

Mucous membrane pemphigoid with antibodies against $\beta 3$ subunit of laminin-332: First report from India

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ABSTRACT

Mucous membrane pemphigoid (MMP) is a chronic, recurrent, progressive, subepidermal blistering disorder, mainly affecting the mucous membranes. Anti-laminin 332 MMP is a distinct subset of MMP with antibodies, mainly targeted against $\alpha 3$ or $\gamma 2$ subunit. Antibodies exclusively against $\beta 3$ subunit are rarely seen. An internal malignancy is frequently associated with anti-laminin 332 MMP. This disorder usually responds poorly to treatment, requiring multidisciplinary approach. Herein, we describe the first case of anti-laminin-332 MMP from India, which showed antibodies exclusively to $\beta 3$ subunit.

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Key words: $\beta 3$ subunit, India, laminin-332, mucous membrane pemphigoid

INTRODUCTION

Mucous membrane pemphigoid (MMP) is a chronic, recurrent, progressive, subepidermal blistering disorder, mainly affecting the mucous membranes. Clinically, it is characterized by erosions and permanent scarring of mucous membranes, mainly oral and conjunctival mucosae. There is variable involvement of skin with blisters and urticarial plaques, which subsequently heal with scarring. MMP is caused by autoantibodies, directed against

basement membrane proteins, chiefly bullous pemphigoid antigen-2 (BP180). Other subtypes with antibodies directed against laminin-332 (also known as laminin-5 and epiligrin) and $\beta 4$ -integrin can also be seen. Laminin-332 is a heterotrimeric glycoprotein of 460 kDa, consisting of $\alpha 3$, $\beta 3$ and $\gamma 2$ subunits that are covalently linked by disulfide bonds.^[1] In anti-laminin MMP, antibodies are mainly targeted against $\alpha 3$ or $\gamma 2$ subunit. Antibodies to $\beta 3$ subunit are rare. We describe the first Indian case of anti-laminin-332 MMP with antibodies directed exclusively against $\beta 3$ subunit.

CASE REPORT

A 60-year-old female presented with a 2-year-history of burning sensation in both eyes, progressing to limitation of eye movement and diminution of vision. She also gave a 1-year-history of recurrent, painful, oral

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10.4103/0378-6323.98079

How to cite this article: Kanwar AJ, Vinay K, Koga H, Hashimoto T. Mucous membrane pemphigoid with antibodies against $\beta 3$ subunit of laminin-332: First report from India. Indian J Dermatol Venereol Leprol 2012;78:475-9.

Received: January, 2012. **Accepted:** April 2012. **Source of Support:** Nil. **Conflict of Interest:** None declared.

erosions, bleeding gums and dysphagia to solid food. There was no history of cutaneous blisters and erosions or change of voice. No new medication or change in dentures prior to onset of symptoms was present. General physical examination was essentially normal. Mucocutaneous examination revealed conjunctival scarring with symblepharon formation [Figure 1a], erosive gingivostomatitis [Figure 1b] and erosions over the buccal mucosa and palate. A provisional diagnosis of MMP was made, and further tests were performed to confirm the diagnosis. On laryngoscopy, the vocal cords were found to be normal and barium meal showed stricture in the mid esophagus. Light microscopy of oral mucosal biopsy showed a subepidermal cleft with a dense polymorphonuclear infiltrate [Figure 2]. Linear deposits of IgG and C3 were found at the basement membrane zone (BMZ)

on direct immunofluorescence (DIF). Indirect immunofluorescence using normal human skin and 1M NaCl-split human skin sections failed to show any circulating antibodies. Immunoblotting (IB) of recombinant protein of C-terminal domain of BP180^[2] did not reveal circulating antibodies for both IgG and IgA classes while IB of purified human laminin-332^[3] detected IgG antibodies to the 140kDa $\beta 3$ subunit [Figure 3].

The patient was started on oral prednisolone 1 mg/kg/day and dapsone 100 mg. Esophageal strictures were treated with an endoscopic dilatation. Her age specific malignancy work up did not yield any significant results. Within 1 month, no new mucosal erosions developed and existing erosions started to heal. The conjunctival congestion and ocular movement also improved, but symblepharon persisted. Prednisolone was subsequently tapered off within 8 months, and dapsone was continued. The patient is completely symptom-free with no signs of disease activity on 1 year of her follow-up.



