Oral Mucous Membrane Pemphigoid without Skin Involvement Treated by Intra-Venous Immunoglobulins: A Case Report with the Correlation of Clinical, Histopathological and Direct Immunofluorescence Findings and a Literature Review of the Treatment Modalities

Manas Bajpai* and Nilesh Pardhe
Department of Oral and Maxillofacial Pathology, NIMS Dental College, India

Abstract
Mucous membrane pemphigoid (MMP) is an autoimmune blistering disorder of mucosa, characterized by subepithelial bullae. The involvement of skin is only seen in one quarter of the patients with MMP. We report a case of 37 years old male presented with painful erosions involving gingiva, tongue and palatal mucosa without any skin involvement. Histopathological features and direct immunofluorescence led to the final diagnosis of MMP.

INTRODUCTION
Mucous membrane pemphigoid (MMP) can be defined as a group of autoimmune heterogeneous disorder characterized by subepithelial blistering disease primarily affecting mucous membrane with or without involvement of skin [1,2]. Various components of basement membrane have been identified as targets of autoantibodies in MMP [3]. Intra-orally MMP shows varied manifestation i.e. painful erosion, desquamative gingivitis, erythematous patches etc [2,4]. We present a case of oral MMP without skin and other mucous membrane involvement; we also describe the histopathological and immunofluorescence findings of the case.

CASE PRESENTATION
An otherwise healthy 37 year old Indian male presented to a private dental clinic with the chief complaint of painful erosions of lip, gingiva and palate from 8 months. He had been treated by oral prednisolone (0.5mg/kg/day) from a general physician since 6 months for which no response was found. The lesions of palate, tongue and lip were extremely painful due to which he experienced difficulty in eating. His family history was non-contributory to the presenting symptom. Intra oral examination revealed erosions of labial mucosa (Figure 1) and palate (Figure 2). Localized desquamative marginal gingivitis was noted with relation to teeth #12, #21, #22 and #33 (Figure 3). Marginal gingiva showed a tendency to bleed and peel off on pressure.

Dorsal surface of the tongue showed bullae covered by a pseudomembrane with reddish and yellowish in color (Figure 4). No ocular and genital lesions were found. Tzanck test was performed which was found to be negative. On clinical grounds a provisional diagnosis of mucous membrane pemphigoid with the differential diagnosis of pemphigus vulgaris was made.

An incisional biopsy was taken from the surrounding mucosa of the bulla of the dorsum of the tongue under local anesthesia and the tissue was submitted to the Department of Oral and Maxillofacial Pathology NIMS Dental College Jaipur (India). The
Central was found after the completion of third cycle. The therapy was further continued till six months. The follow up period of 1 year was found to be uneventful.

DISCUSSION

MMPs are autoimmunaneoe, vesicobullous disease that affects mucosa or mucosa and skin both [1]. There are several variants of MMP, each with distinctive clinical features, pattern of immunopathology and antigenic specificity of autoantibodies. They are oral pemphigoid, anti epiligrin pemphigoid, anti histopathological examination of hematoxylin and eosin stained soft tissue section revealed a stratified squamous epithelium with subepithelial separation with the underlying connective tissue stroma (Figure 5). The connective tissue stroma was densely infiltrated with chronic inflammatory cells chiefly lymphocytes and plasma cells (Figure 6). Direct immunuflurosence (DIF) of peribullous mucosa revealed a linear band of IgA, IgG at the zone of epithelium and basement membrane (Figure 7). Based on these features a final diagnosis of MMP was rendered. Intravenous immunoglobulin (IVIG) (2gm/Kg/cycle) started which was repeated every three months. Complete remission of the lesions was found after the completion of third cycle. The therapy was further continued till six months. The follow up period of 1 year was found to be uneventful.

MMPs are autoimmunaneoe, vesicobullous disease that affects mucosa or mucosa and skin both [1]. There are several variants of MMP, each with distinctive clinical features, pattern of immunopathology and antigenic specificity of autoantibodies. They are oral pemphigoid, anti epiligrin pemphigoid, anti
BP antigen mucosal pemphigoid, ocular pemphigoid & multiple antigens. An exhaustive literature review of the published case reports of MMP in English language revealed that MMP is approximately 7 times less common than BP [4]. On the other hand, it is up to 3 times more common than pemphigus, which itself has an annual incidence of 0.5 to 3.2 per 100,000 people [1,2]. There are no known racial or geographic predilections. Most patients ranged from 23 to 75 years age; maximum being 50 to 60 years old. The female/male ratio was found to be 1.8:1[3].

Intra-orally, it most commonly involves gingiva followed by soft and hard palate, presenting as thick walled bullae persisting for 1 to 2 days before rupturing, leaving raw, eroded erythematous or bleeding surface [2,3,5]. The present case showed the involvement of gingiva, labial mucosa and hard palate. Skin lesions are seen in only 25% of the patients. Erythema multiforme, pemphigus vulgaris, bullous pemphigoid, bullous lichen planus and lichenoid reaction can be considered as a clinical differential diagnosis of blistering diseases (Table 1).

Histopathologically it shows subepithelial blisters without acantholysis and connective tissues shows a dense infiltration of inflammatory cells [3-5]. Direct immunofluorescent techniques show homogeneous IgG and C3 complement deposits along the junction between the connective tissue and epithelium [1]. The present case revealed a linear band of IgG and IgG on DIF at epithelium – basement membrane zone. MMP is characterized by subepithelial blisters with the production of autoantibodies targeted to certain components of the basal lamina of the epithelium immunoglobulin G (IgG) (97%), C3 complement factor (78%) and, to a lesser degree, IgA (27%) and IgM (12%) [11]. The diagnosis of MMP is based upon the correlation of clinical, histopathological and DIF findings. DIF is a useful adjunct for the definitive diagnosis of bullous diseases, especially when the clinical and histopathological findings are not conclusive. DIF helps to rule out the differential diagnoses which differ in their treatment protocol. DIF may also be used in order to determine the response of the treatment [3].

