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內文：

Introduction

1. Mucous membrane pemphigoid (MMP) is a heterogeneous group of putative autoimmune subepithelial blistering diseases affecting primarily mucous membranes
2. MMP can develop autoantibodies that target epithelial basement membrane structure
3. Scarring is the clinical hallmark; however, this is not always obvious, particularly in the oral mucosa
4. The relative frequency of mucous membrane location affected is estimated to be oral > ocular > nasal > nasopharyngeal > anogenital > laryngeal > esophageal
5. It is recommended that the diagnosis of MMP should be established by both clinical morphology and a direct immunofluorescence (DIF) finding of linear deposition of IgG, IgA, or C3 at the epithelial basement membrane zone
6. In this chapter we focused on four questions about MMP:

- Does oral pemphigoid really exist as a separate entity?
- Is mucous membrane pemphigoid curable?
- What is the best therapeutic option?
- Does exclusive oral IgA dermatitis exist as a distinct entity from MMP?

Does oral pemphigoid really exist as a separate entity?

1. From a therapeutic point of view

- OP was reported to be better prognosis compared to other MMP variants
- In patients with MMP, scarring and the associated loss of function are the major complications, except patients disease restricted to the oral mucosa
- Both IL-4 and IL-13 are thought to be involved in cicatricial scarring process in MMP. Very recently, has been found a genotype that has been found in 90% of patients with OP, is associated with a reduced response to IL-4 and thus may explain a better clinical outcome for OP patients
- More amenable to medical treatments
- However, there is a paucity of long-term follow-up studies on MMP, and several case reports the difficult treatment for OP
- Because the limited number of reports , it is not possible to determine whether the exclusive oral involvement may account for a difference in the response to therapy and more research is needed

2. From a clinical presentation point of view

- Because MMP is not a single entity, it does not have a unified and predictable natural history
- MMP with exclusive oral involvement does not develop lesions in other sites
- A long-term follow-up (mean length of follow-up was 9.1 years) study of a large cohort of 70 patients with OP showed that no other mucosae or the skin was involved during the course of the disease
- Notably, a recent research suggests that patients with OP, with antibodies to

integrin alpha6 , may have a possible reduced relative risk for developing cancer compared to anti-laminin 332-positive patients

- In several long-term follow-up studies, MMP with exclusive oral involvement does not develop lesions in other sites during the course of the disease and also seems to be often associated with a good prognosis

3. From an immunological point of view

- Circulating autoantibodies (IgG and rarely IgA) can be detected in MMP
- Patients with OP often do not have circulating IgG antibodies
- OP has autoantibodies target the a 6 integrin subunit but MMP doesn't
- These data show that the IgG reactivity against a6 integrin

4. Conclusion

- It is still unclear whether patients with OP could be considered as a distinct subset of MMP
- (i) exclusive involvement of oral mucosa, rarely scarring and typically associated with a good prognosis
- (ii) specific recognition of a6 integrin subunit

Is mucous membrane pemphigoid curable?

- Theoretically, MMP, as an autoimmune disease, cannot be cured
- However, it has been shown that complete and longlasting remission without treatment can be induced

What is the best therapeutic option for MMP?

1. Introduction

- Because of the rarity of the disease clinical treatments for MMP are scarce
- MMP is highly variable and does not have a predictable natural history
- If the mucosal lesions are localized to oral cavity, topical corticosteroid and dapsone (DDS) should be the first line of medications

2. Results

- Three RCTs, all of uncertain quality, and 42 non-randomized trials on the treatment for MMP
- Some studies commented on sulfa drugs , but complete and permanent remissions were rare
- Prednisolone is also used, and generally, systemic corticosteroids were successful
- Some used cyclophosphamide(CYC), it seems particularly effective for aggressive OCP or recalcitrant MMP
- Some commented on azathioprine (AZA), was used as steroid-sparring agent and the results were usually positive
- Some trials assessed intravenous immunoglobulins (IVIg) also as a monotherapy, and the overall response rate was 100%
- Topical corticosteroids have been used in some studies, mostly are patients with OP and with apparently very positive results
- Some commented on cycline family of drugs (mainly minocycline), change drug rate is 67%
- Some use mycophenolate mofetil (MMF) efficacy with general positive results
- Two trials used rituximab (RTX) in particular recalcitrant MMP cases, and this drug showed encouraging results, but two patient die as a result of RTX treatment

3. Discussion

- The amount of evidence to determine the best treatment for this disease remains scarce

- Adverse effects (AE) are supposed to be dose related and mostly not serious at daily dose below 100 mg, but the evidences are controversial

4. Anti-inflammatories

- Cycline group of medications can rarely cause clinical remission, have little effect on ocular disease, and can cause serious and frequent adverse effects, particularly minocycline
- Sulfa drugs, particularly dapsone (DDS), have been widely employed in MMP, but still their efficacy is unclear because of the lack of good-quality RCTs

