Mucous membrane pemphigoid; Etiology, diagnosis and treatment

Nutchaporn Sanguansin* Kraisorn Sappayatosok*

Abstract

Mucous membrane pemphigoid (MMP) is a chronic autoimmune subepithelial vesiculobullous disorder that predominantly affects the mucous membranes more frequently than the skin. Several target antigens in basement membrane zone have been identified in MMP. It is characterized by linear deposition of IgG, IgA or C3 along the basement membrane zone. The disease severity and extension is highly variable. The patients may present with only mucosal or skin lesions or combined multiple sites. In the oral cavity, the most frequently affected site is the gingiva presented as desquamative gingivitis. The diagnosis of MMP is mainly based on clinical findings, histopathologic and immunofluorescence features. There is no gold standard therapy for MMP. The treatment should be individualized based on the sites of involvement, clinical severity and disease progression. Corticosteroids and immunosuppressive agents are the mainstay of treatment. The significant complication is scarring of the oropharyngeal and ocular mucous membranes which can lead to strictures and blindness. Multidisciplinary approach is necessary for the diagnosis and management of MMP. This article reviews the epidemiology, pathophysiology, clinical presentation, diagnosis and treatment of MMP.

Keywords: Autoimmune, Mucous membrane pemphigoid, Corticosteroids, Diagnosis, Treatment

**College of Dental Medicine, Rangsit University, 52/347 Muang Ake, Phaholyothin Road, A. Muang, Pathum Thani 12000 Thailand.*

Introduction

Mucous membrane pemphigoid (MMP) is a chronic autoimmune subepithelial blistering disease which frequently affects oral and ocular mucosa and occasionally the skin. The nasopharynx, esophagus, larynx and anogenital mucosa may also be involved. It is caused by autoantibodies against components of basement membrane zone (1). Clinically, the lesions consist of blisters which finally rupture and develop irregularly shaped ulcerations surrounded by erythematous margin. High variable exists in the clinical presentations. Patients may present with only the oral mucosa or any combinations of sites. Scar formation is commonly seen which can develop esophageal and laryngeal stenosis, strictures and blindness (2). Diagnosis of MMP is mainly based on clinical findings, histopathology and immunofluorescence studies. Early diagnosis and treatment may decrease complications and morbidities associated with MMP. Treatment should be based on severity and extension of the disease and multidisciplinary approach is essential in management of MMP (3). Aim of this article was to review the update published data on MMP. We searched Pubmed/Medline using the term “mucous membrane pemphigoid”. Only relevant published data were selected in this review.

Epidemiology

The incidence of MMP is estimated to be 0.5-3.2 cases per 100,000 people per year (4). In France and Germany, incidence of 1.3 to 2 per 1 million people per year has been reported (5, 6). MMP is less frequent than bullous pemphigoid (BP) about seven times, and up to three times more common than pemphigus (4). MMP predominantly affects elderly people, with commonly observed between 60 and 80 years and the mean age of onset being 60 to 65 years (7). However, children may also be affected. The youngest age which has been reported was 10 months old (8). MMP affects females more than male with a female to male ratio of 2:1. There is no racial or geographic predilection (9).

MMP Pathophysiology

MMP is caused by autoantibodies against components of the basement membrane zone. MMP has been found to be heterogenous with several target antigens. The bullous pemphigoid antigen 2 (BPAg2; a 180-kDa protein; BP180) (10), bullous pemphigoid antigen 1 (BPAg1; a 230-kDa protein; BP230) (11), 97/120 kDa linear IgA bullous dermatosis (LAD) antigen, laminin 332 (laminin 5 or epiligrin), laminin 331 (laminin 6) (12), α6/β4 integrin (11), type VII collagen (13), uncein (14), 168 kDa antigen (15) and 200 kDa antigen (16) have been identified as the target antigens in MMP. Both BPAg2 and BPAg1 are hemidesmosomal proteins which facilitate the stable adhesion of basal epithelial cells to the underlying basement membrane. BPAg2 is a transmembrane protein that spans the lamina lucida and projects into the lamina densa of the epidermal basal membrane zone, whereas BPAg1 is the intracellular component of hemidesmosome (17,18). Approximately, seventy percents of MMP patients have BP180 as the target antigen, while most of BP patients have BP230 as the target antigen (4,19). Additionally, specific antigens between MMP and BP are also different. Carboxy-terminal region of BPAg2 locating at the lamina lucida/lamina densa interface was found to be the specific reactivity

of autoantibodies in MMP, whereas the BPAg2 NC16A domain locating the upper lamina lucida was found to be the major pathogenic epitope in BP (20). Table 1. and Fig 1. show the autoantigens that have been identified in MMP patients.

Table 1. Autoantigens identified in MMP
[Modified from Bagan et al.,2005 (4), Xu et al.,2013 (9), and Pongsiriwet et al., 2018 (21)]

Autoantigens	Location
BPAg2 (BP180)	Hemidesmosome (transmembrane) / Lamina lucida
BPAg1 (BP230)	Hemidesmosone (intracellular)
97/120 kDa linear IgA bullous dermatosis (LAD) antigen	Lamina lucida
Laminin 332 (laminin 5)	Lower lamina lucida
Laminin 331 (laminin 6)	Lower lamina lucida
α6/β4 integrin	Hemidesmosome (transmembrane)
Type VII collagen	Lamina densa / Sub-lamina densa
Uncein	Lamina lucida
168 kDa	Basement membrane (epidermal side of salt-split skin)
200 kDa	Lamina lucida-lamina densa interface

