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Clinical Records

Mucous membrane pemphigoid: nasal and laryngeal manifestations

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Abstract
Mucous membrane pemphigoid (MMP) is a sub-epithelial blistering disease that primarily involves mucosal surfaces but may also involve the skin. Clinically, it appears as vesiculobullous lesions of the oral cavity and eyes, but other tissues such as the nasopharyngeal and laryngeal mucosa can also be affected. Ultimately, scarring and airway stenosis may occur. The condition should be managed by a multidisciplinary team led by a dermatologist. Immunosuppressive therapy forms the mainstay of treatment, with surgery having both a diagnostic role and a use in the treatment of complications such as airway obstruction. There must be a low threshold of suspicion for laryngeal involvement in this group of patients, so that prompt action can be taken. Once laryngeal stenosis has occurred repeated endoscopic laser excision of scar tissue can be used to maintain an adequate airway. Adjuvant use of mitomycin-C can be used beneficially in the treatment of laryngeal complications of MMP.

Key words: Pemphigoid, Benign Mucous Membrane; Nose; Larynx; Mitomycin

Introduction

Mucous membrane pemphigoid (MMP) is a rare, chronic disorder of mucosal tissue manifested largely by vesiculobullous lesions of the oral cavity and eyes.[1–3] Other mucous membranes including the nasal mucosa, pharynx, larynx, anus, skin, oesophagus and genitalia may also be affected. Bronchial involvement was reported by Muller *et al.*[4] in 1988.

It was first defined as a separate pathological condition by Thorst[5] in 1911 and was termed benign mucous membrane pemphigoid in 1953 by Lever.[3] In 1980, Fisher[6] was the first to describe laryngeal involvement in pemphigoid, and Drenger[7] was the first to report airway obstruction in the disease in 1986.

The condition is also commonly termed cicatricial pemphigoid. However, in 1999 the First International Consensus Meeting concluded the most appropriate title for the condition was mucous membrane pemphigoid since the scarring associated with this disease and its potential complications cannot be considered benign and the term cicatricial excludes patients without scarring.[8]

Case report

A 39-year-old woman presented with a six-month history of presumed rhinitis and recurrent mouth lesions that she described as blisters, that eroded into ulcers after about 24 hours. She also developed a sore throat that was treated with antibiotics following which she developed multiple blisters on urticated bases over the soles of her feet and her palms (Figure 1). Following a dermatology consultation, the diagnoses of acute pompholyx type eczema and bullous erythema multiforme were considered. However, skin biopsies revealed subepidermal bullae and immunopathological studies showed dermally binding IgG and C3 antibodies to the basement membrane. Further studies identified IgG antibodies to laminin 5, consistent with a diagnosis of laminin 5 mucous membrane pemphigoid, a rare subtype of mucous membrane pemphigoid. She was reviewed in the ENT outpatient department shortly after this for nasal symptoms and her nasal septum was noted to have a granulomatous appearance with the nose containing copious crusts and clots. She later developed severe adhesions causing obstruction of the nasal passages for which she required repeated division and insertion of splints.

Within a year of diagnosis the patient developed ocular involvement with conjunctivitis, an episode of broad symblepharon and some scarring of the tarsal conjunctiva. She then went on to develop mild inspiratory stridor. On investigation by direct laryngoscopy, gross granulomatous changes with mucosal blistering and sloughing of the mucosa were visualized. These lesions settled on immunosuppressive therapy (prednisolone, cyclophosphamide, minocycline, cyclosporine, dapsone, nicotinamide, topical becloforte and dermovate).

The laryngeal symptoms then remained silent for four years until the patient developed dyspnoea on exertion that progressed to inspiratory stridor. Findings on direct laryngoscopy showed cicatrisation and stenosis of the supraglottis (Figure 2). This scar tissue was divided using CO_2 laser until the vocal folds could be visualized (Figure 3). The same procedure was repeated on a two to three month basis over a year with the later addition of mitomycin-C (2 ml of 0.3 mg/ml). Currently, her laryngeal

