CASE REPORT

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Mucous membrane pemphigoid – a report of four cases

Pemfigoid mukozne membrane

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Abstract

Introduction. Mucous membrane pemphigoid (MMP) is a rare autoimmune, chronic inflammatory disease that affects mucous membranes, most commonly the eyes and mouth, with or without skin involvement. It is a complex disease with several complications, including scarring, especially on conjunctival mucosa, that can lead to visual loss. **Case report**. We report four patients (two men and two women) with MMP. In all patients, the disease started between seventy and eighty years of age. The diagnosis was confirmed based on clinical appearance, histology, direct and indirect immunofluorescence studies, indirect split skin technique, and enzyme-linked immunosorbent assay (ELISA) test. The majority of lesions were on the gums and buccal mucosa; one patient had laryngeal involvement and a lesion on the umbilicus. No ocular involvement and no malignancy were detected. Direct immunofluorescence tests revealed continuous linear IgG deposition in the basal membrane zone in two patients, and they were treated with oral nicotinamide and tetracycline hydrochloride. In two patients, we detected IgG along with IgA linear deposition; they received treatment with methylprednisolone. Complete remission was achieved in all patients. **Conclusion.** Early diagnosis and an adequate therapeutic approach are necessary for the MMP treatment in long-term disease control and reduction of disease-related complications.

Key words:
diagnosis; bullous pemphigoid; enzyme-linked immunosorbent assay; fluorescent antibody technique, direct; remission induction.

Apstrakt

Uvod. Pemfigoid mukozne membrane (PMM) je retka autoimunska, hronična inflamacijska bolest, koja utiče na sluzokože, najčešće očiju i usta, sa ili bez promena na koži. To je složena bolest sa nekoliko komplikacija, koje uključuju ožiljke, posebno na sluzokoži konjunktiva, što može dovesti do gubitka vida. **Prikaz bolesnika**. Prikazana su četiri bolesnika (dva muškarca i dve žene) sa PMM. Kod svih bolesnika bolest se javila u osmoj deceniji života. Dijagnoza je potvrđena na osnovu kliničke slike, histološkog nalaza, analiza drektne i indirektne imunofluorescence, indirektne *split-skin* tehnike i testa – *enzyme-linked immunosorbent assay* (ELISA). Većina lezija nalazila se na desnima i sluzokoži obraza, a kod jednog bolesnika bio je zahvaćen grkljan i postojala je lezija na pupku. Oči nisu bile zahvaćene i nisu primećene promene sumnjive na malignitet. Kod dva bolesnika testovima direktne imunofluoroescence otkriveno je kontinuirano linearno taloženje IgG u zoni bazalne membrane i oni su lečeni oralnim nikotianimidima i tetraciklin hidrohloridom. Kod dva bolesnika otkrili smo linearno nataložene IgG zajedno sa IgA i oni su lečeni metilprednizolonom. Kod svih bolesnika je ostvarena potpuna remisija. **Zaključak.** Za dugoročnu kontrolu bolesti i smanjenje komplikacija povezanih sa PMM neophodni su rana dijagnoza i multidisciplinarni pristup u lečenju obolelih.

Ključne reči:
dijagnoza; pemfigoid, bulozni; elisa; fluorescentna antitela, direktna tehnika; remisija, indukcija.

Introduction

Mucous membrane pemphigoid (MMP) is a rare autoimmune, chronic inflammatory disease that affects mucous membranes, most commonly the oral and conjunctival, but also nasal, oropharyngeal, laryngeal, esophageal, and anogenital, with or without skin involvement [1–3]. MMP lesions are prone to infection, causing fibrosis and granulation tissue

