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A Rare Case of Desquamative Gingivitis due to Linear IgA Disease: Morphological and Immunofluorescence Features

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Abstract. *Linear IgA disease (LAD) is an acquired subepidermal bullous disorder, characterized by linear deposition of IgA along the basement membrane. Although the oral cavity is involved in up to 50% of cases, its exclusive involvement is very rare. The case of a 57-year-old woman with 13 months history of desquamative gingivitis chiefly located in the maxilla gingiva is presented. She had been diagnosed by her dental practitioner with an oral infection one year previously and had been receiving local anti-inflammatory and antibiotic medication, with no improvement. She was referred to our Oral Pathology Department, where the biopsy performed revealed a submucosal blister with chronic infiltrate. Direct immunofluorescence showed a linear deposition of IgA in the basal membrane zone, and a diagnosis of LAD was rendered. The patient was treated with topical cortisone, triamcinolone and systemic oral methylprednisolone at a daily dose of 32 mg, and continued at decreasing doses for 3 months. At the most recent check-up, 7 months after initial presentation, she was no longer taking any medication and remained asymptomatic and disease-free.*

Linear IgA disease (LAD) is a rare chronic autoimmune subepithelial mucocutaneous bullous disorder that can affect both the skin and the mucous membranes. The condition was originally thought to be a variant of bullous pemphigoid or herpetiform dermatitis. However, during the 1970s LAD was recognized as a distinct entity (1).

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LAD affects both adults and children (2), the childhood variant being called chronic bullous dermatosis of childhood or juvenile dermatitis herpetiformis. The adult variant has a peak of incidence between 60 and 65 years of age, with a 2:1 predilection for women (3, 4).

The clinical presentation consists of urticant plaques, papules, vesicles and bullae and can develop on the skin of the upper and lower trunk, shoulders, groin and lower extremities. There is a predilection for flexural areas and the face and perineum are also frequently involved (5, 6). Some studies have reported up to 50% mucosal involvement, including the oral cavity (3, 5-9) and this may precede involvement of the skin. Only in very rare cases does it solely involve the mucosa. Lesions of the mucous membranes may heal, sometimes with scarring and considerable morbidity, often presenting as desquamative gingivitis, which may secondarily damage the teeth (10). Involvement of the conjunctivae, pharynx, larynx, nose, rectum and esophagus has also been reported (11).

LAD is characterized by linear deposition of IgA immunoreactants at the cutaneous or mucosal basement membrane zone (BMZ) (9-11, 12). The key examination to enable diagnosis is indirect immunofluorescence (IIF), which may demonstrate immunoglobulins of the IgA anti-BMZ antibody class (11-13).

A case of a patient with LAD who was referred to our Department of Oral Pathology with a diagnosis of desquamative gingivitis of uncertain origin, resistant to local and systemic therapy is presented. The clinical and histological features are characterized. The immunofluorescent studies were ultimately helpful in establishing the correct diagnosis.

Case Report

A 57-year-old woman was sent by her dental practitioner for oral pathological examination, with a history of oral

