Linear IgA dermatosis adult variant with oral manifestation: A rare case report

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ABSTRACT
Linear immunoglobulin A (IgA) dermatosis (LAD) is a rare autoimmune disorder that presents as a vesiculo-bullous lesion with cutaneous manifestations, but rare oral mucosal involvement. Here we discuss a case of a vesiculobullous lesion with severe oral and ocular mucosal involvement mimicking pemphigoid with histopathological evidence of subepithelial blisters. Direct immunofluorescence (DIF) confirmed the lesion as LAD of adult variant, although with atypical clinical features.

Key words: Cicatricial pemphigoid, linear IgA dermatosis, vesiculobullous lesion

INTRODUCTION
Linear immunoglobulin A (IgA) dermatosis (LAD) is a rare chronic autoimmune disorder, which presents with vesicles and bullae formation affecting both the skin and the mucous membrane, with a characteristic immunofluorescence finding of homogeneous linear deposits of IgA in the cutaneous basement membrane zone.[1,2] It is divided into two types, based on the age of onset, namely Linear IgA bullous dermatosis of childhood and Linear IgA bullous dermatosis of adult.[2-5] The disease is rare and unusual with its atypical clinical presentation in adult presenting with oral and ocular involvement.

CASE REPORT
A 75-year-old female patient reported to the Department of Oral Pathology with complaints of burning sensation in the oral cavity and difficulty in swallowing for the past 2 years. The patient was weak and of thin build with no declared previous history of systemic illness, although she did give a history of viral fever 2 years before and was hospitalized briefly for the same. The patient had a history of betelnut chewing along with tobacco for the past 50 years and reportedly quit the habit 3 years ago.

On extra oral examination, multiple nodules of 0.5 mm were seen distributed over the face and neck region. There were papular lesions on the neck which seemed to have ruptured and healed with scarring. The eyes were noticeably reddish in color and there was visible scarring in bulbar conjunctiva of the right eye [Figures 1 and 2]. Patient also reported a history of recurrent genital vesicles and ulceration, but none was noticed during medical examination by dermatologist during the present visit. Submandibular lymph nodes were palpable bilaterally, tender and freely movable.

On intraoral examination, irregular erythematosus ulcersations of hard palate, soft palate and alveolar mucosa were seen; which were covered by a greyish white pseudomembranous slough. Multiple, intact, translucent vesicles of size ranging from 3 and 5 mm in diameter were present in the anterior hard palate region [Figure 3]. On the right buccal mucosa, an irregular ulceration with erythematous halo, covered by a greyish white slough was seen in relation to 16 and 17 [Figures 3 and 4]. The oral hygiene of the patient was poor, with significant calculus and plaque deposition over the teeth and the gingiva showed generalized erythematous changes.

The clinical features of this case with classical intact vesicles and bullae accompanied with generalized irregular ulceration and symblepharon (scar formation) in right eye led to a provisional diagnosis of cicatrical pemphigoid. Differential diagnoses of LAD and pemphigus vulgaris were also suggested.

Investigation
Routine hematological examination was done. Incision biopsy was subsequently done on representative areas on the hard
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palate for histopathological and immunological examinations, direct and indirect immunofluorescence (DIF and IIF), separately. The specimen for routine histopathological examination was fixed in 10% formalin. The specimens for DIF was put in cold saline and snap freeze before processing. Serum obtained from 5ml of blood drawn from the subject was used for IIF.

**Hematology**

Hematologic investigation done by Beckman Coulter hematology analyzer showed hemoglobin level - 11.3 g%; total leukocyte count - 10,000 cells/mm³; differential leukocyte count showed neutrophil 70%, lymphocyte 23%, eosinophil 6% and monocyte 1%; and erythrocyte sedimentation rate (ESR) - 35 mm for 30 min and 74 mm in 1h.

**Histopathology**

The hematoxylin and eosin-stained soft tissue section showed stratified squamous epithelium with mild acanthosis and subepithelial cleft formation. The underlying connective tissue was collagenous with dense diffuse infiltration of lymphocytes and neutrophils [Figure 5].

**Immunofluorescence**

DIF showed positive linear deposits of only IgA along the basement membrane in the epithelium and connective tissue region in mirror image pattern. IgM, IgG, C3 and fibrinogen were negative in DIF [Figure 6]. IIF tested negative for circulating antibodies.

Sub epithelial cleft with IgA positivity and negativity for IgM, IgG, C3, fibrinogen and IIF prompted the diagnosis of linear IgA disorder.

**Treatment**

The patient was started on a monodrug therapy of prednisolone (20 mg) for 2 weeks. As there was no response observed during the 2 weeks, it was changed over to dapsone (25 mg) for 2 weeks. With no desirable reduction in symptoms, it was decided to start with a combination therapy of prednisolone (20 mg) and dapsone (25 mg) with proper monitoring of hematological values. The patient showed drastic improvement in the symptoms and ulceration healed promptly. The drugs were gradually tapered over time and discontinued as lesions healed [Figure 7].

**DISCUSSION**

LAD is a rare, chronic, autoimmune disorder with cutaneous and mucosal involvement.[2] It was first discussed in 1901 and recognized as a separate entity from dermatitis herpetiformis in 1979 based on the immunopathology.[1] The incidence of the condition is reported to be more in China, Malaysia, Sri Lanka and Thailand.[4] Annual incidence of one per 250,000 was
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reported in England. Based on available literature, reported cases in India are very low and the first reported case of LAD in South India was in 1997.[6]

The etiology of the disease is still unknown.[2] Some authors have proposed that it may be precipitated by drugs like vancomycin and insulin, infection and may be associated with malignancy.[3-5] In the present case, the reported history of hospitalization following viral fever and subsequent undefined medication could have played an etiological role.

