Mini Review

Mucous Membrane Pemphigoid: A Review

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Abstract

Mucous membrane pemphigoid (MMP) belongs to the group of subepidermal blistering diseases and refers to a subgroup characterized by predominant mucosal involvement. Various target antigens are involved within the basement membrane zone.

INTRODUCTION

Mucous membrane pemphigoid (MMP) belongs to the group of sub epidermal blistering diseases and refers to a subgroup characterized by predominant mucosal involvement. Various target antigens are involved within the basement membrane zone. The average annual incidence is estimated to be 1/500,000 to 1/770,000 in western countries and is regularly increasing. A slight male predominance is reported. In most cases, the treatment is based on anti-inflammatory drugs (corticosteroids, dapsone or sulfasalazin) in association to immunosuppressants (ciclophosphamid, mycophenolatemofetil (MMF)). Rituximab and etanercept have also been proposed for resistant MMP but need further evaluations [1,2]. MMF is theoretically a treatment of choice due to its good long term tolerance and efficacy especially in the elderly patients.

CLINICAL DESCRIPTION

The average age of onset is 60-70 years. The median age at diagnosis in our center is 78 years. The average time for diagnosis is 28 months [1].

The disease is rare in children. Mucous membrane pemphigoid is a chronic disease with periods of more rapid evolution. The disease manifests as fragile bullous lesions that give way to superficial erosions. The principle sites affected are the oral (80-90% of cases), ocular (50-70% of cases), pharyngolaryngeal (8-20% of cases), genital (15% of cases) and esophageal mucous membranes. Some forms affect only one mucosal membrane, in particular the buccal (erosive gingivitis) or ocular mucosa. An exclusively cutaneous form has also been observed in some cases. The ocular manifestations are initially inflammatory but then lead to retractile scarring of the conjunctive membrane, associated with corneal metaplasia resulting in vision loss.

PHYSIOPATHOLOGY AND DIAGNOSTIC TOOLS

The main antigens are the C term portion of collagen 17 and laminin 332. Whilst the etiology is unknown, several different antigens are implicated in the autoantibody response including BPAg1, BPAg2, integrin subunits alpha-6/beta-4, laminin 5 and 6, and type VII collagen.

Immunological Studies Reveal the presence of auto-antibodies against several antigens such as PB180, the alpha Laminin-5 subunit and the beta subunit of the integrin alpha-6 beta-4 complex. Histologically, the cutaneous or mucosal blisters are subepithelial, without evidence of acantholysis, and are indistinguishable from those of bullous pemphigoid. Diagnosis can be confirmed by direct (DIF) or indirect immunofluorescence analysis. Electronmicroscopy can differentiate bullous from cicatricial pemphigoid by the precise location of immune deposits along the basement membrane. Immune deposits in MMP are located deeper than in bullous pemphigoid where they are restricted to the hemidesmosomal area [2].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes the full range of autoimmune bullous disorders. Pemphigus vulgaris is differentiated by the DIF pattern with a labelling of the intercellular substance. Bullous pemphigoid is characterized by a predominant cutaneous involvement. Epidermolysis bullosa acquisita is a difficult to differentiate and relies on ELISA (enzyme-linked immunosorbent assay) anti collagen VII, a different localization of immune deposits along the basement membrane as imaged by immunoelectron microscopy, or DIF on salt separated skin. Oral erosive lichen planus and recurrent aphthous do not show any immune deposits on DIF.

MANAGEMENT AND TREATMENT

Management should be multidisciplinary with close follow-up in specialized center, in particular for the management of the ocular manifestations. The choice of therapeutic strategy (anti-inflammatory drugs, immunosuppressive therapy, intravenous immunoglobin or local treatments) depends in the severity of the ocular disease.

Dapsone is the reference treatment for MMP with response rates of 50 to 80% in monotherapy [3] (Rogers 1988). The oral and inflammatory subtypes of MMP are the best responder to dap-
There are 10–25% of adverse events and agranulocytosis can occur (1/400 at the beginning of treatment) for sulfasalazine or ciclosporines as alternative options in patients intolerant to dapsone.

Mycophenolate mofetil (MMF) is an inhibitor of purine synthesis and targets B and T lymphocytes. MMF can be considered as the reference immunosuppressive drugs for the management of MMP and related disorders. MMF is more efficient than ciclosporine and less toxic than cyclophosphamide. MMP score improvement ranges from 60 to 85% for inflammation and ocular pain. A control of the disease can be obtained for up to 80% of patients [5–7].

The optimization of MMF dose is efficient for refractory patients we have recently demonstrated in 8 patients with 15 adjustments that the median AUC before Treatment was 36 mg.h/l whereas the therapeutic objective was 45–50 mg.h/l. In most patients the adjustment has led to a better control of the disease (unpublished results).

Rituximab has been proposed for patients with refractory MMP. Most patients are now treated with the autoimmune regimen two cycles of 1000mg Two weeks apart. The clinical benefit of the treatment occurs within 12 weeks with 86% of control of the disease [8]. Long term remissions seems more questionable and it seems that a maintenance treatment is necessary in decrease of 40% the relapse risk. Oesophageal involvement should be carefully monitored in patients with severe oral involvement and can be found in 10 to 40% of MMP patients whereas they present with clinical symptoms or not [9].

Ocular inflammation leading to corneal involvement with symblepharon and corneal opacification with a progressive risk of blindness is one of the major goals for the treatment of ocular MMP. Many studies have demonstrated that MMF allowed good control of ocular inflammation in 60 to 70% of patients. We have treated 18 patients with ocular MMP with control of 81% of ocular inflammation. The combination of rituximab and intravenous immunoglobulin for recalcitrant ocular cicatricial pemphigoid may help to increase the control of inflammation [10].

Topical treatment plays a major role for MMP control.

Antiseptics and topical corticosteroids may help to control oral involvement. Ocular inflammation control is also improved by artificial tears anti-inflammatory drops vitamin B and regular ablation of entropion is eyelashes with the use of scleral lens.

INTERFERON OR CYCLOSPORINE EYE DROPS HAVE BEEN PROPOSED TO IMPROVE OCULAR MMP.

PROGNOSIS

The prognosis also revolves around the ocular manifestations, which may lead to blindness due to scarring of the conjunctival membrane and corneal metaplasia.

REFERENCES