Treatment strategies in mucous membrane pemphigoid

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Abstract: Mucous membrane pemphigoid (MMP) is an autoimmune blistering disorder that is characterized by subepithelial bullae. Various basement membrane zone components have been identified as targets of autoantibodies in MMP. Considerable variability exists in the clinical presentation of MMP. Mucous membranes that may be involved include the oral cavity, conjunctiva, nasopharynx, larynx, esophagus, genitourinary tract, and anus. A multidisciplinary approach is essential in the management of MMP. Early recognition of this disorder and treatment may decrease disease-related complications. The choice of agents for treatment of MMP is based upon the sites of involvement, clinical severity, and disease progression. For more severe disease, or with rapid progression, systemic corticosteroids are the agents of choice for initial treatment, combined with steroid-sparing agents for long-term maintenance. Due to the rarity of this disease, large controlled studies comparing the efficacy of various agents are lacking.

Keywords: mucous membrane pemphigoid, cicatricial pemphigoid

Clinical findings and diagnosis

Mucous membrane pemphigoid (MMP) is an autoimmune blistering disorder of mucous membranes that is characterized by subepithelial bullae (Chan et al 2002; Egan et al 2003; Thorne et al 2004). Mucous membranes that may be involved include the oral cavity, conjunctiva, nasopharynx, larynx, esophagus, genitourinary tract, and anus. The oral mucosa is most commonly involved, followed by the conjunctiva (Thorne et al 2004). The skin is involved in approximately one-quarter of patients (Ahmed and Hombal 1986), often limited to the head, neck, and upper torso regions (Figure 1).

Various basement membrane zone components have been identified as targets of autoantibodies in MMP. These include bullous pemphigoid antigen 1 (BPAg1, 230 kd) (Bernard et al 1990), bullous pemphigoid antigen 2 (BPAg2, 180 kd) (Balding et al 1996), laminin 5 (Domloge-Hultsch et al 1994), laminin 6 (Chan et al 1997), α_6-integrin subunit (Rashid et al 2006b), β_4-integrin subunit (Tyagi et al 1996), collagen VII (Luke et al 1999; Wieme et al 1999), and other proteins of unknown identity and/or function (Ghohestani et al 1996; Sarret et al 1989). There is no definitive evidence linking specific disease phenotypes with particular target antigens. However, a recent study found that sera of patients with cicatricial ocular disease and generalized MMP contained antibodies to β_4-integrin, and sera of those with oral MMP contained antibodies to α_6-integrin (Rashid et al 2006a). These patients maintained selectivity to the target antigen throughout their clinical course.

Diagnosis of MMP rests mainly upon the clinical findings and immunofluorescence studies. Histopathologic examination reveals a subepithelial blister with a variable inflammatory cell infiltrate. Direct immunofluorescence of perilesional mucosa or skin is essential for diagnosis, and reveals linear deposition of IgG, C3, or less commonly IgA along the basement membrane zone (Fine et al 1984; Leonard et al 1988; Rogers et al 1977). The use of salt split skin or mucosal epithelium for indirect