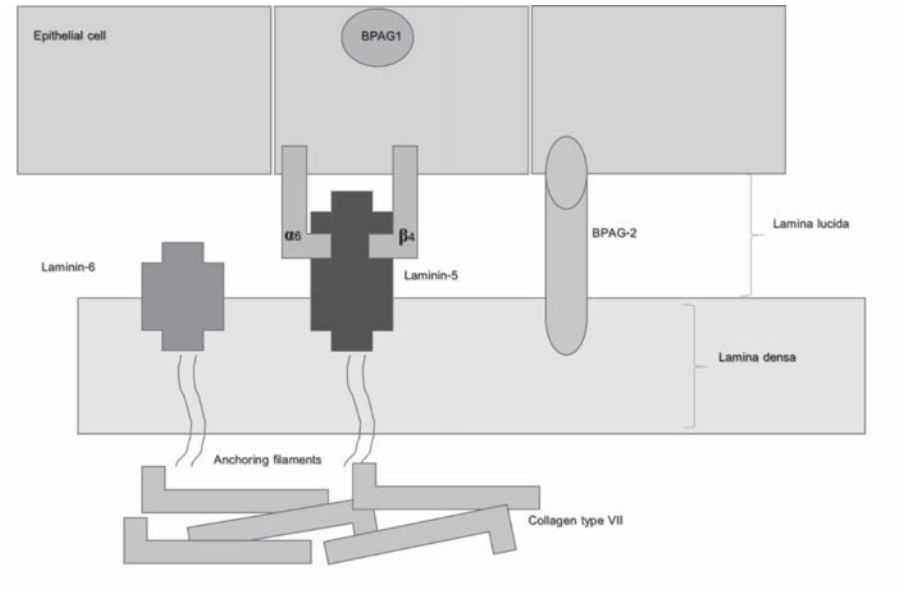


Fig 1. Antigens involved in pathogenesis of MMP.
[Modified from Xu et al., 2013 (9) and Pongsiriwet et al., 2018 (21)]

Some studies have shown the relationship between α6/β4 integrin and the involvement of MMP. Autoantibodies against α6 subunit have been described in patients with oral involvement, while β4 integrin subunit has been demonstrated in patients with generalized MMP and ocular involvement (12).

In vitro and *in vivo* studies have demonstrated the pathogenicity of anti-laminin 332 antibodies. Passive transfer of anti-laminin 332 IgG to mice induced subepidermal blisters of both skin and mucous membranes (22). The epidermal detachment was also induced in mice injected with Fab fragments directed against laminin (22). The pathogenicity of anti-laminin 332 antibodies was confirmed in an experimental human skin graft model. Human anti-laminin 332 autoantibodies induced subepidermal blisters (23). Additionally, autoantibodies against α6 integrin also induced the separation of epithelium from basement membrane (24).

The antibody-induced complement activation can lead to epithelial detachment resulting from either direct cytotoxic action or the effect of lysosomal proteolytic enzymes. Activated complement results in the expression of inflammatory mediators which induce migration of lymphocytes, eosinophils, neutrophils and mast cells to the lesion. These cells secrete proteolytic enzymes causing the destruction of tissue and resulting in the separation of epithelium from basement membrane leading to subepithelial blisters (9).

Several studies have shown the role of cell-mediated immunity in pathogenesis of MMP. The biopsy examinations from conjunctiva of MMP patients were significantly shown a high intensity of CD4+ T cells and Langerhans cells (25). The significantly increasing infiltration of Th17 lymphocytes in conjunctival biopsies was also observed in MMP patients (26). In addition, the association of HLA DQB1*0301 and MMP have been reported that HLA DQB1*0301 has a role in T-cell recognition of basement membrane antigens (27).

The progressive scarring in MMP is still incompletely understood, but recently the release of soluble fibrogenic factors by inflammatory infiltrating cells has been considered as pathogenesis of this process. In conjunctiva, scarring may be caused by fibroblasts which secrete fibrogenic cytokines, matrix metalloproteinases and collagen type I (28). Furthermore, both IL-4 and IL-13 are thought to be involved in scar formation in MMP (29).

Clinical presentation

MMP is a chronic and progressive autoimmune blistering disease which affects mucous membranes more often than skin. The most common site is the oral mucosa (85% of patients), followed by ocular involvement (65%). It may also involve nasal cavity (20-40%), skin (25-30%), anogenital area (20%), pharynx (20%), larynx (5-15%), and esophagus (5-15%) (7). The lesions at all affected sites tend to heal with scarring resulting to disease-related morbidity, although lesions in oral cavity may heal without scarring (10).

Clinical presentation and severity of MMP patients are highly variable. The patients may present with only mucosal or skin lesions or combined multiple sites. The First International Consensus Group on MMP divided patients into “low-risk” and “high risk” group based on the site of involvement. “Low-risk” patients are those who have the lesions occurring only oral mucosa and/or skin. While “high-risk” patients are defined

as having the disease affecting in the following sites: ocular, nasopharyngeal, esophageal, laryngeal and genital mucosa (1). However, localized disease can progress to extensive disease which is more difficult to control (9).

In the oral cavity, the most frequently affected site is the gingiva which is referred to as desquamative gingivitis (9), as shown in Fig 2. The palate, labial mucosa, buccal mucosa, buccal vestibule, floor of the mouth, tongue and lips can also be affected. Other clinical manifestations, including blisters, erythema, erosions and ulcerations can also present. The blisters typically rupture within 24 hours and form irregularly shaped ulcerations with pseudomembranous coverage. The patients usually have burning sensation, pain, bleeding, dysphagia and desquamation of oral mucosa. Lesions commonly demonstrate Nikolsky's sign which is a clinical sign elicited by lateral pressure with a finger, mouth mirror or periodontal probe (3).