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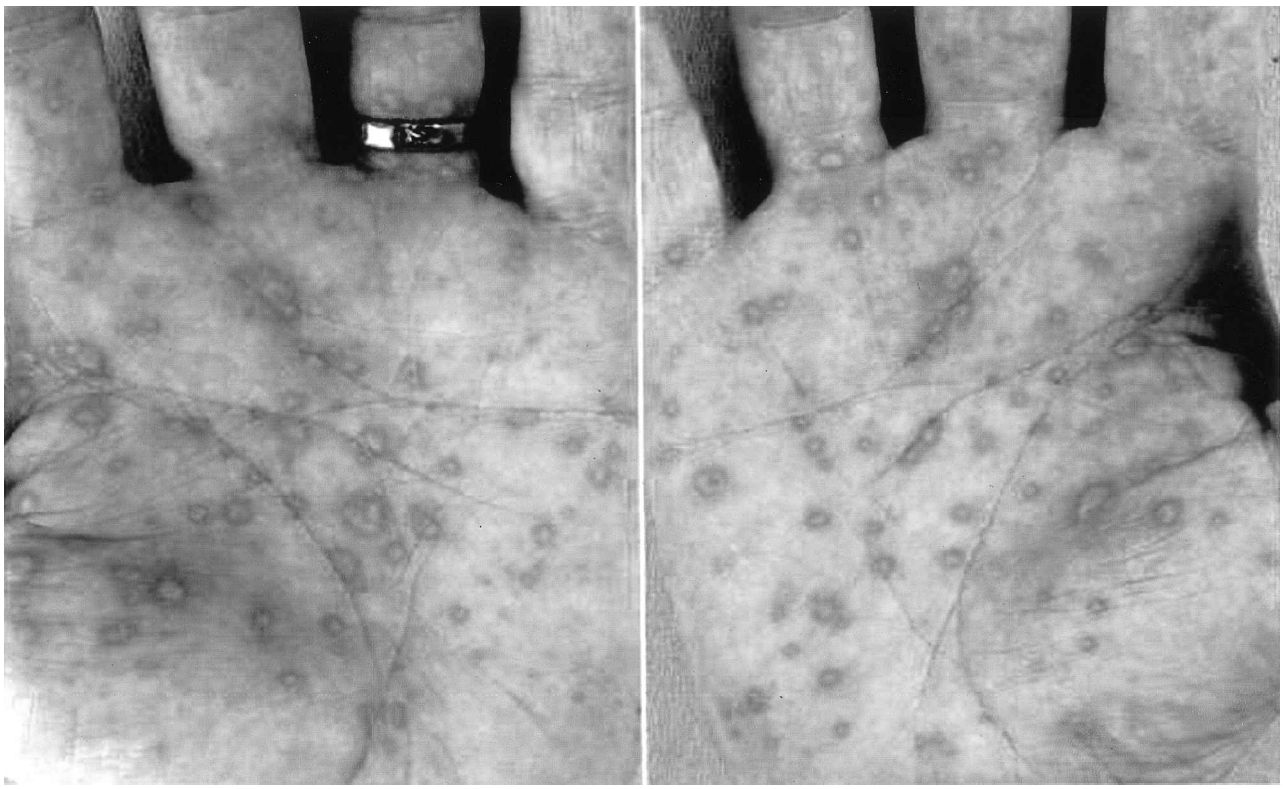

FIG. 1
Skin blisters on urticated bases affecting both palms.

symptoms are controlled with regular scar excision with CO_2 laser and application of topical mitomycin to prevent further stenosis. The nasal mucosa has improved greatly with no adhesions at present.

During the course of her disease she has developed intermittent blisters over the hands, mouth, vulva and rectum. She continues immunosuppressant therapy.

Discussion

Mucous membrane pemphigoid occurs most frequently in the sixth and seventh decades of life, although it has been reported between the third and ninth decades.[9] Although there does not appear to be a racial preponderance for the disease, females are affected twice as commonly as males.[3] HLA associations have been identified between ocular disease and HLA-DR4 and DQw7. HLA-DQB1*0301 is linked to both oral and ocular forms of MMP.[10]

Immunopathology

Immunobullous diseases are distinguished by the level at which the skin is split and by the target antigens that cause the blister formation. In bullous pemphigoid, blisters occur sub-epidermally at the level of the lamina lucida. It is felt that the blisters in MMP form below those of bullous pemphigoid and as a result are more likely to cause permanent scarring. Immunofluorescence microscopy is used to identify deposits of immunoreactants in the epithelial basement membrane. In MMP, continuous deposits of IgG and C3 at the dermoepidermal junction are seen most commonly although IgA, IgM and fibrin are detected in some patients. Perilesional skin from mucosa is the preferred biopsy site for direct immunofluorescence studies.[11,12]

Indirect immunofluorescence studies use serum from patients to detect circulating autoantibodies against basement membrane antigens. Patients with MMP may have circulating IgG and/or IgA autoantibodies. A minority of patients with MMP also have IgG class antibodies against laminin 5. These form the subtype of MMP previously called anti-epiligrin cicatricial pemphigoid. Recent consensus agreement has since termed it laminin 5 mucous membrane pemphigoid.[8,13]

Clinical findings

Mucous membrane pemphigoid differs from skin pemphigoid in its preponderance for mucosal involvement and the scarring nature of lesions. The clinical manifestations of mucous membrane pemphigoid are varied but the oral and conjunctiva mucosa are most frequently involved.