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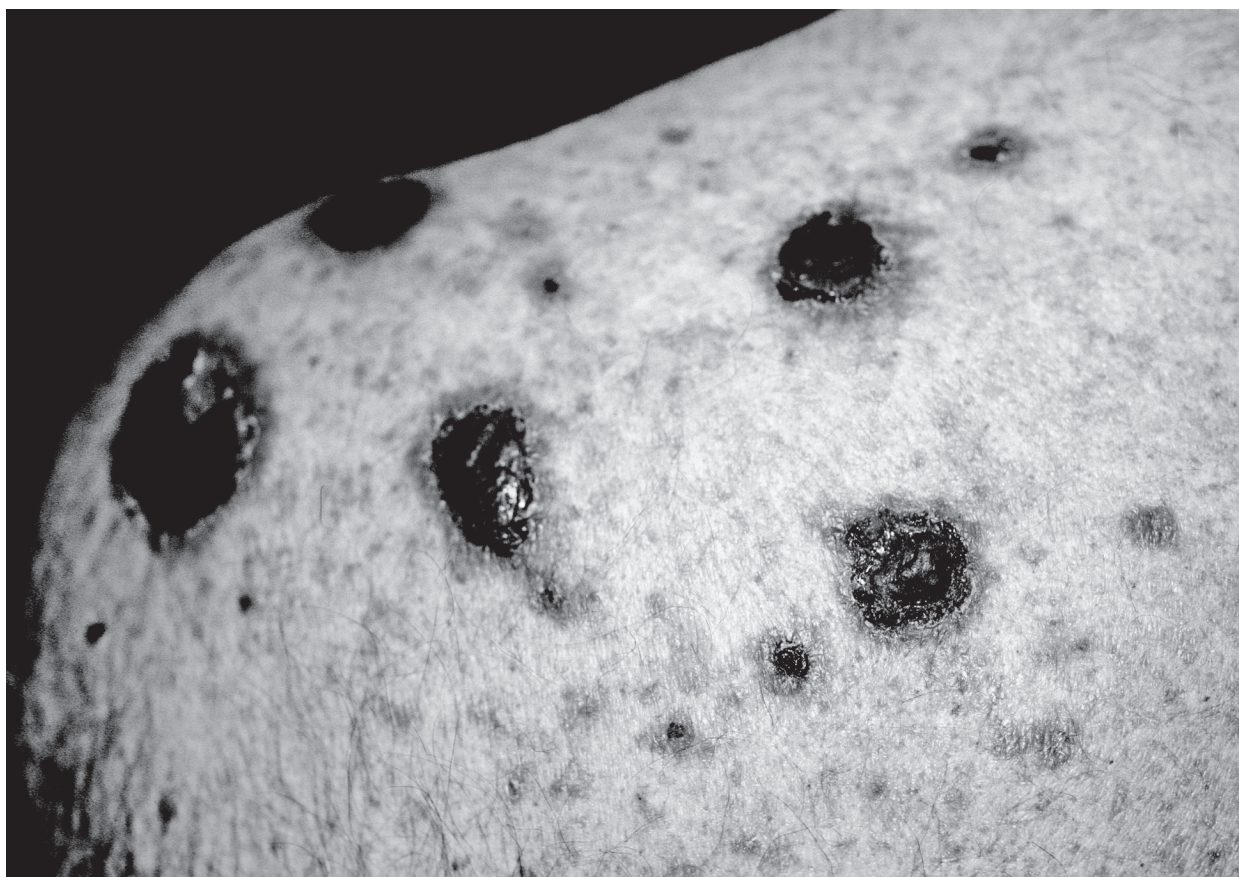Fax +1 513 558 0198
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Figure 1 Vesicles and erosions on the trunk.

immunofluorescence studies may increase the sensitivity of this technique. Indirect immunofluorescence utilizing salt split skin may reveal binding to the roof and/or floor depending upon the antigen targeted (Ghohestani et al 1997; Kelly and Wojnarowska 1988).

Considerable variability exists in the clinical presentation of MMP. Patients may present with only one mucosal or skin site involved, or any combination of sites. Manifestations of oral disease, the most common site of involvement, include vesicles, erosions, desquamative gingivitis, and occasional scarring (Figure 2). Scarring is common at nonoral sites of involvement, contributing to disease-related morbidity.

Ocular complications of MMP result from conjunctival erosions with subsequent scarring and progressive cicatrization with foreshortening of the fornices (Elder et al 1996). The palpebral conjunctiva lining the lids may fuse with the bulbar conjunctiva, resulting in symblepharon or scar bands between the lid and globe (Figure 3). The scarring of the conjunctiva also results in loss of goblet cells with subsequent dry eye and disruption of the corneal epithelium (Ralph 1975).

