Acta Scientific DENTAL SCIENCES (ISSN: 2581-4893)

Volume 4 Issue 10 October 2020

Review Article

Linear IgA Disease - A Rare Sub Epithelial Disorder: A Current Appraisal

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Received: September 03, 2020

Published: September 28, 2020

Abstract

Linear IgA disease is a non hereditary, autoimmune sub epidermal bullous disease, characterized by the presence of linear deposition of IgA auto antibodies along the basement membrane zone. The disease has a bimodal occurrence, manifesting in both children and adults. The cause is usually obscure in childhood, although, adult onset cases are primarily due to drugs (vancomycin), malignancies and infections. Skin and several mucous membrane involvement usually occur, and oral lesions are rarely seen in the disease. Dapsone forms the mainstay of treatment along with corticosteroids.

Keywords: Dapsone; Desquamative Gingivitis; Immunofluorescence; Linear IgA Disease; Subepithelial Blistering

Introduction

Autoimmune subepidermal bullous dermatoses are rare diseases of the skin and mucous membranes. Currently, bullous pemphigoid, Cicatricial pemphigoid, epidermolysis bullosa acquisita, linear IgA disease, and Dermatitis herpetiformis may be differentiated [1]. Linear IgA disease (LAD) is an autoimmune, subepithelial blistering disorder. The condition is characterized by a linear deposition of IgA along the dermo epidermal basement membrane zone [2]. Originally, the condition was thought to be a variant of bullous pemphigoid or herpetiform dermatitis. LAD was considered as a distinct clinical entity during the 1970's [3]. Tadeusz Chorzelski (1979) was the first to provide a clinical description of the disease [4]. The disease is rare and unusual with its atypical clinical presentation in adult presenting with oral and ocular involvement [5].

Epidemiology

LAD is one of the rarer blistering diseases, with an incidence of only 0.5 per one million in Western Europe. LAD is more commonly found in other parts of the world, including China, Southeast Asia, and Africa. Unfortunately, accurate data regarding LAD is not available [6]. Based on available literature, reported cases in India are very low and the first reported case of LAD in South India was in 1997 [7]. The condition has a bimodal age predilection and occurs in children between 6 months and 10 years of age, rarely persisting after puberty. Adults tend to be affected after the age of 60 years, with a slight predilection in the female sex [8,9]. In children, the disease is known as "chronic bullous disease of childhood" and tends to have a distinct clinical appearance, but the underlying pathogenesis of the disease remains the same. In the adult form of the disease, a drug-induced etiology must be thoroughly considered [10].

Etiopathogenesis

The pathophysiological mechanism that triggers the autoimmune response in linear immunoglobulin A dermatosis is still unknown. Investigations over the past 30 years have identified different related antigens, which are in the epithelial basement membrane zone [11]. The target antigens associated with a majority of disease are BP 180, BP 230, and LAD 285. Patients with CBDC often show an increased frequency of HLA-B8 [12]. Both the humoral and cellular responses appear to be involved in the pathogenesis of the disease [8].

In majority of cases, there is no known cause and most cases are idiopathic. The most significant etiological factors are drug therapy, antibiotics, usually vancomycin and nonsteroidal anti-inflammatory drugs [13,15], viral infection, autoimmune disorders, trauma and malignancy [16-20]. Gluten-sensitive enteropathy occurs in 25% to 33% of cases, and is milder than that observed in 90% of patients with dermatitis herpetiformis [16,21].

Vancomycin use has been increasing steadily due to the recent rise in the rate of methicillin-resistant Staphylococcus aureus infection, emphasizing the importance of recognizing the adverse effects from this medication. The first case of vancomycin-induced linear IgA bullous dermatosis was reported in 1988 [22]. Lesions develop within 24 hours to 15 days after the first dose of vancomycin and new lesions usually cease to appear within one to three days after discontinuation of drug [23].

Clinical manifestations

The presence of bullae suggests bullous dermatoses. The lesions appear as clear or haemorrhagic vesicles or bullae with an erythematous or utricarial base. They are generally tense and vary in size [24]. In children, lesions are often localized to the lower abdomen, perineal area, and inner thighs. The face, hands, and feet are rarely involved [9]. The skin lesions of LAD are characterized by annular pruritic papules, and blisters, giving a "cluster of jewels" appearance [12]. In adults, LABD mainly affects the extensor surfaces, trunk, buttocks, and face. Mucous membranes may be involved; the oral cavity and eyes are the most affected [25]. Ocular involvement has been reported in 50% of cases and mostly heals by scar formation, there by leading to blindness, as in cicatricial pemphigoid [26].

