; but resistant to amoxicillin. Other cultures were negative.

A skin biopsy was taken at that time for routine processing with hematoxylin and eosin (H&E) staining and for immunofluorescence testing. The slide No. P04/3586 revealed subepidermal blistering with mononuclear, eosinophilic and neutrophilic dermal cellular infiltrate (Fig. 2).



**Fig. 2.** Subepidermal blistering with neutrophils/eosinophils cell infiltrates (H&E stain, X20)

The diagnosis was read as dermatitis herpetiformis or bullous pemphigoid. DIF showed a strongly positive (+++) linear IgA (Fig. 3) and a faintly positive (+) linear IgM deposits at the epidermal BMZ. IgG and C3 were not reactive. Subsequently, the diagnosis of LABD was made.



**Fig. 3.** A granular linear fluorescence pattern at the dermoepidermal junction with IgA

The patient was started on daily intravenous (IV) Hydrocortisone 100mg four times a day. Other medications included oral Paracetamol, Hydroxyzine hydrochloride, Loratadine, and Famotidine. Cephalexin was prescribed for her urinary tract infection. Topical emollients and moderate steroids were applied twice daily.

After 11 days in hospital, her skin lesions settled well and no new bullae were seen. IV hydrocortisone was discontinued and replaced with oral prednisolone (60mg/day). The patient was discharged on systemic and topical steroids. On her appointment at the clinic two weeks later, she was enjoying a normal life free of bullae and her Prednisolone dose was tapered gradually to zero over the following 10 weeks, needing only occasionally to use topical steroids.

## Discussion

LABD is a rare autoimmune bullous disorder, characterized by linear deposition of IgA along the BMZ. It was originally thought to be a manifestation of dermatitis herpetiformis. However, based on immunopathology and immunogenetics, it is now known that LABD is a distinct entity, with characteristic clinical and histopathological features.<sup>(2-4)</sup> It is a distinct subepidermal blistering disorder, characterized by tissue-bound and circulating IgA autoantibodies targeting the dermoepidermal junction.<sup>(7)</sup>

The diagnosis of LABD is based on four major criteria: (1) itchy vesiculobullous lesions with a circinate pattern on skin and/or mucous membranes, (2) subepidermal bulla with neutrophilic infiltrate by histology, (3) exclusive linear IgA deposition along the epidermal BMZ by immunofluorescence microscopy, and (4) a prompt response to Dapsone therapy.<sup>(6)</sup> In addition to skin involvement, mucous

membrane involvement may occur in LABD and ranges in severity from mild oral ulcers to severe oral or conjunctival disease.<sup>(1,2)</sup>

The onset of adult-type LABD is after puberty, with a peak around 60 years of age. Another IgA bullous disease is chronic bullous disease of childhood (CBDC), which appears usually before the age of five.<sup>(1,2)</sup> CBDC follows a much different course from the adult type, with resolution occurring within two-three years of onset in most cases.

Infections, drugs or malignant processes may provoke the onset of LABD, but most frequently it is of idiopathic origin.<sup>(1,2,4)</sup> Vancomycin is the most frequently incriminated drug causing LABD. Other drugs include Captopril, Phenytoin, Furosemide,<sup>(9)</sup> Somatostatin, Rifampicin, Trimethoprim, sulfamethoxazole, Atorvastatin, Piroxicam, Lithium carbonate, Amiodarone, Cyclosporine, and Diclofenac sodium.<sup>(1-4)</sup> As drugs are important triggering factors, this should be sought in the clinical history as the withdrawal of the offending drug often results in clinical improvement.<sup>(10)</sup>

Due to the drug history of taking Furosemide recently and the fact that this drug has been implicated in the development of LABD, a drug-induced linear IgA bullous dermatosis was suspected in our patient, and she was advised to avoid this drug. Another implicated etiology in this patient is the urinary tract infection, revealed by urine culture.

Cutaneous reactions due to Furosemide are relatively rare, but may be life threatening. These include erythema multiforme, bullous skin eruptions including bullous pemphigoid and LABD, lichenoid reactions, photosensitive reactions, and acute generalized exanthematic pustulosis.<sup>(9,11,12)</sup> LABD differs from other reactions clinically (vesiculobullous / urticarial eruption), and by its characteristic direct immunofluorescence.

Clinical, histomorphological and immunohistological heterogeneity is presumably caused by differences in fine epitope specificity, the isotype of autoantibodies and associated effector mechanisms.<sup>(7)</sup> The simultaneous positivity for IgG and IgA observed in some patients makes the distinction especially between bullous / cicatricial pemphigoid and LABD difficult. In such cases, the comparison of intensity of particular immunoglobulins is of major relevance for making the proper diagnosis. This is well illustrated in our case report. Her skin biopsy showed strongly

positive linear IgA deposits along the epidermal basement membrane, which permitted the differentiation between bullous pemphigoid and LABD.

A strong association between LABD and autoimmune haplotypes HLA-B8, CW7 and DR3 has been reported.<sup>(1,2)</sup> However, there is no associated gluten-sensitive enteropathy.<sup>(1)</sup> There are many reports associating LABD with various conditions,<sup>(2,13,14)</sup> including rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, inflammatory bowel disease, and multiple sclerosis. LABD has also been linked to various malignancies including urinary bladder, esophageal, thyroid and ovarian carcinoma, hydatidiform mole and lymphoproliferative malignancies.<sup>(13-15)</sup>

In mild cases of LABD, the disease might be controlled with topical steroids alone.<sup>(1,2)</sup> In more severe cases of idiopathic adult LABD, Dapsone is the treatment of choice with Sulfapyridine as an alternative drug. As Dapsone may cause a hemolytic anemia, decreased hemoglobin values or even methemoglobinemia, the G6PD enzyme has to be assayed before beginning the treatment. In cases similar to our patient, where G6PD levels are low and there is a risk of hemolysis, prednisolone is a good alternative treatment. In some patients Azathioprine or Cyclosporine may be necessary<sup>(1)</sup>. Success has also been reported with the use of Erythromycin, Colchicine, Mycophenolate mofetil, intravenous immunoglobulins, Tetracyclines and Nicotinamide.<sup>(1,2,9,16)</sup> In cases triggered off by drugs, a prompt remission may follow the withdrawal of the incriminated drug.

The course of linear IgA dermatosis is variable and unpredictable. The disease may spontaneously remit in some cases; however, it may last for years with few episodes of remission in others. In view of its ultimate spontaneous recovery, the physician should avoid over treating patients with LABD.

In conclusion, our case report of a Jordanian patient with linear IgA bullous dermatosis illustrates the clinical presentation, diagnosis and management of this rare disease.

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