Eyelid malposition is also a common occurrence, with entropion or inward turning of the lid margin resulting from the scarring process of the conjunctiva (Faraj and Hoang-Xuan 2001; Shiu and McNab 2005) (Figure 4). This results in inadequate ocular surface protection and abrasion of the ocular surface by misdirected eyelashes, further compromising the corneal integrity and contributing to corneal scarring and neovascularization. Blindness and even loss of the globe due to perforation and endophthalmitis may occur (Messmer et al 2000; Nouri et al 2001).

Anogenital involvement presents with blisters and erosions that may result in scarring. Severe vulvar scarring and phimosis have been reported (Frith et al 1991; Fueston et al 2002; Goldstein et al 2005). Life-threatening complications may result from involvement of the larynx, esophagus, and rarely the lower airway (Muller and Salzer 1988; Anstey et al 1991; Alexandre et al 2006; Gamm et al 2006).

Management

A multidisciplinary approach is essential in the management of MMP. Early recognition and treatment may decrease disease-related complications. In a patient who presents with involvement of one site, a thorough review of symptoms highlighting other potential areas of involvement should

Figure 2 Gingival erosions.

be obtained. The choice of agents for treatment of MMP is based upon the sites of involvement, clinical severity, and disease progression.

Unfortunately, large randomized controlled trials comparing the efficacy of various agents in the treatment of MMP are lacking in the literature, but there is general consensus on the guidelines of treatment based on clinical experience. The First International Consensus on MMP recommended dividing patients into "low-risk" and "high-risk" groups based upon the site(s) of involvement, with "low-risk" patients defined as having only oral mucosal or oral and skin involvement (Chan et al 2002). "High-risk" patients were defined as having involvement of the ocular, genital, nasopharyngeal, esophageal, and/or laryngeal mucosae, and require more aggressive treatment.

Mild disease

For mild disease without rapid progression, dapsone may be initiated at 25 to 50 mg per day, increasing monthly by 25 to 50 mg until clinical remission is achieved or until the maximum tolerated dose is reached (usually 200 mg per day). Successful use of this agent has been reported in patients with moderate to severe oral disease, and ocular disease as well (Ciarrocca and Greenberg 1999; Miserocchi et al 2002).

Failure to develop marked improvement within approximately 3 months should prompt consideration of another agent such as azathioprine, methotrexate, or cyclophosphamide if the disease is affecting a high-risk site such as the ocular surface.

Appropriate pretreatment laboratory studies must be performed, including a glucose-6-phosphate dehydrogenase level due to the risk of hemolysis. Monitoring during therapy is required to assess for adverse effects including dose-related hemolytic anemia and methemoglobinemia, and other idiosyncratic side effects such as agranulocytosis and hepatitis (Raizman et al 1994; Miserocchi et al 2002; Wertheim et al 2006). Fatal hypersensitivity syndrome has been reported with the use of dapsone in other disease settings (Agrawal and Agarwalla 2005; Kosseifi et al 2006).

Severe disease
Systemic therapy
Corticosteroids

For more severe disease, or with rapid progression, systemic corticosteroids are the agents of choice for initial treatment, combined with steroid-sparing agents for long-term maintenance. Prednisone is usually given at a dose of 1–1.5 mg/kg/day, with appropriate monitoring for side effects.

Figure 3 Conjunctival inflammation and symblepharon.

Therapy with prednisone lasts several months. Accordingly, calcium and vitamin D supplementation, along with bisphosphonate therapy and baseline dual energy X-ray absorptiometry (DEXA) scanning, should be considered. Once patients achieve and maintain clinical remission, the steroid dose is decreased gradually. Generally, the adjuvant immunosuppressive drug is continued for approximately two years.