The disease affects both the skin and the mucosa and upto 50% of patient's presents with oral lesions. The bullae that are seen as a part of the lesion are generally intact, with negative Nikolsky's sign. There are cases that have been reported as involving only oral mucosa with no cutaneous manifestation and vice versa [27].

Oral manifestations

Hard and soft palate, tonsillar pillars, buccal mucosa, tongue and gingiva are the affected sites. An unusual oral feature is desquamative gingivitis, either alone or in conjunction with vesicles, painful erosions and ulceration [3,18,21] (Figure 1).

"Desquamative gingivitis" is a descriptive term, first introduced by Prinz in 1932 that is synonymous with the presence of erythema, desquamation, erosion, and blistering of attached and marginal gingiva. Desquamative gingivitis is primarily seen in dermatological disorders. Overall, Mucous membrane pemphigoid (MMP), oral lichen planus and pemphigus vulgaris have emerged as the most common causes of desquamative gingivitis, with the first two accounting for about 80% of cases [28]. Linear IgA disease constitute for a rarer variety in which desquamative gingivitis is seen.

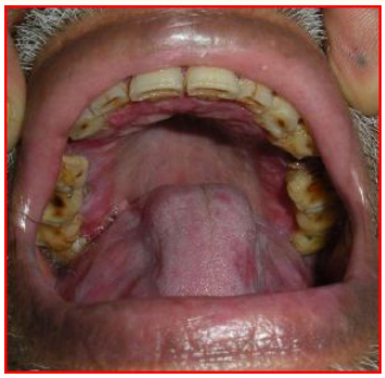

Figure 1: Desquamative gingivitis on the palatal aspect of marginal and attached gingiva in a patient with Linear IgA disease.

Diagnosis

As per the criteria given by Egan and Zone, LAD may be diagnosed based on: (a) the presence of a vesicular or bullous eruption, usually confined to the skin, but which may involve the mucous membranes; (b) the presence of a subepidermal vesicle with a predominantly neutrophilic infiltrate on histology of lesional skin (Figure 2), and (c) the presence of BMZ specific IgA antibody deposited in a linear pattern in the absence of other immunoglobulins on DIF of perilesional skin [19].

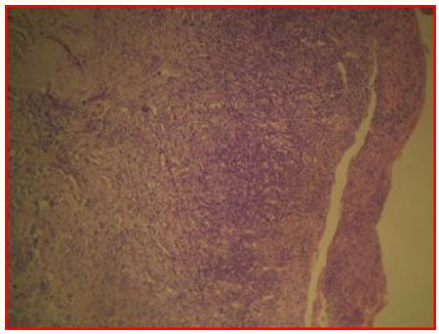

Figure 2: Histopathology showing sub epithelial cleft and basal cell degeneration, along with hemorrhagic areas.

Direct immunofluorescence reveals linear deposition of IgA immunoreactants at the skin or mucosal basement membrane zone (BMZ) [24,29,30] (Figure 3). Indirect immunofluorescence demonstrates immunoglobulins of the IgA anti- BMZ antibody class [9,24,30]. On comparing with the other vesiculobullous diseases producing subepithelial split such as pemphigoid, dermatitis herpetiformis and epidermolysis bullosa, the DIF shows linear deposition of IgG and C3 in the basement membrane of bullous pemphigoid [31]. Direct immunofluorescence features of MMP specimen show a linear deposition of complement (usually C3) and IgG with IgA in about 20% of cases at the basement membrane zone [32]. Epidermolysis bullosa shows a linear deposition of IgG, IgM, IgA and C3 [31].

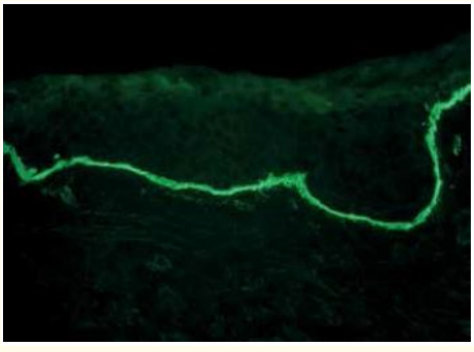

Figure 3: Direct immunofluorescence of skin with anti-IgG antibody showing high-intensity, linear patterns along the basal membrane.