The ocular involvement is the second most commonly affected site. The initial ocular manifestation is chronic conjunctival inflammation and erosions with burning sensation, dryness, sensation of foreign body, photosensitivity and excessive lacrimation. Most patients initially have the symptoms affecting one eye, but if left untreated, the disease can involve the other eye within 2 years. Additionally, the repeated fibrosis can proceed to the adhesion of the palpebral conjunctiva of the eyelid to the bulbar conjunctiva of the eyeball (symblepharon), adhesion of the edges of upper eyelid with the lower eyelid (ankyloblepharon) that can lead to blindness. The eyelid malposition with entropion or inward turning of the lid margin results in abnormal position of the eyelashes that grow inwards toward the eye and irritate the corneal conjunctiva. This can also cause scar formation and may result in blindness (4). All MMP patients should be seen by ophthalmologist. The annual risk for developing ocular lesions is 5% over the first 5 years in MMP patients without any eye involvement (30).

Nasopharyngeal lesions present as ulcerations, stenosis and can lead to airway obstruction. Esophageal involvement may present as ulcerations, strictures and stenosis which influence food taking and result in dysphagia and odynophagia. Scarring of the laryngeal mucosa can result in sudden asphyxiation which is the life-threatening complication (9). Skin lesions are uncommon and located on face, neck, scalp, axilla, trunk and extremities (4). Anogenital lesions manifest as blisters, erosions and scarring. These may result in urinary and sexual dysfunction which can significantly affect the daily activities of patients (9).

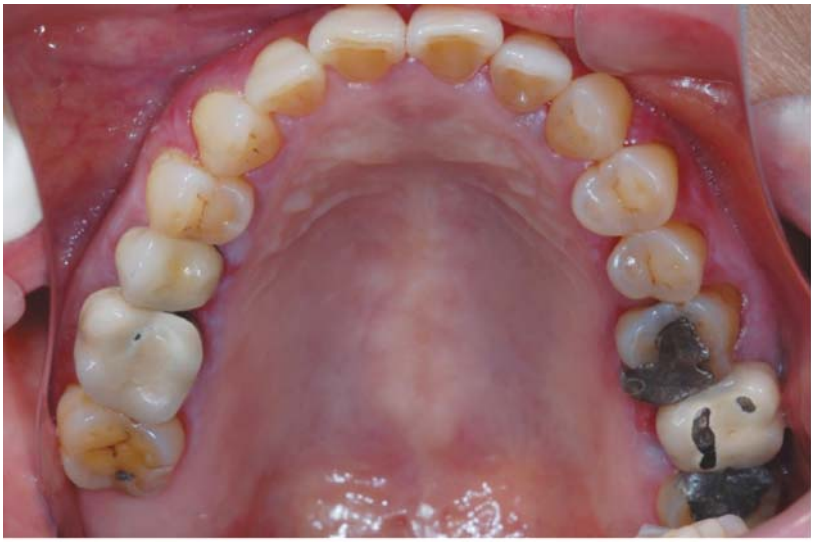


Fig 2. MMP presents as desquamative gingivitis.
[Courtesy of Dr. Piamkamon Vacharotayangul]

Subgroups of MMP

MMP can be classified into 6 subgroups depending on the clinical features, involved locations, immunofluorescence findings, circulating autoantibodies in a patient's serum and the target antigens (21,31).

1). Oral pemphigoid or OMMP

Oral pemphigoid affects only the oral mucosa even after a long-term follow-up. It rarely causes scarring and typically associated with a good prognosis. Indirect immunofluorescence (IIF) typically shows negative finding with no serologic reactivity to BP antigens or other MMP antigens. The target antigen is still unclear. The first study of six patients with disease limited to the oral cavity showed the antibodies against 168-kDa protein (15). However, in recently several studies have demonstrated that circulating antibodies against the α6 integrin subunit can induce a separation of the epithelium from basement membrane in organ culture. Therefore, α6 integrin subunit may represent the specific reactivity of oral pemphigoid (11,24).

2). Anti-laminin 5 MMP (anti-epiligrin pemphigoid; AECP)

Anti-laminin 5 MMP is uncommon and characterized by autoantibodies against the major basement membrane component laminin 5. The involving locations are the mucous membranes and skin. IIF reveals the serologic reactivity only to the dermal site of salt-split skin and shows a low titer of circulating IgG antibodies to basement membrane zone (31). The target antigens have been identified as the α3 subunit (32) or α3 and γ2 subunits (33) or β3 and γ2 subunits of laminin 5 in the basement membrane (34). The anti-laminin 5 MMP patients have an incidence in developing solid cancer more than normal population (35). Diagnostic criteria for anti-laminin 5 MMP includes 1. chronic subepithelial blisters of mucous

membrane and skin, 2. *in situ* and circulating antibodies against lamina lucida-lamina densa interface, and 3. circulating IgG autoantibodies against the laminin 5 from human keratinocyte extracts, culture media or both (36). Previous studies found that anti-laminin 5 MMP has been associated with cancer of lung (37), endometrium (38), cervix (39), colon (39) and stomach (40). Furthermore, there are also reports of non-Hodgkin's lymphoma (41) and B-cell lymphoproliferative disorders in some patients with MMP (42). A review of anti-laminin 5 MMP patients in Japan demonstrated that 5 of 16 cases were complicated by internal malignancy (37).

3). Anti-BP antigen mucosal pemphigoid

It can be manifested with oral and skin lesions with or without other mucosal involvement. IIF study shows a high frequent reactivity to BP antigens and high frequency of circulating autoantibodies which is similar to BP findings. Antibodies against BPAg1 and BPAg2 have been demonstrated in anti-BP antigen mucosal pemphigoid patient (31).