The pathophysiology of subepidermal cleft formation in drug-induced LAD, is by the activation of T-cell specific immunological reaction to the drug which releases Th₂ cytokines, interleukin (IL)-4, IL-5, IL-6, IL-10 and transforming growth factor-β, leading to the excess production of IgA antibodies targeted against the proteins that are responsible for basement membrane attachment like BP 180, 120-kDa protein, 97-kDa hemidesmosomal protein and transmembrane glycoprotein.[1,6-10] BP 180 antigen has been identified from pemphigoid in subepithelial split.[11] An alternate pathway suggested that plasmin activated from the plasminogen by keratinocyte will lead to cleavage of type XVII collagen. While the activated neutrophil converts the promatrixmetalloproteinase-9 to matrix metalloproteinase-9, inactivation of α1-proteinase inhibitor leads to chemoattraction of neutrophils, finally resulting in subepithelial split by the action of neutrophil elastase.[8]

The LAD is divided into two variants showing a typical bimodal age of onset as: 1) Linear IgA bullous dermatosis of childhood and 2) linear IgA bullous dermatosis of adult.[11] The adult variant of LAD occurs in individuals older than 40 years with high incidence at 60–65 years and with reported female predilection,[3,11,12] which is in accordance with the present case. Heterogeneous vesicle formation is a reported feature of the adult variant of the condition, as opposed to the classical vesicle formation pattern, described as ‘cluster of jewels’ mucosal involvement in the childhood variant.[8] The type of vesicle formation in the present case supports the diagnosis of LAD adult variant. Another typical feature is the presence of ocular, oral and genital lesions; common with concurrent cutaneous involvement.[2] The present case had these typical ocular and oral lesions at the time of examination. Although there were no active genital or cutaneous lesions at the time of examination, the patient did give a history of genital involvement. Healed papular lesions on the skin of face were probably a part of the cutaneous manifestation of the condition. 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.[4] In oral mucosa there is prevalence of occurrence in hard palate, soft palate and the buccal mucosa, along with lesions in the conjunctiva, larynx, pharynx, trachea, vaginal mucosa, or balanopreputial sulcus. External surface involvement is more in trunk, extremities and perineum.[2] Ocular involvement has been reported in 50% of cases and mostly heal by scar formation, there by leading to blindness, as in cicatricial pemphigoid.[4,13]

Histologically, perilesional incisional biopsy reportedly shows subepidermal blisters below the basement membrane.
Very rarely, used as an adjunct to DIF to detect the immunoglobulins two-third of the cases. IIF is positive only for one-third of patients and negative in on both epidermal and connective tissue base of the split. Whereas in LAD and epidermolysis bullosa acquista, IgG positivity is seen only on the connective tissue base of the split. It is also reported that IgA deposition in “mirror image pattern” is considered to be more common in LAD.

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. The mucous membrane pemphigoid shows linear IgG and C3 in the basement membrane with IgA in 20% of cases. Epidermolysis bullosa shows a linear deposition of IgG, IgM, IgA and C3.

Salt split technique is a useful tool in the diagnosis of subepidermal 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).

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.

IIF is positive only for one-third of patients and negative in two-third of the cases. In addition, salt split technique maybe used as an adjunct to DIF to detect the immunoglobulins in lesion with subepidermal blisters. In the present case the sex, the age and the observed clinical features of the patient which includes asymmetrical vesicle distribution on the palate, presence of ocular involvement, along with histopathological evidence of subepithelial blister, linear deposition of IgA along the basement membrane and absence of other immunoglobulins and fibrinogens in DIF as well as negative findings in IIF are all correlating with LAD of adult type. It is the DIF and the IIF findings that are essential to differentiate LAD from other vesiculobullous lesions, especially cicatricial pemphigoid, which is otherwise clinically almost indistinguishable.

Dapsone is considered as the first line of drug for the LAD and is used as a monodrug therapy system, but is to be used with consideration for tolerance and hemolysis. It may also be used with systemic corticosteroids. Flucloxacillin and sulfamethoxydiazine is the second line of drug and may also be used along with steroid. Other medications such as sulfapyridine, corticosteroid, colchicine, tetracycline and nicotinamide and intravenous immunoglobulins have also been reported to provide satisfactory results. Tacrolimus has also been reportedly used for topical medication as an adjunct. In the present case, the treatment was started with monodrug therapy of tapering doses of prednisolone which did not give expected result and so dapsone was introduced for 2 weeks as a replacement drug, all the while keeping a check on the red blood cell count and glucose-6-phosphate dehydrogenase deficiency levels. Since the response was not effective, a combination therapy was introduced with dapsone and prednisolone and the patient has responded well with marked reduction in symptoms and lesions.

CONCLUSION

Vesiculobullous lesions are relatively common in the oral mucosa, but LAD is a rare entity. It has an atypical clinical presentation leading to misdiagnosis as pemphigoid-like lesion and may cause blindness if not treated appropriately. It is also rarely associated with malignancy. Auxiliary histopathological staining namely DIF and IIF should be considered in a vesiculobullous lesion to differentiate LAD from pemphigoid. It is also to be noted that dapsone therapy which would otherwise not be considered for most vesiculobullous lesion has to be started along with a combination of systemic steroids for effectively controlling the condition.

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