Salt split technique is a useful tool in the diagnosis of sub epidermal bullous disorders. In this technique, the tissue is incubated in 1.0 M sodium chloride solution for 72 hrs at 4°C, which causes the epithelium to split from the underlying connective tissue at the level of the basement membrane. The connective tissue side of the basement membrane contains type IV and type VII collagen and laminin 5. The epidermal side contains antigen associated with hemidesmosomes (plectin and BP antigen BP-230) [5].

In epidermolysis bullosa acquista, IgG positivity is seen only on the connective tissue base of the split. Whereas in LAD and bullous pemphigoid, immunofluorescence positivity is seen on both epidermal and connective tissue base of the split [31,33] (Table 1).

Management

As with any subepithelial blistering disease, the clinician should consider the possibility of an underlying drug reaction or malignancy [12].

Oral lesions of Linear IgA disease may prove difficult to treat [35,36]. Topical or systemic steroids alone do not result in remission of oral ulceration, bullae, and desquamative gingivitis, a feature that suggests the diagnosis. Dapsone, used primarily as an anti-leprotic and anti-malarial drug is the first-line systemic treatment, and is used because of its bacteriostatic, anti-inflammatory and immunomodulating properties [17]. Dapsone is often poorly tolerated and is associated with potentially fatal complications like agranulocytosis, the dapsone syndrome, Steven-Johnson syndrome and toxic epidermal necrolysis. If poor tolerance to dapsone occurs, the sulphonamides (sulfamethoxypyridazine or sulfapyridine) are an alternative treatment. Dapsone combined with cimetidine and vitamin E, or with corticosteroids enhances the drug's efficiency. However, other approaches involving the use of tetracycline with colchicines, nicotinamide, azathioprine, methotrexate, immunoglobulins, and cyclosporin have been reported to be useful in controlling LAD [37,38].

Disease	Clinical features	Histopathology	Direct Immunofluorescence	Indirect Immunofluorescence	Treatment
linear IgA disease [11]	Children- "cluster of jewels" pattern, vesicles or bullae on peri genital area, extremities, trunk, face Adults	Sub epidermal cavity with neutrophils along the basement membrane vacuolar degeneration, eosinophils may be present	Linear deposition of IgA along the basement membrane, rare associated deposits of IgG, IgM, and C3	Negative in the majority of cases	Dapsone, alone or in combination with steroids
Bullous Pemphigoid [11]	Tense vesicles or bullae on erythematous base on the inner surface of the thighs, forearms, axillary folds, palms, soles inflammatory infiltrate,	Subepidermal cavity with a predominantly of eosinophils	Linear deposition of C3 and IgG along the basement membrane	Linear deposition of c3 and igg along the basement membrane	Steroids

Dermatitis Herpetiformis [11]	Pruritic papules and vesicles on the extensor surfaces of the limbs, buttocks, shoulders, nape of neck, scalp	subepidermal cavity with neutrophils in the dermal papillae, edema of the papillary dermis, eosinophils may be present	Granular deposition of IgA in dermal papillae	Negative	Gluten free diet and drugs such as Dapsone, sulfones and steroids
Erythema multiforme [34]	Asymmetrical erythematous maculopapular lesions eventually break and coalesce to form plaques on the skin. Target or iris lesion ("bull's eye") is the classical cutaneous lesion of EM. Characteristic haemorrhagic lip crusting.	Sub epidermal blister with infiltrate of lymphocytes in the underlying dermis, a few eosinophils, the epidermis overlying the blister may show necrosis, apoptotic keratinocytes present in the epidermis adjacent to the blister	Negative	Negative	Self-resolution with Symptomatic management.

Table 1: Depicts the differential diagnosis of Linear IgA disease.

Conclusion

Linear immunoglobulin A disease is an uncommon immune-mediated disorder characterized by the presence of linear deposits immunoglobulin A in the basal membrane zone, visible with direct immunofluorescence. Clinically it can be divided into an adult or pediatric presentation. Although its idiopathic form is the most frequent, the presence of triggering factors such as drugs or malignancies should always be ruled out. The treatment of choice is dapsone, and there are numerous alternatives, including sulfa drugs, corticosteroids, and immunosuppressants. The prognosis is usually favorable.

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