4). Ocular pemphigoid

Ocular pemphigoid is considered a subtyped of MMP in patient having ocular involvement with or without oral lesions. Direct immunofluo-rescence (DIF) reveals the much greater deposition of fibrin with a low frequency of IgG and C3. IIF findings on salt-split skin are commonly negative whereas the autoantibodies to BP antigens are typically positive. The target antigens are the human β4 integrin of a 205-kDa protein and a 45-kDa protein (11). In six patients who have ocular lesions only, there was the deposition of antibodies locating in the upper lamina lucida of basement membrane. On the other hand, in seven patients who have oral, ocular and skin involvement, there was the immune deposition in the lower part of the lamina lucida and lamina densa. It has been suggested that pure ocular pemphigoid may be a disease distinct from ocular pemphigoid which disease also involves the other mucosa and skin (43).

5). Multiple antigens

Multiple antigens consist of patients with antibodies directed against more than one antigen (31).

6). Anti-p200 pemphigoid

Anti-p200 pemphigoid is a rare autoimmune subepidermal blistering disease. It is characterized by autoantibodies to a 200-kDa protein (p200) of the dermal-epidermal junction. This protein is a noncollagenous N-glycosylated acidic protein locating at the lamina lucida-lamida densa interface and is thought to be important for adhesion between basal keratinocytes and the underlying dermis (16). DIF usually reveals linear deposits of IgG and C3 along the dermal-epidermal junction. IIF findings on salt-split skin demonstrate circulating IgG autoantibodies at the dermal side. By immunoblotting, these autoantibodies recognize a 200-kDa protein of human dermis (31). Recently, 90% of anti-p200 pemphigoid sera were shown to recognize laminin γ1 (44).

Table 2. Distinctive clinical and immunologic features of 5 subgroups of MMP [Modified from Bagan et al., 2005 (4), Scully et al., 1999 (31), and Chan et al., 1993 (45)]

Subgroups	Involving sites	DIF I (fibrin only)	IF	Reactivity to BP antigens	Main targeted antigens
Oral pemphigoid	Oral mucosa	Negative	Negative	No	BPAg1, BPAg2, laminin 5, laminin 6, α6 integrin subunit, 168-kDa protein
Anti-laminin 5 MMP	Mucous membranes and rarely skin	Negative	Negative	No	Laminin 5
Anti-BP antigen mucosal pemphigoid	Oral and skin lesions with or without other mucosal lesions	Negative	Typically positive	Typically positive	BPAg1, BPAg2, β4 integrin subunit, laminin 5
Ocular pemphigoid	Ocular lesions with or without oral lesions	Typically positive	Negative	Typically positive	205-kDa protein (β4 integrin), 45 kDa protein, laminin 5
Anti-p200 pemphigoid	Typically skin, sometimes progress to mucous membranes	Negative	Positive	No	p200 (laminin γ1)

MMP Diagnosis

Diagnosis of MMP is mainly based on clinical findings, histopathologic examination and immunofluorescence studies (10). For histologic evaluation, the tissue sample should be taken from the lesion including intact epithelium not an erosion or ulceration which will show loss of the epithelium. Some authors suggest rubbing the mucosa to induce a vesicle before taking biopsy. Additionally, gingival biopsy should be avoided because the chronic inflammation of gingiva may confuse the histopathological feature (46). Then tissue sample is submitted in formalin. MMP is typically characterized by the subepithelial seperation with an inflammatory infiltrate in the lamina propria which is composed of eosinophils, lymphocytes and neutrophils (9). However, the other subepithelial blistering diseases can show

the same results and histological finding is often not enough to differentiate from other mucocutaneous disorders (4). Histopathology of MMP is shown in Fig 3.

DIF is essential for diagnosis. The tissue sample should be taken from perilesional mucosa adjacent to new vesicle or bullae rather than the bullous, erosion or ulceration, and submitted in Michele's solution. The DIF typically reveals linear IgG (97%) and/or C3 (78%), and sometimes IgA (27%) deposits along the basement membrane zone in homogeneous linear pattern (9). DIF is useful in two ways: first, a positive result confirms the diagnosis of immune-mediated subepithelial blistering diseases (IMSEBD). Second, DIF can differentiate IgG-mediated diseases (BP, MMP, herpes gestationis (HG) and acquired epidermolysis bullosa acquisita (EBA), from IgA-mediated diseases (dermatitis herpetiformis and linear IgA disease) (47).

IIF is used to detect circulating antibodies in the serum of patient (9). It is performed by incubating patient serum with an epithelial substrate, such as monkey esophagus, rat bladder, guinea pig labial mucosa, human skin or human buccal mucosa and marking the specific antigen with fluorescein-labeled anti-human IgG (4). IIF is usually negative as serum samples from MMP patients contain autoantibodies at low titers [1:10-1:40] (19). Circulating IgA antibodies are detected in about 60% of serum samples, and combined IgA and IgG antibodies are related to more severe disease (10). The sensitivity of this technique is quite low, salt-split skin is more sensitive and helps in detecting circulating autoantibodies (10). Salt-split skin is performed by incubation normal human skin or mucous membrane with 1 mol sodium chloride solution, then separation the epithelium from connective tissue at lamina lucida portion of the basement membrane (9). This technique can distinguish between antigen located on the epidermal and dermal side of the split (48).

In addition, direct and indirect immunogold electron microscopy can be helpful to identify the deposition of autoantibodies, complement and fibrin (49). However, this technique is difficult and expensive, so the diagnosis should still be based on the basis of clinical presentation combined with histopathology, DIF, and serum antibody analysis.