Cyclophosphamide

Cyclophosphamide has been the traditional steroid-sparing agent of choice for patients with severe disease or rapid progression. It is started in conjunction with systemic steroids (Brody and Pirozzi 1977; Elder et al 1995). Cyclophosphamide is an alkylating agent that suppresses B cell function greater than T cell function, and has significant potential adverse effects such as bone marrow suppression, carcinogenesis, and teratogenicity (Baker et al 1987). Dosage usually ranges between 1 to 2.5 mg/kg/day or 50 to 200 mg per day when administered orally, and between 0.5 to 1 g/m^2 when given as monthly intravenous (IV) pulse therapy (Pandya et al 1997). IV infusion given as a three day pulse can be particularly helpful when rapid control is needed, for instance prior to ocular surface surgery (Yesudian et al 2005).

There is evidence that cyclophosphamide is more effective than dapsone in controlling disease (Kirtschig et al 2002), but large controlled studies are lacking. Awareness of the potential adverse effects of cyclophosphamide is critical to allow appropriate monitoring during therapy.

Several other steroid-sparing agents have been used in the treatment of MMP. For patients with mild disease that fail or are intolerant of dapsone, or for those with more severe disease that are not candidates for therapy with cyclophosphamide, azathioprine and methotrexate are potential alternative agents (Dave and Vickers 1974; Mondino and Brown 1983; McCluskey et al 2004). Recent reports have also noted the successful use of mycophenolate mofetil in the treatment of MMP (Megahed et al 2001; Thorne et al 2005; Salzano et al 2006).

Azathioprine

Azathioprine undergoes conversion to 6-thioguanine by the enzyme hypoxanthine-guanine phosphoribosyltransferase. 6-thioguanine is an active purine analog that is incorporated into DNA and RNA with subsequent inhibition of purine metabolism and cell division. The exact mechanism of immunosuppression is not known. Dosage ranges from
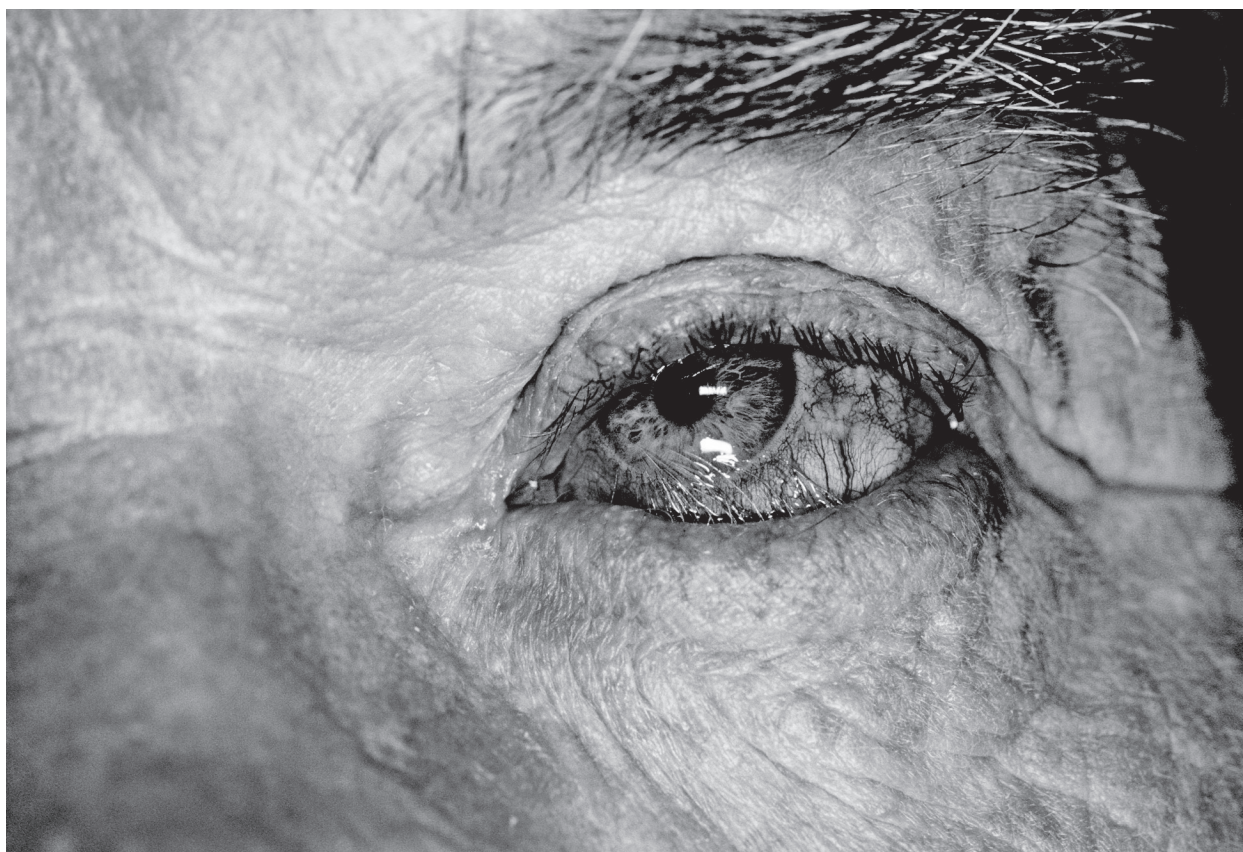
Figure 4 Conjunctival scarring has resulted in lower eyelid entropion.