Figure 1: Clinical features showing symblepharon formation (a) of the left lower conjunctiva, and erosive gingivitis (b)

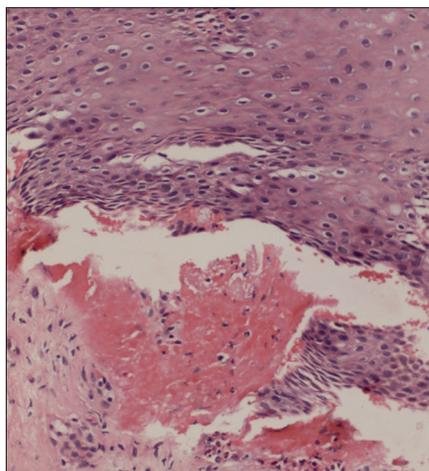


Figure 2: Histopathological features of oral mucosal biopsy showing hyperplastic mucosa and subepidermal cleft containing neutrophils and fresh blood. (H and E, $\times 240$)

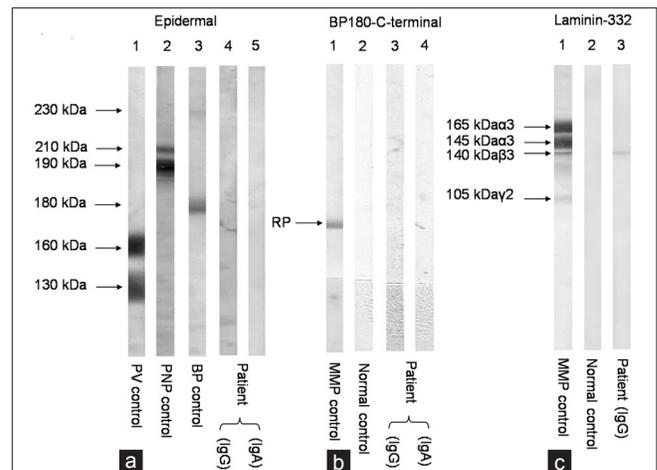


Figure 3: (a) By IB of normal human epidermal extracts (Epidermal), the control pemphigus vulgaris (PV) serum reacted with the 160 kDa desmoglein 1 (Dsg1) and the 130 kDa Dsg3 (lane 1), control paraneoplastic pemphigus (PNP) serum reacted with the 210 kDa envoplakin and the 190 kDa periplakin (lane 2), and the control Bullous pemphigoid (BP) serum reacted with BP230 and BP180 (lane 3). The IgG (lane 4) and IgA (lane 5) antibodies of our case (Patient) did not react with any antigens. (b) By IB of recombinant protein of BP180 C-terminal domain (BP180 C-terminal), the control anti-BP180 type MMP serum reacted with this protein (RP) (lane 1), but normal control serum (lane 2) (normal) did not react with this protein. The IgG from our case (Patient) did not react with this protein (lane 3). (c) By IB of purified human laminin-332 (Laminin-332), the control anti-laminin-332 type MMP serum reacted with the 165 kDa and 145 kDa $\alpha 3$ subunit, the 140 kDa $\beta 3$ subunit, and the 105 kDa $\gamma 1$ subunit of laminin-332 (lane 1), but normal control serum (normal) did not react with any subunits (lane 2). The IgG antibodies of our case (Patient) reacted exclusively with the 140 kDa $\beta 3$ subunit (lane 3)

Table 1: Summary of clinical, immunological features and treatment aspects of anti-laminin-332 MMP

Reference	Age/ gender	Clinical features	Associated malignancy	Histopathological examination	Direct immunofluorescence	Indirect immunofluorescence/ salt split	Immunoblot / immunoprecipitation	Treatment received	Outcome	Follow up period (months)
Kirtschig <i>et al</i> ⁽¹⁰⁾	72/M	Blisters and erosions predominantly at trauma prone sites, and conjunctival oral and laryngeal erosions. Lesions healed with scarring and milia formation	Unknown primary with cervical lymph node metastasis	NM	Linear deposits of IgG and C3 at the BMZ.	IgG autoantibodies binding to the dermal side in a titre of up to 1:160	$\beta 3$ subunit of laminin 5	DAP CYC	No response Complete remission initially later recurrence and death from laryngeal obstruction	24
Seo <i>et al</i> ⁽¹¹⁾	67/F	Recurrent oral erosion conjunctival effusion, hoarse voice and dysphagia. Also had bulla and erosions in trunk which healed with atrophy	No	Sub-epidermal bullae with mixed inflammatory infiltrate	Linear deposits of IgG and IgA along the BMZ	IgG autoantibodies binding to the dermal side in a titre of up to 1:20	$\beta 3$ subunit of laminin 5	PRE + DAP PRE + CYP	No response Controlled with no new lesions	5
Fukushima <i>et al</i> ⁽¹²⁾	90/M	Recurrent erosions on the buccal mucosa, nasal meatus, trunk and extremities	Prostate adeno carcinoma	Sub-epidermal blister with an infiltration of eosinophils and neutrophils	Linear deposits of IgG and C3 at the BMZ	IgG autoantibodies binding to the dermal side	$\beta 3$ subunit of laminin 5	PRE + MINO + NIC + DAP	Partial response	36
Takahara <i>et al</i> ⁽¹³⁾	35/F	Oral mucosal blisters and blisters over face and neck	AML with GVHD	Subepidermal blister containing eosinophils and neutrophils	Linear deposits of IgG and C3 at BMZ	Weak IgG autoantibodies binding to the dermal side	BP 230, periplakin and $\beta 3$ subunit of laminin 5	MINO	Disease progression and death due to AML	1
Our case	60/F	Oral mucosal erosions, conjunctival effusion and dysphagia	No	Subepidermal cleft with a dense polymorphonuclear infiltrate	Linear deposits of IgG and C3 at BMZ	Neg	$\beta 3$ subunit of laminin 5	PRE + DAP	Complete remission	12