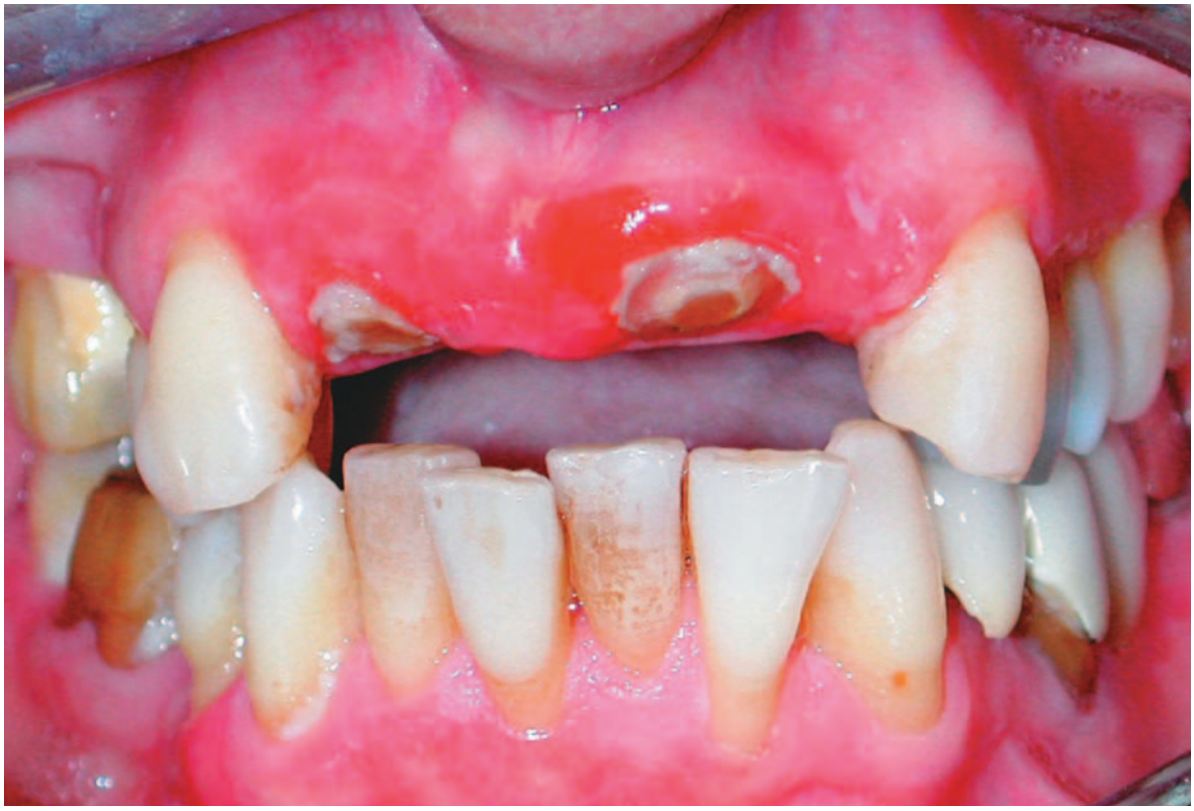

Figure 1. *Oral view showing desquamative gingivitis located in the maxilla gingiva.*

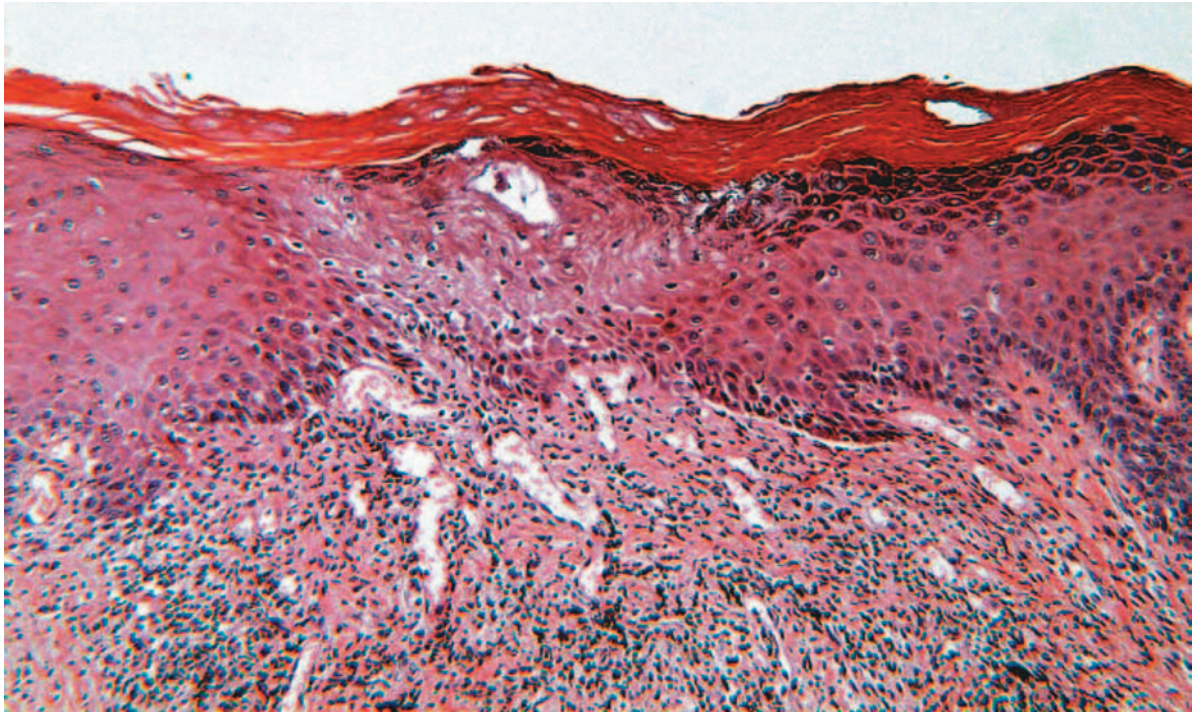

Figure 2. *Histopathological appearance of the bullous lesion displaying a subepithelial bulla (hematoxylin and eosin, original magnification x200).*