1–4 mg/kg/day depending upon the patient's thiopurine methyltransferase level. Azathioprine has been used effectively in the treatment of autoimmune bullous diseases, including MMP (Dave and Vickers 1974; Tauber et al 1991). Bialasiewicz and colleagues (1994) reported the successful use of azathioprine in 9 patients undergoing nasal mucosal grafting to the ocular surface. Miserocchi and colleagues (2002) noted 32 instances of treatment-related side effects in 23 patients treated with azathioprine.

Knowledge of the potential adverse reactions and appropriate monitoring are essential for the successful use of this agent. Serious adverse effects include leukopenia, pancytopenia, infection, malignancy and drug-induced hypersensitivity syndrome. The most common side effects are nausea, vomiting, and diarrhea, which may be improved by decreasing the dose, taking the medication with food, or giving divided doses. Appropriate monitoring includes periodic complete blood count and liver function testing.

Methotrexate

Methotrexate is an antimetabolite that irreversibly binds to dihydrofolate reductase. This prevents the conversion of dihydrofolate to tetrahydrofolate, a cofactor necessary for the synthesis of nucleotides needed in DNA and RNA synthesis. Immunosuppression results from inhibition of DNA synthesis in immunocompetent cells. McCluskey and colleagues (2004) reported on their use of methotrexate as a solo agent in the treatment of ocular MMP and drug-induced ocular MMP in 17 patients. Dosage ranged from 5 to 25 mg given as a weekly dose. Mean duration of therapy was 15 months, ranging from 8–22 months. Control of ocular inflammation was achieved in 89% of patients with MMP and 100% of patients with drug-induced MMP. In a review of treatment-related side effects in 61 patients with MMP, Miserocchi and colleagues (2002) reported that methotrexate had the least number of adverse effects compared to azathioprine, cyclophosphamide, and dapsone.

Serious adverse effects may occur with methotrexate therapy. These include hepatotoxicity (liver fibrosis and cirrhosis), idiosyncratic acute pneumonitis, pulmonary fibrosis, pancytopenia, and malignancy. Gastrointestinal complaints such as nausea and anorexia are the most common side effects, frequently reduced by daily folic acid supplementation. Periodic laboratory monitoring includes complete blood

count, renal panel, and liver function testing. Consideration should be given for liver biopsy after a cumulative dose of 1.5 grams, or sooner based on concomitant risk factors (such as prior hepatic disease, alcohol or intravenous drug abuse) and comorbidities (such as diabetes and obesity).