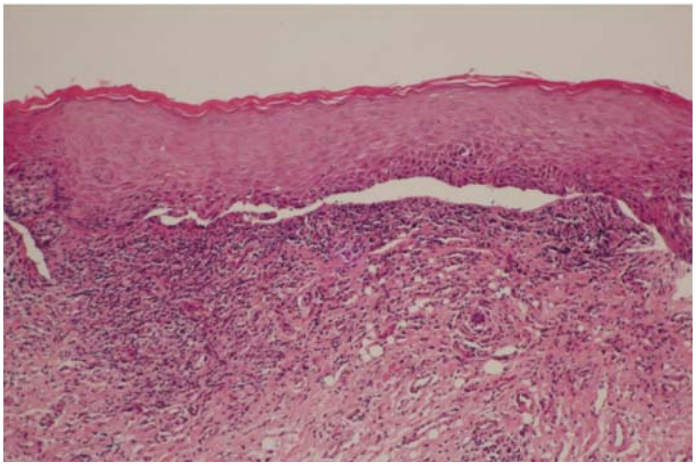


Fig 3. MMP histopathology (X10).

Differential diagnosis

Clinical presentation of MMP should be differential diagnosis from the other vesiculobullous diseases such as pemphigus vulgaris (PV), BP, EBA, linear IgA disease and others mucocutaneous diseases such as lichen planus, bullous systemic lupus erythematosus and erythema multiforme (9). MMP and BP have the same histopathologic features and DIF, so the differential diagnosis should be made on the combination of clinical findings and IIF examination. MMP predominantly involves the mucous membrane, whereas BP typically affects the skin. In addition, circulating antibodies in BP are more common than in MMP (9). More specific immunological analysis has demonstrated that autoantibodies produced by MMP patients bind to the C-terminal portion of the BPAg2 antigen, while antibodies produced by patients with BP bind to the BPAg2 NC16A domain (50).

EBA and MMP may also present the same clinical, histopathological and immunopathological features. The distinction can be achieved by salt-split skin technique using human skin. If antibodies deposit on the roof side of the induced separation, the diagnosis is most possibly to be MMP. In contrast, if the deposition is on the floor (dermal side), the diagnosis is EBA (51).

The general features of MMP compared with PV and BP are showed in table 3.

Table 3. General features of PV, MMP and BP
[Modified from Xu et al., 2013 (9) and Pongsiriwet et al., 2018 (21)]

Features	PV	MMP	BP
Mean age	Fourth to sixth decade	Sixth to seventh decade	Seventh to eighth decade
Target antigen	Desmosome (desmoglein 3 and desmoglein 1)	Hemidesmosome (most common = BPAg2)	Hemidesmosome (most common = BPAg1)
Common location	Oral cavity and skin	Oral cavity and ocular mucosa	Skin
Blisters	Intraepithelial blisters	Subepithelial blisters	Subepithelial blisters
Histopathology	Intraepithelial separation, acantholytic cells	Subepithelial separation	Subepithelial separation
DIF	IgG and/or IgM deposit in the epithelial intercellular space	IgG and/or C3 sometimes IgA linear deposit along the basement membrane zone	linear IgG and/or C3 deposit along the basement membrane zone
Circulating antibodies in serum	80-90% of patients	Usually negative	50-90% of patients

MMP Management

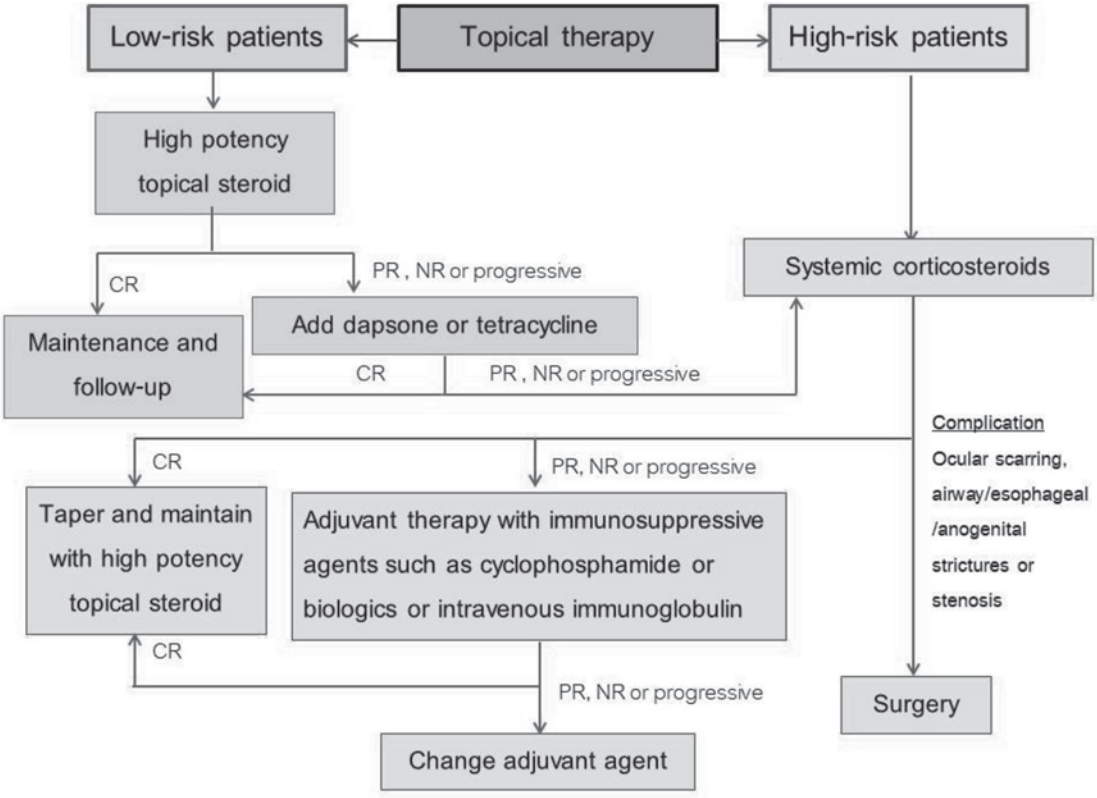
Treatment of MMP is based on the involved sites, severity and disease progression (9). Additionally, it should be individualized depending on age, medical history and contraindications of any systemic medications (9). Early diagnosis and treatment may decrease disease-related complications, especially airway obstruction, stricture and blindness (3). In low-risk patients with lesions affecting oral mucosa and/or skin can be treated effectively with topical therapy, such as topical corticosteroids or topical calcineurin inhibitors. For more severe or recalcitrant lesions or during exacerbation of disease in low-risk patients, the treatment should be combined with systemic therapy (9). High-risk patients with rapid progression or multiple involving sites including ocular, genital, esophageal or nasopharyngeal mucosa require more aggressive systemic treatment with topical treatment (9). A multidisciplinary approach including oral medicine experts, ophthalmologists, gastroenterologist, otolaryngologist, gynaecologist, and dermatologists is essential for the management of MMP and related to the treatment outcome (3).