M, male; F, female; AML, acute myeloblastic leukemia; GVHD, graft versus host disease; NM, not mentioned; BMZ, basement membrane zone; Neg, negative; DAP, dapsone; CYC, cyclosporine; PRE, prednisolone; CYP, cyclophosphamide; MINO, minocycline; NIC, nicotinamide;

DISCUSSION

MMP is a rare subepidermal blistering disorder, commonly affecting females in their 5th or 6th decade. MMP clinically has 4 distinct clinical phenotypes, associated with one of several different anti-BMZ autoantibodies. In pure ocular type, patients rarely have circulating IgG anti-BP180 antibodies, but produce IgG antibodies against the $\beta 4$ integrin subunit.^[4] The mucocutaneous variant shows both cutaneous and mucosal lesions and demonstrates serologic reactivity mainly against BP180.^[5] The oral pemphigoid variant shows mainly oral involvement, few lesions on the skin or other mucosae may be present. Another major group shows blistering at multiple mucosal surfaces, without any cutaneous involvement.^[6] Anti-laminin-332 MMP is an immunologically distinct subset affecting skin and mucous membranes. This type is associated with an increased relative risk of solid cancer.^[7]

Recently, Terra *et al.*, proposed a modified diagnostic criterion for anti-laminin-332 MMP, on clinical, histopathological and immunological basis.^[8] On histopathology, MMP shows subepidermal bullae with lymphohistiocytic and eosinophilic infiltrate. Deposition of IgG in an n-serrated pattern on DIF was reported to be characteristic of anti-laminin-332 MMP.^[8] Our case also showed linear deposition of immune reactants at the BMZ. Because laminin-332 is present deep in the lamina lucida localized to anchoring filaments, circulating antibodies react with dermal side of salt split human skin. By IB using purified laminin-332, antibodies directed against the subunits of laminin-332 can be determined. Commonly, antibodies are found to react with the $\alpha 3$ and $\gamma 2$ subunit.^[9] Rarely, cases of antibodies directed solely against $\beta 3$ subunit have also been reported.^[10-13] Because of the limited literature on this entity, no clear clinical differences are seen among the cases with reactivity with different subunits. Although previous cases of anti- $\beta 3$ -laminin-332 MMP had both cutaneous and mucosal involvement, our case showed only mucosal lesions. Three of the previous cases of anti- $\beta 3$ -laminin-332 MMP had an associated neoplasm^[10,12,13] while there was no evidence of malignancy in our patient on screening. All of the previously reported cases showed subepidermal cleft on histopathological examination with linear immune deposits at BMZ on DIF, which is consistent with our findings. Although IIF was negative in

our patient, previous cases showed binding of immune deposits to the dermal side of the salt split skin. The clinical and pathological features of the reported cases of anti- $\beta 3$ -laminin-332 MMP has been summarized in Table 1.

The outcome of MMP is poor compared to other subepidermal bullous disorders. Various treatment modalities, including corticosteroids, azathioprine, cyclophosphamide, doxycycline and dapsone have been used to treat MMP. Rituximab has also been tried in a few cases.^[14] Previous cases of anti- $\beta 3$ -laminin-332 MMP have been treated with oral corticosteroids, cyclosporine, cyclophosphamide, dapsone and nicotinamide with variable response [Table 1]. Our patient had complete clinical improvement with corticosteroids and dapsone.

In conclusion, we describe the first Indian case of anti-laminin-332 MMP. Significant morbidity associated with limited response to treatment makes MMP a challenging disease for the treating physician. Multidisciplinary approach involving the dermatologist, ophthalmologist, oral health specialist and otolaryngologist is required in caring for such patients.

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