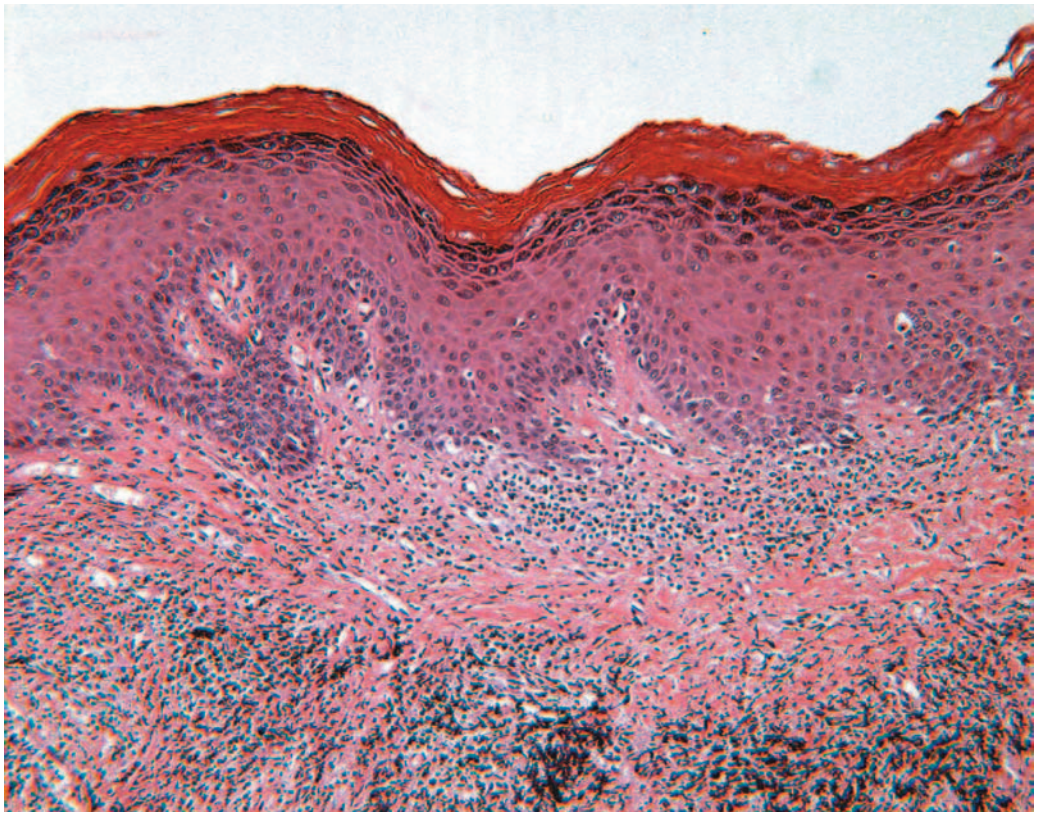

Figure 3. *A conspicuous infiltrate of neutrophils and lymphocytes and rare eosinophils in various areas, similar to a lichenoid infiltrate (hematoxylin and eosin, original magnification x200).*