The treatment of MMP depends upon the severity of disease ranging from topical steroids to systemic steroids and ant metabolites [12]. (Table 2) IVIgs are biologic immune modulators comprised of polyclonal antibodies derived from a large pool of healthy plasma donors [20]. They are approved treatment modality for several diseases including immune thrombocytopenic purpura, primary and secondary immunodeficiency, pediatric HIV, Systemic lupus erythematosus (SLE), Kawasaki disease, multiple sclerosis, pemphigus, pemphigoid etc [20-23]. The mechanism of action of IVIg is not clearly understood, although several theories have been proposed (Figure 8). For autoimmune diseases IVIg is not considered as a first line treatment and it is reserved for the patients who are unresponsive to the conventional therapy and patients with rapidly progressive disease [22]. Immuno suppressive drugs are the well accepted mode of treatment for the patients with
Table 1: Differential diagnoses of MMP with differentiating features [6-10].

<table>
<thead>
<tr>
<th>S. No</th>
<th>Differential diagnosis</th>
<th>Differentiating features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Erythema multiforme (EM)</td>
<td>EM is generally associated with reaction infections of herpes simplex and mycoplasma and/or drug reactions while MMP is autoimmune disease. Histopathologically MMP can be easily differentiated from EM.</td>
</tr>
<tr>
<td>2</td>
<td>Pemphigus vulgaris (PV)</td>
<td>Histopathologically PV shows suprabasilar splitting and MMP shows sub basilar splitting between basement membrane zone and underlying connective tissue stroma. In pemphigus, direct immunofluorescence shows deposition of IgG and C3 in lower layer of epithelium, in MMP direct immunofluorescence exhibits a linear band of IgG, IgA and C3 at epithelium and basement membrane zone.</td>
</tr>
<tr>
<td>3</td>
<td>Bullous pemphigoid (BP)</td>
<td>BP seldom affects mucosa unlike MMP. Histopathologically BP exhibits relatively normal epithelium without acantholysis and the basement membrane remains attached to the underlying connective tissue.</td>
</tr>
<tr>
<td>4</td>
<td>Bullous lichen planus (BLP)</td>
<td>Clinically BLP is usually bilaterally symmetrical unlike MMP. Histopathologically OBLP shows classical features of lichen planus including degeneration of basal cell layer, saw toothed rete ridges and sub epithelial band of lymphocytes.</td>
</tr>
<tr>
<td>5</td>
<td>Lichenoid reaction (LR)</td>
<td>LR is a drug reaction so the cause effect relationship can be made. Histopathological features of LR resemble LP.</td>
</tr>
</tbody>
</table>

Table 2: Treatment modalities for mild and severe forms of MMP [14-19]

<table>
<thead>
<tr>
<th>Severity of the disease</th>
<th>Treatment modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild disease</td>
<td>For mild disease without rapid progression, dapsone can be given at 25 to 50 mg per day, increasing monthly by 25 to 50 mg until clinical remission is achieved.</td>
</tr>
<tr>
<td>Severe disease</td>
<td><strong>Systemic therapy</strong></td>
</tr>
<tr>
<td></td>
<td><em>Corticosteroids</em> are the choice of initial medication. Prednisone is usually prescribed with 1 - 1.25 mg/kg/day.</td>
</tr>
<tr>
<td></td>
<td><em>Cyclophosphamides</em> are traditional steroid sparing agents can be prescribed in severe disease with conjunction of systemic steroids. Dosage ranges between 50 - 200 mg/day orally and 0.5 – 1 g/m² when given monthly intravenous.</td>
</tr>
<tr>
<td></td>
<td><em>Methotrexate</em> are antimetabolites can be given in severe MMP with the dosage range of 5 - 25 mg/week.</td>
</tr>
<tr>
<td></td>
<td><em>Intravenous immunoglobulins</em> Indicated for patients present with progressive, recalcitrant disease despite treatment. For patients that fail therapy with systemic steroids and cyclophosphamide, or for those with rapidly progressive disease, high-dose intravenous immunoglobulin (IVIG) provides a therapeutic alternative.</td>
</tr>
<tr>
<td></td>
<td><em>Mycophenolate mofetil</em> blocks de novo purine synthesis resulting in inhibition of the response of T cell and B cell. Dosage ranges between 1000 – 2000 mg/day.</td>
</tr>
<tr>
<td></td>
<td><strong>Topical therapy</strong></td>
</tr>
<tr>
<td></td>
<td>Topical steroid (Tacrolimus and cyclosporines) can be given with the conjunction of systemic therapy and to patients with relatively milder disease.</td>
</tr>
</tbody>
</table>

autoimmune diseases, but this type of therapy is associated with a significant risk of developing infections owing to the suppression of immune system. IVIGs are immune modulators and could be an ideal means of treatment for the patients who are at a risk of viral infections [24]. The present case was treated with IVIGs successfully, considering the fact that patient had been treated with prednisolone from last six months without any positive results.

It can be concluded that the resemblance of MMP on clinical and histopathological grounds with other diseases makes its diagnosis challenging moreover the means of investigations in order to differentiate MMP with other lesions are costly, technique sensitive and not routinely performed. The diagnosis of MMP needs a thorough evaluation clinical, histopathological and immunofluorescence findings. The treatment of MMP is often difficult. In present case also patient did not respond to systemic steroids; hence the mode of treatment we adopted is not very commonly used in limited diseases. IVIGs are although new but an ideal mode of treatment for the patients who are unresponsive to the conventional therapy and at a risk of infections.

REFERENCES