5. Corticosteroids

- Topical corticosteroids have an excellent compliance and seem effective, particularly clobetasol propionate used for OP
- The main longterm complication of systemic corticosteroids, which is osteoporosis, can be now efficiently prevented
- The overall safety and optimal dosage regimen are still an issue Immunosuppressives
- Diverse drugs such as CYC, AZA, and MMF have been proposed as systemic immunomodulatory agents for MMP
- CYC and prednisolone are more effective than the latter alone
- CYC use without corticosteroids has a rapid efficacy in refractory MMP. However, half of the patients discontinued CYC due to the AE

6. Intravenous Immunoglobulin (IVIg)

- IVIg is a blood product prepared by cold ethanol fractionation from the pooled plasma of 10 000 -20 000 donors per batch
- The use of IVIg improve clinical status and reduce systemic corticosteroids and also prevent disease progression and relapse
- IVIg is a relatively safe and well-tolerated therapy, but serious adverse effects requiring discontinuation have been reported in MMP

7. Rituximab (RTX)

- RTX is a anti-CD20 antibody that targets pre-B cells and mature B cells and has been increasingly used in blistering diseases
- It almost always in association with immunosuppressive and anti-inflammatory drugs
- Although 96% of the patients went in complete remission, major attention should focus also on the adverse effects of RTX treatment, as two patients died as a result of severe bacterial infections

8. Conclusion

- There is a lack of good-quality trials on MMP, and available recommendations are solely based on generally small patients' case series.
- Some of the 2002 consensus experts' opinions should be possibly updated
- Medicine with high-potency: topical corticosteroids, MMF, and IVIg, should be urgently examined in RCTs given the promising preliminary results

Does exclusive oral IgA dermatitis exist as a distinct entity from MMP?

1. Introduction

- Linear immunoglobulin A (IgA) bullous dermatitis(LABD) or linear IgA disease (LAD) is a unique immunobullous disease that was first recognized as an entity distinct from dermatitis herpetiformis (DH) or bullous pemphigoid (BP)
- There is also a childhood variant of LAD termed chronic bullous dermatosis of childhood (CBDC)
- Two variants: adult-onset LAD vs childhood-onset LAD

- CBDC occurs in children with a peak incidence of about 4.5 years, the lesions can appear as ‘cluster of jewels’
- LABD is a disease of adults mainly aged 60–65 years, are generally like linear or ‘sausage’ like in shape and frequently tend to form annular or polycyclic
- LAD may be diagnosed based on the following three criteria:

(i) The presence of a vesicular or bullous eruption,usually confined to the skin, but which may involve the mucous membranes;
(ii) The presence of a subepidermal vesicle with a predominantly neutrophilic infiltrate on histology of lesional skin; and
(iii) The presence of BMZ specific IgA antibody deposited in a linear pattern in the absence of other immunoglobulins on DIF of perilesional skin

2. Results

- The literature search retrieved 29 cases of suspicious predominantly mucosal LAD
- Four of the cases were diagnosed as cases of MMP
- 25 had oral lesions and 18 had exclusive oral, in most of the cases, gingival lesions
- clinical pictures provided, almost all the oral lesions had the appearances suggestive of MMP
- Main histologic features were subepithelial split and a dermal inflammatory infiltrate, but only one patient with predominance of neutrophils
- All but three cases had exclusive linear IgA staining at BMZ
- The course of the cases was mixed and not always reported but mostly with partial remission of the lesions

3. Discussion

- In 2002, an international consensus proposed that subepithelial blistering disorders with predominant mucosal involvement previously classified as LAD should be comprised under the same term of MMP
- So, perilesional mucosa and/or skin showing continuous deposits at the BMZ of IgG, IgA, or C3 or combination are diagnostic of MMP
- More importantly, almost all the published cases of oral LAD did not show any common features clinically, histologically, and/or immunologically to justify a diagnosis different from MMP
- Two of the reported patients with predominantly oral LAD had IgA or IgG against BPAg 1 and 2 and were both associated with the typical MMP HLA-DQB* 03:01 allele, supporting MMP as the final diagnosis

4. Conclusion

- We did not find any strong evidence to support an exclusive oral form of LAD as a separate entity
- We urge to investigate target antigens and typical HLA allele’s link in every case suggestive of MMP
- we would suggest that future reports follow the 2002 consensus proposal as a standard reporting method

題號	題目
1	78 歲男性，最近三個星期於軀幹及上下肢發生數個大水皰。皮膚病理檢查顯現表皮下裂解，且有嗜伊紅性細胞浸潤於真皮上層。最可能的診斷為： (A) 帶狀皰疹(herpes zoster)

	(B) 膿痂疹(impetigo) (C) 類天皰瘡(pemphigoid) (D) 天皰瘡(pemphigus)
答案(C)	出處：
題號	題目
2	Which one is wrong about benign mucous membrance ?
	(A) The cause of benign mucous membrance was unknown (B) It's frequency :women twice higher than man (C) The disease affects younger individuals (D) It is usually reported in the white population
答案(C)	出處：DD of oral and maxillofacial lesions