Drug induced linear IgA dermatosis  
Case report and a short review  

A. Benedičič Pilih, A. Vizjak, F. Wojnarowska, M. Berčič, A. Pejovnik Pustinek, J. Arzenšek and A. Kansky

A significant number of reports incriminate various drugs, especially vancomycin and amiodarone of provoking bullous linear IgA dermatosis. This entity also includes the subset of IgA-mediated epidermolysis bullosa acquisita.

We report on a patient with histopathologically and immunologically proven bullous linear IgA dermatosis, who developed this condition during treatment for hypertension with enalapril. Treatment with low doses of dapsone, 25 mg daily, was efficient. There is strong evidence that the condition was triggered by enalapril.

Introduction

There are many publications asserting that bullous autoimmune diseases, such as pemphigus, bullous pemphigoid and linear IgA dermatosis (LAD) may be provoked by medication. Inhibitors of the angiotensin converting enzyme (ACE) like captopril or diuretics like furosemide have frequently been incriminated as causing bullous pemphigoid (BP), as well as other skin conditions (1,2). Litt mentioned in his publication (3) that captopril was held responsible in 38 references as the cause of angioedema, in 31 it was associated with exanthema and lichenoid eruptions, in 23 with bullous manifestations, mostly pemphigus and in three reports with LAD. Enalapril was reported to have induced angioedema in 55 cases, and has also been reported as having induced exanthema and rash, urticaria and other skin manifestations (3). There is ample evidence in literature that a number of drugs have been incriminated as provoking LAD (Table 1) including vancomycin, somatostatin, rifampin, captopril, trimethoprim, sulfamethoxazole, phenytoin, atorvastin, piroxicam, lithium carbonate, amiodarone, cyclosporine, cefamandole and diclofenec (4,5).

The diagnosis of LAD is based on the following criteria:

- Itchy vesicobullous lesions on skin and/or mucous membranes
- subepidermal bulla with neutrophilic infiltrate
- linear IgA deposits along the epidermal basement membrane
- prompt response to treatment with dapsone (4).

Two main subsets of IgA antibodies have been identified in LAD, binding to the opposing sides of salt split human skin. The first subset comprises antibodies directed against bullous pemphigoid 230 kDa antigen BP 230 and 180 kDa antigen BP 180 (collagen XVII). They bind to the roof of the salt split skin and are responsible for the development of classic LAD. 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 (4). Wojnarowska et al demonstrated by indirect immunofluorescence on salt split skin that autoantibodies in LAD patients may bind to the epidermal side, to the dermal side or in a combined pattern (6). They suggested that autoantibodies in LAD targeted multiple antigens associated with hemidesmosomes and anchoring fibrils (7).

**Case report**

**History.**

A 66-year-old male patient with linear IgA bullous dermatosis is presented. He appeared for consultation in April 2002 because of an erythematous vesicular rash on his legs. He had observed a few erythematous lesions on his legs about one year prior to admission. He was treated for hypertension with enalapril tablets, 2.5 to 5.0 mg daily for approximately six months. He had one kidney removed due to tuberculosis at the age of 17 years, but otherwise enjoyed good health.

Multiple erythematous lesions, some of them slightly vesicular, were seen on his thighs and legs, when he appeared for consultation in October 2002. Figure 1.

**Table 1. Reports on drugs incriminated as inducing linear IgA dermatosis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Incriminated drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mc Whirter JD et al</td>
<td>Arch Dermatol 1987; 123: 1120-2</td>
<td>Lithium carbonate</td>
</tr>
</tbody>
</table>

**Table 2. Reports on angiotensin receptor antagonists and angiotensin converting enzyme inhibitors inducing linear IgA dermatosis or bullous pemphigoid**

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Incriminated drug</th>
<th>Confirmed diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman IS et al</td>
<td>Int J Dermatol 1998;37:608-12</td>
<td>Captopril</td>
<td>LAD</td>
</tr>
<tr>
<td>Mullins PD, Choudhury SL</td>
<td>BMJ 1994;309:1411</td>
<td>Enalapril</td>
<td>BP</td>
</tr>
</tbody>
</table>

Abbreviations: AR antagonist – angiotensin receptor antagonist
LAD – linear IgA dermatosis
BP – bullous pemphigoid
Case report

Drug induced linear IgA dermatosis

Figure 1. Erythematous lesions on the thigh, some are slightly vesicular, first consultation October 2002.