Low-risk patients

Potent topical corticosteroids are advised initially, applied 2-3 times/day (52). In patients with isolated severe or recalcitrant lesions, intralesional corticosteroid injections with triamcinolone acetonide 10mg/ml 0.1 cc/cm^2 can be used (9). For desquamative gingival lesions, topical corticosteroids in gel form are recommended and should be applied with custom tray which covers the involved gingiva (9). Additionally, combination therapy of topical tacrolimus with prednisolone 40mg/day has been shown to be effective after 3 months of treatment (53). If the patients do not response to topical therapy, dapsone (50-200 mg/day) or tetracycline (1-2 g/day) or nicotinamide (2-3 g/day) can be added. For non-responsive patients with above regimens, systemic corticosteroids such as prednisolone (1-2 mg/kg) can be used (52). Systemic corticosteroids may be combined with immunosuppressive agents such as azathioprine (1-2 mg/kg/day) or mycophenolate mofetil (1-2 g/day) (1).

High-risk patients

Systemic corticosteroids in combination with immunosuppressive drugs are the treatment of choice for severe or rapidly progressive disease (3). Prednisolone 1-1.5 mg/kg/day combined with cyclophosphamide 0.5-2 mg/kg/day is recommended (52). Alternatively, prednisolone can be added with other immunosuppressive agents such as mycophenolic acid 2-2.5 g/day or azathioprine 1-2 mg/kg/day (52). For mild disease, dapsone 50-200 mg/day can be given (1). When the disease becomes effectively controlled, prednisone should be tapered gradually while continuing immunosuppressive drug (52). Generally, the adjuvant immunosuppression should be continued for 2 years (52). In patients with progressive ocular lesions refractory to corticosteroids and immunosuppressive drug, intravenous immunoglobulins can be used to prevent complications, especially blindness (54). Additionally, biologic agents such as rituximab, etanercept or TNF-alpha inhibitors have been reported to treat severe and recalcitrant MMP successfully and should be an alternative treatment option (52). Long-term treatment with prednisolone can cause several side effects, so carefully monitoring should be performed appropriately (3).



(CR; complete response, PR; partial response, NR; no response)

Fig 4. Treatment algorithm for MMP.

[Modified from Bagan et al., (4), Xu et al., 2013 (9), and Pongsiriwet et al., 2018 (21)]

Conclusion

MMP is a chronic autoimmune disease characterized by subepithelial blisters that typically affects mucous membranes more often than skin. It is more common in female and mainly affects elderly people. The most frequently involving site is the oral cavity, followed by conjunctiva. Clinical presentation and severity of MMP patients are highly variable. Clinical manifestations in the oral cavity include desquamative gingivitis, blisters, erythema, erosions and ulcerations. Diagnosis is mainly based on clinical findings, histopathologic examination and immunofluorescence studies. There is no gold standard therapy for MMP. The treatment depends on the sites of involvement, clinical severity and disease progression. Topical therapy is the mainstay of treatment for localized disease. For more severe and widespread disease, more aggressive and systemic therapies are the treatment of choice. Scarring is commonly seen, especially in oropharyngeal and ocular mucosa which can progress to esophageal and laryngeal stenosis, strictures and blindness. Early diagnosis and treatment may decrease disease-related morbidity and mortality. Multidisciplinary approach is necessary for the diagnosis and management of MMP.

References

1. Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, et al. The first international consensus on mucous membrane pemphigoid: Definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Arch Dermatol. 2002;138 (3):370–9.

2. Srikumaran D, Akpek EK. Mucous membrane pemphigoid: recent advances. Curr Opin Ophthalmol. 2012;23(6):523-7.

3. Neff AG, Turner M, Mutasim DF. Treatment strategies in mucous membrane pemphigoid. Ther Clin Risk Manag. 2008; 4(3):617–26.

4. Bagan J, Lo Muzio L, Scully C. Mucosal disease series. Number III. Mucous membrane pemphigoid. Oral Dis. 2005;11(4):197-218.

5. Bernard P, Vaillant L, Labeille B, Bedane C, Arbeille B, Denoeux JP, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. Arch Dermatol. 1995;131(1):48-52.

6. Bertram F, Bröcker EB, Zillikens D, Schmidt E. Prospective analysis of the incidence of autoimmune bullous disorders in Lower Franconia, Germany. J Dtsch Dermatol Ges. 2009;7(5):434-40.

7. Thorne JE, Anhalt GJ, Jabs DA. Mucous membrane pemphigoid and pseudopemphigoid. Ophthalmology. 2004;111(1):45-52.

8. Jolliffe DS, Sim-Davis D. Cicatricial pemphigoid in a young girl: report of a case. Clin Exp Dermatol. 1977;2(3):281–4.