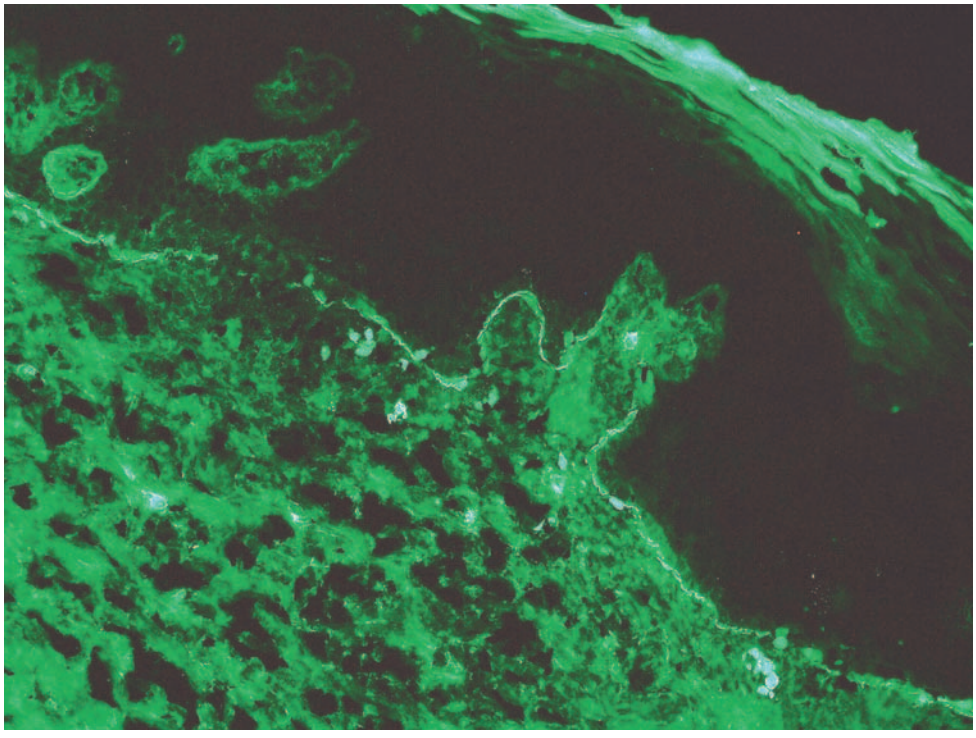

Figure 4. *Direct immunofluorescence showing linear band of IgA in the basement membrane zone (original magnification x100).*

ulceration that had been present for 13 months. The patient complained of a sore mouth and difficulty in eating. She was otherwise healthy and a non-smoker. She had just completed a 14-day course of mouthwash, consisting of a 0.12% chlorhexidine solution and oral scaling had been performed. Her general dental practitioner, who believed the symptoms were due to oral infection, had initially prescribed topical treatment with triamcinolone and a cycle of antibiotic medication with amoxicillin. There was no other history of medication. Extraoral examination failed to reveal any abnormality. Intraorally there were two large areas of erosion and erythema in the maxillary and mandibular gingiva (Figure 1). In addition, small bullous areas were detected in the area of the tuberosity.

The patient underwent incisional biopsy from the mucosa immediately adjacent to an area of gingival bullae. A portion of tissue was sent fresh for direct immunofluorescence and another portion placed in formalin for routine histopathology. A full blood count, biochemical analysis, urine analysis and erythrocyte sedimentation rate were normal. Anti-Nuclear Antibodies (Anti-ANA) and Anti-DNA antibodies (anti-DNA) were negative.

At direct immunofluorescence, linear IgA deposition in the basal membrane zone was detected, and a diagnosis of linear deposition of IgA was rendered.

The patient was treated with topical cortisone, 0.1% triamcinolone, for 3 months and oral methylprednisolone at a daily dose of 32 mg for 8 days, 24 mg for 20 days and 20 mg for a further 20 days. After 6 weeks the patient reported a significant reduction in discomfort, and the vestibular lesions had improved considerably. At subsequent follow-up there was complete resolution of the mucosal lesion, and the prednisolone therapy was reduced. At the most recent check, 7 months after initial presentation, the patient was no longer taking any medication and remained asymptomatic.

Histology. A biopsy specimen from the bullous lesion displayed a subepithelial bulla (Figure 2), and an infiltrate of neutrophils and lymphocytes and rare eosinophils, similar to a lichenoid infiltrate (Figure 3). The site of bulla formation was below the basal cell membrane. Some spongiosis and a few necrotic keratinocytes were present within the epidermal roof of the blister.

Direct immunofluorescence revealed prominent IgA deposits in a linear pattern at the BMZ of the oral mucosa (Figure 4).

Discussion

Linear IgA disease is a rare chronic autoimmune disorder whose clinical presentation is not uniform, making diagnosis from clinical signs and symptoms alone impossible. It is thus diagnosed by demonstrating a homogeneous linear band of IgA in the basement membrane zone (14-19). The disease can involve both the skin and the mucosa. Of the cutaneous forms, approximately 80% of sufferers have some form of ocular, oral, nasal or genital mucosal lesion. Up to 50% of patients have oral lesions, which affect, in order of decreasing frequency, the hard and soft palate, tonsillar pillars, buccal mucosa, tongue and gingiva. Occasionally in the oral cavity it presents as desquamative gingivitis alone or in conjunction with vesicles, painful erosions and ulceration (1, 19, 20).

In our case, the dominant clinical aspect was desquamative gingivitis, in some areas associated with bullae and in others with erosions, and the lesions, in comparison with which, the differential diagnosis was made considering lichen planus, mucous membrane pemphigoid, bullous pemphigoid, dermatitis herpetiformis, pemphigus and drug reaction (4, 21).

