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**Systematic Review**

# Oral mucous membrane pemphigoid without skin involvement: A systematic review

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**Abstract**

Mucous membrane pemphigoid (MMP) is an autoimmune blistering disorder of mucosa, characterized by subepithellial bullae. We review the clinical. Histopathological, immunofluoresence and treatment modalities of MMP.

**Keywords:** Mucous membrane pemphigoid, oral mucosa, immunoflurescence, intra-venous immunoglobulins

## 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, desqumative gingivitis, erythematous patches etc. [2, 4]. We describe the histopathological and imminofluoresence diagnostic features of MMP along with the differential diagnoses and review the various treatment modalities.

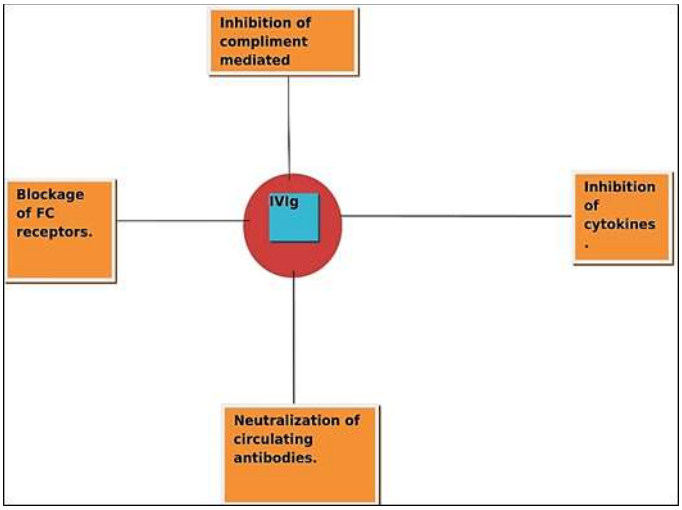


**Fig 1:** Mode of action of IVIg

**Table 1:** Differential diagnoses of MMP with differentiating features [6, 7, 8, 9, 10]

| S. No. | Differential diagnosis | Differentiating features |
|---|---|---|
| 1. | Erythema multiforme (EM) | 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. |
| 2. | Pemphigus vulgaris (PV) | 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. |
| 3. | Bullous pemphigoid | BP seldom affects mucosa unlike MMP. Histopathologically BP exhibits relatively |

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| | | |
|---|---|---|
| | (BP) | normal epithelium without acantholysis and the basement membrane remains attached to the underlying connective tissue. |
| 4. | Bullous lichen planus (BLP) | 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. |
| 5. | Lichenoid reaction (LR) | LR is a drug reaction so the cause effect relationship can be made. Histopathological features of LR resemble LP. |

**Table 2:** Treatment modalities for mild and severe forms of MMP [14, 15, 16, 17, 18, 19]

| Severity of the disease | Treatment modalities |
|---|---|
| Mild disease | 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**.** |
| Severe disease | **Systemic therapy**<br>*Corticosteroids* are the choice of initial medication. Prednisone is usually prescribed with 1-1.25 mg/kg/day.<br>*Cyclophosphamides* 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 0.5-1g/$m^2$ when given monthly intravenous.<br>*Methotrexate* are antimetabolites can be given in severe MMP with the dosage range of 5-25 mg/week.<br>*Intravenous immunoglobulins* 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.<br>*Mycophenolate mofetil* blocks de novo purine synthesis resulting in inhibition of the response of T cell and B cell. Dosage ranges between 1000-2000 mg/day.<br>**Topical therapy**<br>Topical steroid (Tacrolimus and cyclosporines) can be given with the conjunction of systemic therapy and to patients with relatively milder disease. |

**Review**

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 100000 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]. 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, 4, 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 eryhematosus (SLE), Kawasaki disease, multiple sclerosis, pemphigus, pemphigoid etc. [20, 21, 22, 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

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the conventional therapy and patients with rapidly progressive disease [22]. Immuno suppressive drugs are the well accepted mode of treatment for the patients with 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, 25]. 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 immunofluroscence findings. The treatment of MMP is often difficult. 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.

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