9. Xu HH, Werth VP, Parisi E, Sollecito TP. Mucous membrane pemphigoid. Dent Clin North Am. 2013;57(4):611-30.

10. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet 2013;381(9863):320–32.

11. Rashid KA, Gurcan HM, Ahmed AR. Antigen specificity in subsets of mucous membrane pemphigoid. J Invest Dermatol. 2006;126(12): 2631-6.

12. Domloge-Hultsch N, Gammon WR, Briggaman RA, Gil SG, Carter WG, Yancey KB. Epiligrin, the major human keratinocyte intergrin ligand, is a target in both an acquired autoimmune and an inherited subepidermal blistering skin disease. J Clin Invest. 1992;90(4):1628–33.

13. Luke MC, Darling TN, Hsu R, Summers RM, Smith JA, Solomon BI, et al. Mucosal morbidity in patients with epidermolysis bullosa acquisita. Arch Dermatol. 1999;135(8):954–9.

14. Horiguchi Y, Ueda M, Shimizu H, Tanaka T, Matsuyoshi N, Utani A, et al. An acquired bullous dermatosis due to an autoimmune reaction against uncein. Br J Dermatol. 1996;134(5):934–8.

15. Ghohestani RF, Nicolas JF, Rousselle P, Claudy AL. Identification of a 168-kDa mucosal antigen in a subset of patients with cicatricial pemphigoid. J Invest Dermatol. 1996;107(1):136–9.

16. Egan CA, Yee C, Zillikens D, Yancey KB. Anti-p200 pemphigoid: diagnosis and treatment of a case presenting as an inflammatory subepidermal blistering disease. J Am Acad Dermatol. 2002;46(5):786–9.

17. Walko G, Castañón MJ, Wiche G. Molecular architecture and function of the hemidesmosome. Cell Tissue Res. 2015;360(2): 363–78.

18. Kasperkiewicz M, Zillikens D, Schmidt E. Pemphigoid diseases: pathogenesis, diagnosis, and treatment. Autoimmunity. 2012;45(1):55-70.

19. Schmidt E, Skrobek C, Kromminga A, Hashimoto T, Messer G, Bröcker EB, et al. Cicatricial pemphigoid: IgA and IgG autoantibodies target epitopes on both intra- and extracellular domains of bullous pemphigoid antigen 180. Br J Dermatol. 2001;145(5):778–83.

20. Bédane C, McMillan JR, Balding SD, Bernard P, Prost C, Bonnetblanc JM, et al. Bullous pemphigoid and cicatricial pemphigoid autoantibodies react with ultrastructurally separable epitopes on the BP180 ectodomain: evidence that BP180 spans the lamina lucida. J Invest Dermatol. 1997;108(6):901–7.

21. Pongsiriwet S, Sangkaew P. Mucous membrane pemphigoid: A Review of literature. CM Dent J. 2018;39(1):25-42.

22. Lazarova Z, Yee C, Darling T, Briggaman RA, Yancey KB. Passive transfer of anti-laminin 5 antibodies induces subepidermal blisters in neonatal mice. J Clin Invest. 1996;98(7):1509–18.

23. Lazarova Z, Hsu R, Yee C, Yancey KB. Human anti-laminin 5 autoantibodies induce subepidermal blisters in an experimental human skin graft model. J Invest Dermatol. 2000;114(1): 178–84.

24. Bhol KC, Goss L, Kumari S, Colon JE, Ahmed AR. Autoantibodies to human alpha6 integrin in patients with oral pemphigoid. J Dent Res. 2001;80(8):1711–5.

25. Bodaghi B, Bertin V, Paques M, Toublanc M, Dezutter-Dambuyant C, Hoang-Xuan T. Limbal conjunctival Langerhans cell density in ocular cicatricial pemphigoid: an indirect immunofluorescence study on Dispase-split conjunctiva. Curr Eye Res. 1997;16(8):820–4.

26. Lambiase A, Micera A, Mantelli F, Moretti C, Di Zazzo A, Perrella E, et al. T-helper 17 lymphocytes in ocular cicatricial pemphigoid. Mol Vis. 2009;15:1449–55.

27. Setterfield J, Theron J, Vaughan RW, Welsh KI, Mallon E, Wojnarowska F, et al. Mucous membrane pemphigoid: HLA-DQB1*0301 is associated with all clinical sites of involvement and may be linked to antibasement membrane IgG production. Br J Dermatol. 2001;145(3):406–14.

28. Saw VP, Schmidt E, Offiah I, Galatowicz G, Zillikens D, Dart JK, et al. Profibrotic phenotype of conjunctival fibroblasts from mucous membrane pemphigoid. Am J Pathol. 2011;178(1):187–97.

29. Giomi B, Caproni M, Fabbri P. IL-4 and cellular adhesion molecule (CAM) pathway are involved in cicatricial pemphigoid scarring process. J Dermatol Sci. 2005;38(1):57–9.

30. Schifter M, Yeoh SC, Coleman H, Georgiou A. Oral mucosal diseases: the inflammatory dermatoses. Aust Dent J. 2010;55(s1):23-38.

31. Scully C, Carrozzo M, Gandolfo S, Puiatti P, Monteil R. Update on mucous membrane pemphigoid: a heterogeneous immune-mediated subepithelial blistering entity. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;88(1):56-68.

32. Kirtschig G, Marinkovich MP, Burgeson RE, Yancey KB. Anti-basement membrane autoantibodies in patients with anti-epiligrin cicatricial pemphigoid bind the alpha subunit of laminin 5. J Invest Dermatol. 1995;105(4):543–8.