Figure 2. Light microscopy, H&E - Small subepidermal bulla and an inflammatory infiltrate in the superficial dermis, including lymphocytes and some neutrophils and eosinophils.

Figure 3. Direct immunofluorescence shows continuous linear IgA deposits along the epidermal basement membrane zone.

Figure 4. Erythematous lesions at the time of recurrence, February 2003, are very similar to those presented in Figure 1.
Under local treatment with steroids, bullous eruptions continued to appear, the erosions left over healed, but brown pigmentation became visible. The withdrawal of enalapril was followed by a remission lasting a few weeks. A vesicular rash later appeared on the legs and also on the trunk.

**Laboratory investigations.**

Basic blood findings were within the normal range. Pemphigoid, pemphigus, antigliadin and antimiyoisin antibodies in blood serum were negative. Histopathology of lesional and perilesional skin revealed a subepidermal bulla filled with fluid, fibrin and a few eosinophils. Figure 2. Direct immunofluorescence (DIF) revealed continuous linear IgA deposits, as well as granular C3 and fibrin deposits along the epidermal basement membrane zone. There were no IgG deposits and only a few fine granular deposits of IgM along the dermo-epidermal zone and in the upper dermis.

After three months, erythematous skin lesions on his lower extremities recurred and the biopsy was repeated (February 2003). Histopathology again showed two small subepidermal vesicles. In the superficial dermis there was a lymphocytic inflammatory infiltrate, including some neutrophils and eosinophils. DIF again showed linear IgA deposits characteristic for LAD. Indirect immunofluorescence with the patient’s sera on intact and salt split skin was negative for IgG and C3. An IgA antibody was detected in the basement membrane zone of intact skin and on the epidermal side of the split skin at low dilutions (1:5 and 1:10). By immunoblotting, IgA and IgG antibodies to BP 180 (collagen XVII) were detected in low titers. Immunologic tests confirmed the diagnosis of LAD. Figure 4.

**Therapy.**

Our patient refused the recommended dose of 100-150 mg dapsone daily, because of his single kidney, although his renal function was normal. Treatment with 25 mg of dapsone daily, but after 10 days he stopped the therapy due to impaired vision. During the 10-day treatment, the bullous skin lesions cleared and the patient refused further treatment with dapsone. After two months the bullous lesions reappeared. Treatment with 25 mg of dapsone was reintroduced and within one month the skin manifestations again cleared. This time, there were no side effects, the patient continued the therapy for three months, when he again discontinued the treatment. He was still without symptoms three months after the discontinuation of the treatment.

**Discussion**

There are an increasing number of reports that mention various drugs provoking LAD. In the past, penicilamine (8) and furosemide (9) were repeatedly mentioned as being associated with LAD. Cases of LAD induced by piroxicam (5), statins (10), lithium carbonate (11), acetaminophen (12), amiodarone (13,14) and diclophenac (15) have also been reported (Table 1). In the last few years, vancomycin has been the most frequently incriminated drug (16-22). The majority of these conditions were clinically similar to our case, with fairly small vesicles, mostly on the legs, thighs and forearms. However, cases of drug-induced LAD with more severe lesions, such as erythema multiforme (23) or lesions mimicking toxic necrolysis (14) have also been described. Furthermore, LAD cases limited to gingiva have been reported (24).

Only limited data are available so far on LAD attributed to inhibitors of ACE. One reported case was associated with captopril (25) and a few cases with other ACE inhibitors (26-28). There have been more reports connecting the ACE inhibitors with bullous pemphigoid, and at least two reports incriminated enalapril (29,30) (Table 2).

It has also been suggested that LAD could be associated with various malignant conditions, e.g. renal carcinoma (31) and myeloproliferative disease (32). It seems that LAD is a polymorphic disorder (33).

**Conclusion**

Dapsone is accepted as the drug of choice in LAD. The recommended doses used to be 100-150 mg daily until clearing of the skin lesions, followed by gradually reducing the dose to a maintenance dose of 50 mg every other day. It has recently been suggested that it is possible to start the treatment of LAD with a lower dose, <0.5 mg/kg body weight, and to increase the dose later, if necessary, until the complete control of blistering and pruritus. Our patient refused the usually recommended dose of dapsone, because of his single kidney, although his renal function was normal. Treatment with low doses of dapsone, 25 mg daily, was efficient.

The fact that the skin lesions did not reappear after discontinuing enalapril, strongly suggest its etiologic role in our case.

**References**


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