Mycophenolate mofetil

Mycophenolate mofetil inhibits the enzyme inosine monophosphate dehydrogenase, blocking de novo purine synthesis. This results in inhibition of the proliferative response of B and T cells. Dosage usually ranges from 1000 to 2000 mg per day, but higher dosages may be required. Zurdel and colleagues (2001) reported the successful treatment of MMP in 9 of 10 eyes in 5 patients. Patients received 2000 mg daily and were followed for at least 1 year. Gastrointestinal complaints were the most common side effect, but the drug is generally well-tolerated. Ingen-Housz-Oro and colleagues (2005) reported on their experience in treating 14 patients with mycophenolate mofetil after dapsone failed to control disease. Patients received 1500 to 2000 mg daily in conjunction with dapsone. 10 of 14 patients achieved control of their disease, and 7 of these patients were able to decrease the dose of dapsone. Mycophenolate mofetil was ineffective in 4 of the 14 patients. More studies are needed to assess the efficacy of mycophenolate mofetil in the treatment of MMP.

Mycophenolate mofetil is usually well tolerated. Nausea, anorexia, and diarrhea may occur, and appear to be dose-related. Laboratory monitoring includes periodic complete blood count due to possible medication-induced leukopenia.

Intravenous immunoglobulin

Occasionally, 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) offers a therapeutic alternative. Over the last decade, there has been increased use of IVIG in the treatment of autoimmune and inflammatory skin diseases. Multiple different theories have been proposed to explain the mechanisms of action of IVIG. These include blockage of Fc receptors, alteration of cytokine production, cytokine antagonism, inhibition of complement-mediated damage, and neutralization of circulating autoantibodies (Andersson et al 1996; Jolles et al 1998). The successful use of IVIG in the treatment of MMP was initially reported in two patients (Urcelay et al 1997). Foster and Ahmed (1999) later reported on their experience in ten patients. Four to twelve cycles were required to achieve complete quiescence of conjunctival inflammation.

In long-term follow-up of these patients, the length of therapy ranged from 25–43 months (Sami et al 2004). Eight of the ten patients finished their study protocol, and all maintained remission after gradual withdrawal of IVIG therapy.

In a nonrandomized trial of 16 patients comparing the use of IVIG with conventional immunosuppression, IVIG was found to be more effective and safer than conventional therapy (Letko et al 2004). Studies evaluating the cost of IVIG therapy versus conventional therapy, both annually and over the total disease course, have suggested IVIG to be more cost-efficient than conventional immunosuppressive therapy (Daoud et al 2005; Daoud and Amin 2006). This was mainly attributed to the cost of treatment-related adverse effects in those given conventional immunosuppressive therapy. These findings have not been confirmed by other authors.

IVIG dosage ranges from 2 to 3 g/kg/cycle, usually infused in divided doses over 3 to 5 days. The frequency of infusion varies from every 3 to 4 weeks initially, until disease activity subsides. The interval between cycles is then gradually increased as long as clinical remission is maintained. The endpoint of therapy has been suggested as a sustained clinical remission with two cycles 16 weeks apart (Sami et al 2004).

The most common adverse reaction related to IVIG use is an infusion reaction, and symptoms may include flushing, headache, chills, nausea, tachycardia, hypotension, and wheezing. The infusion should be slowed or discontinued based on the severity of the reaction. Premedication with an antihistamine and acetaminophen or intravenous steroid may be helpful in patients with a previous infusion reaction. Other rare adverse effects include anaphylaxis, disseminated intravascular coagulation, thrombosis, and acute renal failure. Pre-treatment screening labs may include complete blood count, renal panel, liver function tests, hepatitis panel, HIV testing, IgA level, rheumatoid factor, and cryoglobulins. Periodic assessment of complete blood count, renal and liver panels, and HIV and hepatitis screening should be considered.