33. Nousari HC, Anhalt GJ. Pemphigus and bullous pemphigoid. Lancet. 1999;354(9179): 667–72.

34. Fujimoto W, Toi Y, Okazaki F, Lazarova Z, Yancey KB, Arata J. Anti-epiligrin cicatricial pemphigoid with IgG autoantibodies to the beta and gamma subunits of laminin 5. J Am Acad Dermatol. 1999;40(4):637–9.

35. Egan CA, Lazarova Z, Darling TN, Yee C, Coté T, Yancey KB. Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. Lancet. 2001;357(9271):1850–1.

36. Vodegel RM, de Jong MC, Pas HH, Yancey KB, Jonkman MF. Anti-epiligrin cicatricial pemphigoid and epidermolysis bullosa acquisita: differentiation by use of indirect immunofluorescence microscopy. J Am Acad Dermatol. 2003;48(4):542–7.

37. Matsushima S, Horiguchi Y, Honda T, Fujii S, Okano T, Tanabe M, et al. A case of anti-epiligrin cicatricial pemphigoid associated with lung carcinoma and severe laryngeal stenosis: review of Japanese cases and evaluation of risk for internal malignancy. J Dermatol. 2004;31(1): 10–5.

38. Lenz P, Hsu R, Yee C, Yancey K, Volc-Platzer B, Stingl G, et al. Cicatricial pemphigoid with autoantibodies to laminin 5 (epiligrin) in a patient with metastatic endometrial carcinoma. Hautarzt. 1998;49(1):31–5.

39. Leverkus M, Schmidt E, Lazarova Z, Bröcker EB, Yancey KB, Zillikens D. Antiepiligrin cicatricial pemphigoid: an underdiagnosed entity within the spectrum of scarring autoimmune subepidermal bullous diseases?. Arch Dermatol. 1999;135(9):1091–8.

40. Taniuchi K1, Takata M, Matsui C, Fushida Y, Uchiyama K, Mori T, et al. Antiepiligrin (laminin 5) cicatricial pemphigoid associated with an underlying gastric carcinoma producing laminin 5. Br J Dermatol. 1999;140(4):696–700.

41. Shannon JF, Mackenzie-Wood A, Wood G, Goldstein D. Cicatricial pemphigoid in non-Hodgkin's lymphoma. Intern Med J. 2003;33(8): 396–7.

42. Aractingi S, Bachmeyer C, Prost C, Caux F, Flageul B, Fermand JP. Subepidermal autoimmune bullous skin diseases associated with B-cell lymphoproliferative disorders. Medicine (Baltimore). 1999;78(4):228–35.

43. Hoang-Xuan T, Robin H, Demers PE, Heller M, Toutblanc M, Dubertret L, et al. Pure ocular cicatricial pemphigoid. A distinct immunopathologic subset of cicatricial pemphigoid. Ophthalmology. 1999;106(2):355–61.

44. McCarty M, Zillikens D, Fivenson D. Anti-p200 pemphigoid (anti-laminin-γ1 pemphigoid) demonstrating pathergy. Int J Womens Dermatol. 2015;1(4):173–4.

45. Chan LS, Fine JD, Briggaman RA, Woodley DT, Hammerberg C, Drugge RJ, et al. Identification and partial characterisation of a novel 105-kDalton lower lamina lucida autoantigen associated with a novel immune-mediated subepidermal blistering disease. J Invest Dermatol. 1993;101(3):262-7.

46. Siegel MA, Anhalt GJ. Direct immunofluorescence of detached gingival epithelium for diagnosis of cicatricial pemphigoid. Report of five cases. Oral Surg Oral Med Oral Pathol. 1993;75(3):296–302.

47. Mutasim DF. The accuracy of indirect immunofluorescence on sodium chloride-split skin in differentiating subepidermal bullous diseases. Arch Dermatol. 1997;133(9):1158–60.

48. Barnadas MA, Gelpi C, Curell R, de Moragas JM, Alomar A. Repeat direct immunofluorescence (DIF) test, using, 1 M NaCl treated skin, in the subepidermal autoimmune bullous diseases that contain IgG at the dermal epidermal junction. J Cutan Pathol. 1999;26(1):37–41.

49. Karpouzis A1, Vamvassakis E, Stavrianeas N, Koumantaki-Mathioudaki E, Karpouzi M, Vareltzides A. Ultrastructural immunocytochemistry of autoimmune bullous diseases. Australas J Dermatol. 2002;43(2):113–9.

50. Yancey KB, Egan CA. Pemphigoid: clinical, histologic, immunopathologic, and therapeutic considerations. JAMA. 2000;284(3): 350–6.

51. Mutasim DF, Pelc NJ, Anhalt GJ. Cicatricial pemphigoid. Dermatol Clin. 1993;11(3): 499–510.

52. Knudson RM, Kalaaji AN, Bruce AJ. The management of mucous membrane pemphigoid and pemphigus. Dermatol Ther. 2010;23(3):268-80.

53. Assmann T, Burchardt T, Becker J, Ruzicka T, Megahed M. Topical immunomodulators: a therapeutic option for oral cicatricial pemphigoid. Hautarzt. 2004;55(4):390-2.

54. Ata-Ali F, Ata-Ali J. Pemphigus vulgaris and mucous membrane pemphigoid: Update on etiopathogenesis, oral manifestations and management. J Clin Exp Dent. 2011;3(3):e246-50.

Corresponding author:
Assoc.Prof.Dr. Kraisorn Sappayatosok
College of Dental Medicine, Rangsit University,
52/347 Muang Ake, Phaholyothin Road,
A. Muang, Pathum Thani 12000 Thailand.
Tel: +662-9972000.
E-mail: kraisorn.s@rsu.ac.th

Received Date: Sep 11, 2019
Revised Date: Sep 18, 2019
Accepted Date: Nov 19, 2019