Conjunctival involvement occurs in up to 75 per cent patients. The most serious complication of this is blindness

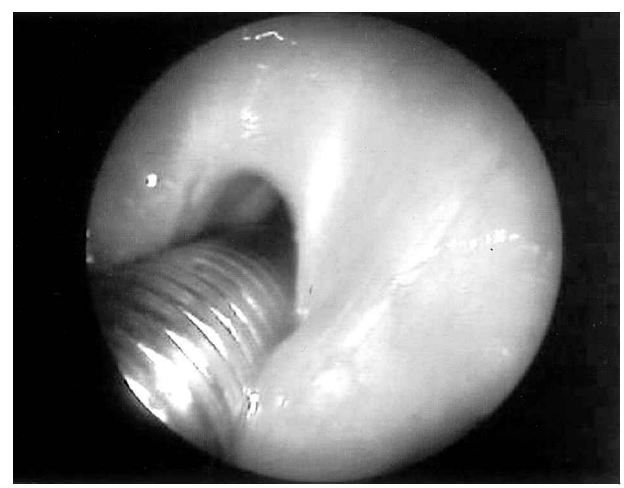

FIG. 2
Direct laryngoscopy view showing supraglottic stenosis as a result of scarring secondary to MMP.

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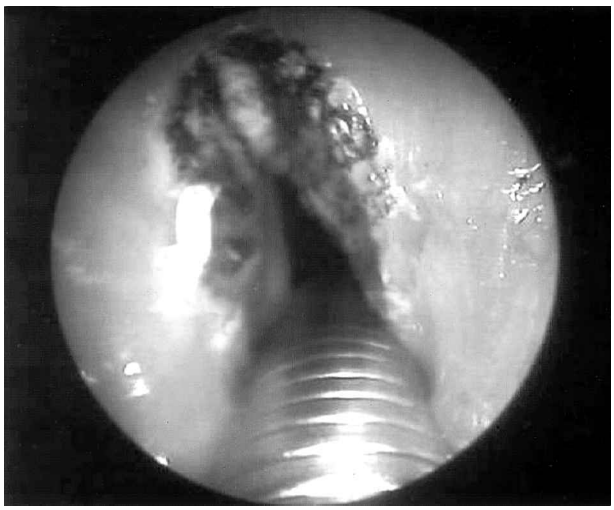

FIG. 3
The scarred tissue was divided using CO_2 laser until the vocal folds could be visualized.

in up to 20 per cent patients. The earliest indication of ocular involvement is conjunctivitis but this may be followed by the development of anhyloblepharon, whereby fibrous adhesions occur between the superior and inferior palpebral conjunctiva, and symblepharon, whereby the palpebral and bulbar conjunctiva become adhered. Gradually entropion can develop leading to corneal damage and ultimately blindness. Tear glands and ducts may also become inflamed and consequently obliterated.

Oral lesions most often occur on the gingivae, the buccal mucosa and palate. The alveolar ridge, tongue and lips may also be involved. In the mouth it commonly presents as a desquamative gingivitis that often leads to periodontal disease and loss of teeth. On other areas of the buccal mucosa, tense vesicles may erupt progressing to erosions that heal with scarring. If the frenulum is involved, ankyloglossia or limited tongue mobility can result.[13,14]

Nasal lesions tend to occur in the form of crusty ulcers on the septum or turbinates and may be associated with epistaxis or chronic serosanginous discharge. Scarring and adhesions can also occur and may result in nasal airway obstruction.

Laryngeal involvement can occur and may be life-threatening. It ends to occur in patients with concurrent disease in other areas of the upper aerodigestive tract, however, isolated laryngeal involvement has been reported sporadically.[6,7,15] Laryngeal lesions also appear in the form of erythema and oedema of the supraglottis with widespread vesicles and ulceration and later on extensive scarring of the larynx. The clinical picture of laryngeal involvement is of acute upper airway obstruction due to initial laryngeal oedema. After the acute phase has been managed successfully, provided the airway has not had to be secured with surgical intervention, there is a quiescent phase. However, there is frequently a gradual and progressive onset of upper respiratory obstruction due to extensive supraglottic scarring.

Skin lesions are seen in 25–35 per cent of patients. The most commonly affected areas are the scalp, head, neck and upper trunk. Typical lesions appear as small vesicles or bullae on erythematous or urticarial bases. These rupture easily forming crusted papules. Occasionally the skin is affected exclusively, the 'Brunsting-Perry' type pemphigoid.[10]

Ocular, genital, nasopharyngeal, oesophageal and laryngeal involvement are associated with a worse prognosis due to a higher incidence of resistance to medical therapy resulting in loss of function through scarring. Sole involvement of the oral cavity and or skin has the best prognosis.