Other treatment

Successful treatment with other relatively new agents has recently been reported. Antitumor necrosis factor α agents, such as etanercept and infliximab, have been reported to be efficacious in the treatment of recalcitrant MMP (Sacher et al 2002; Canizares et al 2006; Heffernan and Bentley 2006). Daclizumab, an interleukin-2 receptor antagonist, was studied in a retrospective nonrandomized case series for the treatment of ocular inflammatory diseases. This study included the successful treatment of one patient with recalcitrant MMP

using daclizumab monotherapy (Papaliodis et al 2003). The anti-CD20 agent rituximab has been successfully utilized in the treatment of pemphigus vulgaris (El Tal et al 2006) and bullous pemphigoid (Szabolcs et al 2002), and may be a useful agent for treatment-resistant MMP. Further studies are needed to assess the efficacy of these newer agents.

After discontinuation of systemic therapies, continued monitoring for disease activity is extremely important. Neumann and colleagues (1991) reported on their experience with 104 patients with MMP, noting that 22% of patients eventually relapsed after discontinuation of therapy. Patients also need to be monitored long-term for onset of disease at sites other than their initial areas of involvement (Thorne et al 2004; Higgins et al 2006).

Topical therapy

Oral disease
Topical treatments are often used as adjunctive therapy in the treatment of MMP, and occasionally as monotherapy in patients with limited oral disease. Successful treatment of oral lesions has been reported with the use of topical steroids, tacrolimus, and cyclosporine (Aufdemorte et al 1985; Eisen et al 1990; Lozada-Nur et al 1991; Hall et al 2003; Assman et al 2004; Suresh et al 2006). Topical therapy of MMP involving the oral mucosa can be augmented with specialized application devices and administration at bedtime when oral secretions are relatively low.

Ocular disease
Although topical therapy alone has been successful in treating limited oral involvement, topical medications are used only as an adjunctive measure with systemic therapy in the treatment of ocular disease. Topical and subconjunctival corticosteroids may offer palliation of symptoms, but are ineffective in halting disease progression (Foster 1986).

Experience in treating ocular disease with topical formulations of the calcineurin inhibitors, cyclosporin A and tacrolimus, has been reported. Holland and colleagues (1993) noted lack of a therapeutic response to topical cyclosporine in a small series of patients. Hall and colleagues (2003), and more recently Michel and Gain (2006), reported successful use of topical tacrolimus in the treatment of one patient with MMP. Interestingly, systemic tacrolimus has not been found to be efficacious in controlling MMP (Letko et al 2001).

Mitomycin C is an alkylating agent that has been shown to inhibit DNA synthesis and fibroblast proliferation. Both topical and subconjunctival applications of mitomycin C have been described in the treatment of advanced ocular disease in MMP.

Secchi and Tognon (1996) treated ten eyes of five patients with intraoperative topical mitomycin C after surgical lysis of conjunctival synechiae. After 12–19 months of follow-up, no recurrences were noted. Donnenfeld and colleagues (1999) described the use of subconjunctival mitomycin C injection in the more severely affected eye of 9 patients with severe ocular MMP. After 12–40 months of follow-up, treated eyes showed less conjunctival erythema and shrinkage compared with the untreated control eyes. In contrast, Celis Sanchez and colleagues (2002) found no benefit of subconjunctival mitomycin C in preventing disease progression in 4 patients with severe ocular MMP.

Prevention of scarring and complications
Prevention of scarring and cicatrization is of utmost importance in the treatment of MMP, as surgical correction can be difficult and fraught with complications. Therefore, control of disease progression by halting inflammation is paramount. Patients should be followed by the appropriate subspecialists based upon the systems involved.

Oral care
Oral care includes appropriate dental hygiene, referral for dental care, monitoring for candidiasis, and topical anesthetics for pain. Soft, bland foods may cause less injury to eroded mucosa when disease is flaring. Fortunately, oral disease does not commonly result in functionally significant scarring.

Eye care
Eye care should be provided by an ophthalmologist as disease progression may be subtle. Ocular lubricants such as nonpreserved artificial tears, ointment, and gels are useful in improving surface lubrication. Placement of punctal plugs or punctal occlusion by cautery or surgery decreases tear drainage through the lacrimal drainage system. This can be helpful in increasing the tear lake, and increasing the retention of topically applied lubricants. Topical steroids may be used as adjunctive treatment, but should be dispensed and monitored by an ophthalmologist due to the risks of infection, increased intraocular pressure, and cataract. Squamous metaplasia with keratinization of the conjunctiva may be treated with topical retinoids formulated or compounded for use on the ocular surface.