The histological evaluation of the lesion suggested bullous pemphigoid. Immunofluorescence, enabled a diagnosis of linear IgA lesion to be made by showing a homogeneous linear deposition of IgA along the basement membrane, differentiating LAD from dermatitis herpetiformis, which is characterized by granular IgA deposits on the tips of connective tissue papillae and not as a linear band (15). Circulating anti-basement membrane IgA may be detected using IIF, and this has been reported in approximately one-third (30%) of patients with LAD (15, 3).

The cause of LAD in the majority of cases is unknown, thus most cases are idiopathic. The most significant etiological factors are drug therapy, antibiotics, usually vancomycin and nonsteroidal anti-inflammatory drugs (23-25), viral infection, autoimmune disorders, trauma and malignancy (15, 17, 19, 26, 27). Gluten-sensitive enteropathy has been reported in 25% to 33% of cases, but appears to be milder than that observed in 90% of patients with dermatitis herpetiformis (15, 20). In our case no association with any of the above factors was found and a diagnosis of idiopathic LAD was rendered.

The IgA autoantibodies from both variants of LAD are directed against the hemidesmosomal transmembrane glycoprotein BP180 (type XVII collagen). Various antigenic sites on the extracellular domain of this anchoring filament protein have been shown to be targeted by autoantibodies in different autoimmune bullous diseases (15, 17, 22). Bullae appear after IgA autoantibodies are deposited, causing neutrophils and other defensive cells to migrate to the basal membrane of the affected connective tissue. This suggests that IgA is responsible for the associated inflammatory events, through an unproven mechanism likely to involve IgA-mediated neutrophil chemotaxis (17, 4). The connective tissue in the region where IgA antibodies have been deposited becomes necrotic (50% of specimens showing micro-abscesses) and the epithelium separates from the

underlying connective tissue to form bullae. Subsequently, these bullae rupture to produce areas of erosion and ulceration (17, 3, 20, 28).

The treatment of LAD involves the use of immunomodulating drugs, with or without the simultaneous use of corticosteroids. Dapsone is the usual first-line systemic treatment, it is an antileprosy and anti-malarial drug, and is used because of its bacteriostatic, anti-inflammatory and immunomodulating properties (17, 29). However, dapsone has many side-effects and is often poorly tolerated, potentially fatal complications include agranulocytosis, the dapsone syndrome, Steven-Johnson syndrome and toxic epidermal necrolysis. The sulphonamides (sulfamethoxypyridazine or sulfapyridine) are an alternative treatment if dapsone is poorly tolerated, but cutaneous allergic complications are more frequent than with dapsone. Benefits have been reported with dapsone combined with cimetidine and vitamin E, or with corticosteroids to enhance the drug's efficiency. However, other approaches involving the use of tetracycline with nicotinamide, colchicine, azathioprine, methotrexate, immunoglobulins, and cyclosporin have been reported to be useful in controlling LAD (16, 30).

Mycophenolate (a semisynthetic derivative of an antifungal drug metabolized into mycophenolic acid, which prevents purine synthesis in activated T and B cells by inhibiting inosine monophosphate dehydrogenase) has also been reported to be valuable in the treatment of patients with autoimmune blistering disorders such as pemphigus, cicatricial pemphigoid and acquired epidermolysis bullosa (16, 31). There are also reports of successful treatment with antibiotics such as the tetracyclines plus nicotinamide (32, 33), oxacillin, dicloxacillin (34, 35) and erythromycin (36).

Our treatment regimen was chosen because of its demonstrated efficacy in the treatment of subepidermal blistering disease.

With regard to follow-up, this must be considered as a chronic disease, with periods of exacerbation followed by remission, and that the disease can resolve entirely (3, 7). Up to 52% of cases undergo remission (13), however the recurrence rate is high and each episode follows a prolonged course (12). Multiple episodes of relapse during the first 2-3 years after diagnosis may be expected. In our case the time between diagnosis and remission of the disease was short, long-term follow-up is programmed.

To sum up, diagnosis of LAD is suggested by the presence of vescicles or bullae, but is confirmed by histopathology and direct immunofluorescence. With regard to etiology, infections, drugs or malignant processes may cause LAD, but it is often of idiopathic origin as in our case. Many different approaches to treatment have been attempted, yet LAD remains a difficult disease to manage due to its nature and development, which is characterized by exacerbation followed by remission and a high rate of recurrence. Monitoring and long-term follow-up of the patient are necessary.

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