- **Mucous membrane pemphigoid (MMP) is a sub-epithelial blistering disease which primarily involves mucosal surfaces but may also involve skin**
- **Clinically appears as vesiculo-bullous lesions of the oral cavity and eyes, but other tissue such as nasopharyngeal and laryngeal mucosa can also be affected. Ultimately scarring and airway stenosis may occur**
- **MMP should be managed by a multidisciplinary team lead by a dermatologist**
- **Immunosuppressive therapy forms the mainstay of treatment. Surgery has a diagnostic approach and can be used in the treatment of airway obstruction**

Diagnosis

Diagnosis of the condition requires a combination of clinical and immunopathological evidence and, in addition, histological evidence is desirable, although not essential. Differential diagnoses are numerous and it is not an easy diagnosis to reach. A study by Laskaris *et al.*[16] revealed that an average time of 13.2 months elapsed between the onset of symptoms and the diagnosis being made.

The differential diagnosis must include pemphigus, erythema multiforme, lichen planus, Stevens-Johnson syndrome, bullous pemphigoid, desquamative gingivitis, dermatitis herpetiformis, lupus erythematosus, epidermolysis bullosa, toxic epidermal necrolysis and bullous amyloidosis. Wegener's granulomatosis and Bechet's may also be difficult to distinguish from MMP. Other acute blistering diseases including herpes simplex and zoster, herpangina, varicella and tend to be more easily distinguished.

Histopathological examination of oral lesions reveals non-specific subepithelial vesicles with a chronic inflammatory infiltrate. Epithelium is clearly separated from the underlying connective tissue but remains intact until the later stages of the bullae. The upper corium is infiltrated with plasma cells, histiocytes and lymphocytes. The inflammatory reaction is less pronounced in deeper tissue. The fact that acantholysis is never seen in MMP lesions is a feature that distinguishes it from pemphigus.

Bullous pemphigoid is known to have an association with carcinoma of the rectum and uterus.[17] There is evidence to suggest that, like bullous pemphigoid, MMP is also a marker of malignancy[18] since severe mucosal subepidermal bullae have been associated with bronchial carcinoma by Gold.[19] Chadfield and Kanagaundarum[20] reported basal cell carcinoma and melanoma occurring in MMP and Foster and Nally also described the occurrence of melanoma in MMP. Palatal carcinoma has been reported in an area of mucosa affected by MMP.[21] Other studies have found that the incidence of cancer in MMP patients is no greater than that of the normal population.[22]

Treatment

Both local and systemic measures may be utilized in order to achieve symptomatic control and delay disease progression but since the aetiology of MMP is unknown, treatment is not specific or curative and no large, controlled studies have evaluated it. A multi-disciplinary approach is vital if the patient has multi-focal disease in order to delay progression and treat any complications promptly.

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According to the 1999 consensus report,[8] patients may be divided, according to their likelihood of developing disabling or life-threatening complications, into high-risk and low-risk.

The decision to immunosuppress a patient is dependent upon the severity of the condition and requires careful consideration owing to the many undesirable and potentially serious side-effects with which it is associated. However, those patients with ocular, genital, nasopharyngeal, oseophageal or laryngeal involvement or those with severe or rapidly progressing disease should be considered to be at high-risk of complications of the disease. Initial therapy with dapsone is appropriate. If this fails, or as an alternative, prednisolone and cyclophosphamide or azathioprine may be used, with appropriate monitoring. Prednisolone may later be reduced as symptoms abate.

Low-risk patients are those with oral and or skin involvement and topical treatment with corticosteroids is recommended as first line management by the consensus report. This has only been moderately useful in the oral cavity unless applied beneath a denture that allows prolonged tissue contact.[23,24]

Tetracycline and nicotinamide have also been used with some success.[25,26] Intravenous immunoglobulin has also been used as a treatment for resistant ocular disease.[27] Since maintenance of a balanced diet is also important in the condition, topical anaesthetic agents may be useful for painful oral lesions.

Repeated endoscopy with dilatation may be indicated in patients with oesophageal stricture in order to enable adequate oral intake.

Surgery may form a critical aspect of treatment where there is laryngeal involvement. Tracheostomy may be a life-saving procedure in order to stabilize the airway whilst the appropriate therapy can be undertaken. Supraglottic scarring is treated effectively with the carbon dioxide laser. Whilst excision in the acute period is not recommended,[5] repeated division of laryngeal scar tissue may be necessary to stabilize the airway. Use of adjuvant mitomycin seems to reduce the severity of stenosis and lengthen the symptom-free interval.[28–30]

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