Concomitant blepharitis should be recognized and treated appropriately. Classically divided into anterior and posterior varieties, blepharitis is an inflammation of the eyelids with bacterial colonization centered on the eyelashes and associated follicles or meibomian glands, respectively.

Blepharitis can contribute to eyelid scarring with trichiasis, and cause conjunctival and corneal inflammation as well. Treatment consists of daily or twice daily warm compresses, followed by eyelid scrubs with diluted baby shampoo. Nightly application of a topical antibiotic ointment such as erythromycin or bacitracin is also helpful. For significant conjunctival or corneal inflammation, topical steroids in combination with an antibiotic are useful. For significant meibomian gland disease with inspissation and inflammation, oral tetracycline or doxycycline is often used.

Significant ocular scarring from MMP resulting in functional impairment may be amenable to surgical correction. However, repair should not be attempted until the disease is in remission. Premature interventions are likely to fail as surgical manipulation can cause flaring of disease.

Entropion with secondary trichiasis may be treated with cryotherapy, marginal rotation of the eyelid, or lid splitting with repositioning of the lash-bearing portion of the lid margin (Elder and Bernauer 1994; Elder and Collin 1996). Surgical reconstruction of the fornices may be accomplished with mucous membrane grafting or amniotic membrane grafting, possibly augmented with topical or subconjunctival mitomycin (Shore et al 1992; Barabino and Rolando 2003; Barabino et al 2003; Tseng et al 2005; Yesudian et al 2005).

Microbial keratitis may occur due to a combination of factors including ocular surface disease, dry eye, corneal exposure, and corneal anesthesia. Prompt culture and institution of broad spectrum topical antibiotics are essential for prevention of corneal perforation and subsequent endophthalmitis. Corneal perforation may also occur due to dry eye, particularly in combination with ocular surface inflammation, and also requires immediate intervention. Treatment options include procedures such as suturing, cyanoacrylate glue with bandage contact lens placement, and corneal grafting.

Corneal transplant can restore the clarity of the visual axis scarred from MMP, but stem cell deficiency, dry eye, lid malposition, and conjunctival inflammation can contribute to graft failure or rejection (Tugal-Tutkun et al 1995; Tsubota et al 1996). Limbal stem cell deficiency may be addressed with limbal stem cell grafting prior to corneal transplant to increase the success of the corneal graft. Placement of a keratoprosthesis or osteo-odonto-keratoprosthesis also offers an alternative for patients with severe visual disability due to end-stage scarring (Falcinelli et al 2005; Hollick et al 2006).

Upper aerodigestive system

Upper aerodigestive complications of disease include atrophic rhinitis, crusting, erosions, synechiae, stenoses, and potentially life-threatening laryngeal stenosis (Alexandre et al 2006). Treatment of the nasal manifestations may include local steroids and irrigation. Patients should be questioned regarding any nose and throat symptoms and referred for otolaryngology consultation (Whiteside et al 2003). Dysphagia due to esophageal strictures may occasionally occur and can be treated with esophageal dilation (Isolauri and Airo 1989; Syn and Ahmed 2004).

Summary

The diagnosis of MMP remains a challenge as patients may present to a variety of specialists, depending upon their initial symptomatology, and due to the diverse clinical manifestations. Maintaining a level of suspicion for the diagnosis is crucial for early recognition and treatment. Due to the relative rarity of this disorder, large, randomized controlled trials comparing the efficacy of various therapeutic agents are lacking. Therapy is guided by each individual patient's disease course and comorbid risk factors. A multidisciplinary approach aids in choosing the appropriate therapy, and improves patient outcomes.

Disclosure

The authors report no conflicts of interest.

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