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formation. They often heal with scars which can cause permanent disfigurement and complications such as dysphagia and blindness [1, 4]. That is the reason why synonyms for MMP in the literature include benign MMP but also cicatricial (scarring) pemphigoid and ocular cicatricial pemphigoid. The incidence is 1–5 cases per million individuals [1]. Elderly females are commonly affected. The mean age of onset is between 50 and 80 years [5]. Changes in the oral mucosa present as erythematous patches, blisters, erosions, and ulcerations, located most commonly on gingival and palatal mucosa. The diagnostic process involves a combination of clinical, histological, and immunopathological studies [6]. Dentists and ophthalmologists can be the first to suspect or diagnose this rare disease because of mucosal involvement [7, 8]. Direct immunofluorescence (DIF) tests of mucous membranes detect continuous linear deposition of immunoglobulins (Ig) G and/or IgA and/or complement (C3) along the basement membrane zone (BMZ) [6]. To detect circulating autoantibodies to the BMZ, indirect immunofluorescence (IIF) tests with normal human skin as the substrate are usually performed; however, autoantibodies are detected in only 17–53% of MMP cases [6]. The IIF technique can be used to cause separation of the BMZ at the level of *lamina lucida* with 1M NaCl because it might be helpful to differentiate autoantigens located on the epidermal side of the BMZ from those located on the dermal side [3, 6]. Enzyme-linked immunosorbent assays (ELISAs) are also widely used to detect autoantibodies directing specific autoantigens – bullous pemphigoid antigens BP230 (BPAg1) and BP180 (BPAg2) [3].

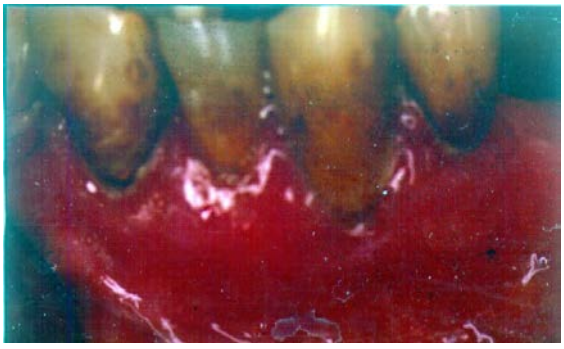
Methods

Case 1

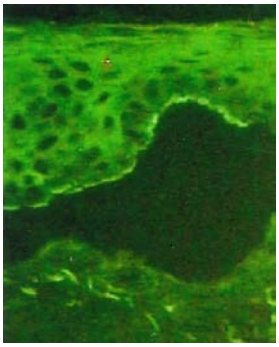
A 75-year-old man presented with a lower gingival painful ulceration that appeared 4 months earlier (Figure 1a). The DIF test revealed continuous linear IgG and IgA depositions in the BMZ. On the IIF split skin (ss) test (ssIIF), there was IgA binding to the roof (epidermal side) of the separated skin (Figure 1b). IIF showed circulating IgG anti-BMZ antibodies detected to a titer of 1 : 10. ELISA test showed positive BP180. The patient was treated with methylprednisolone 0.5 mg/kg, nicotinamide [1 g/daily(d)], and tetracycline hydrochloride (1 g/d) in combination with topical triamcinolone.

Case 2

A 78-year-old man presented with a one-year history of a lesion on the gingival mucosa. The DIF test revealed a continuous linear IgG and C3, i.e., BMZ. On the ssIIF test, there was IgG binding to the roof (epidermal side) of the separated skin (Figure 2). IIF showed circulating IgG anti-BMZ antibodies detected to a titer of 1 : 80. ELISA test showed positive BP180. The patient was treated with nicotinamide (1 g/d) and tetracycline hydrochloride (1 g/d) in combination with topical triamcinolone.



a)



b)

Fig. 1 – a) Ulceration of the lower gingival mucosae; b) Indirect split skin: IgA – Linear basement membrane zone (Roof).

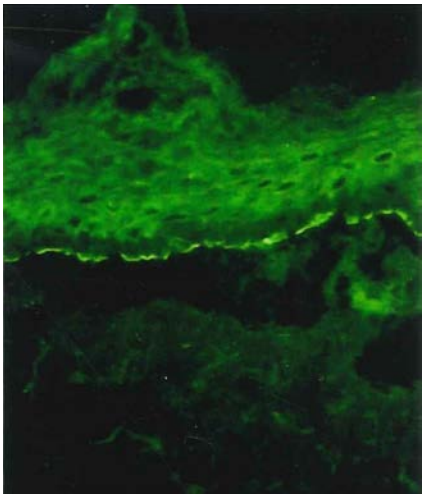


Fig. 2 – Indirect split skin: IgG – Linear basement membrane zone (Roof).

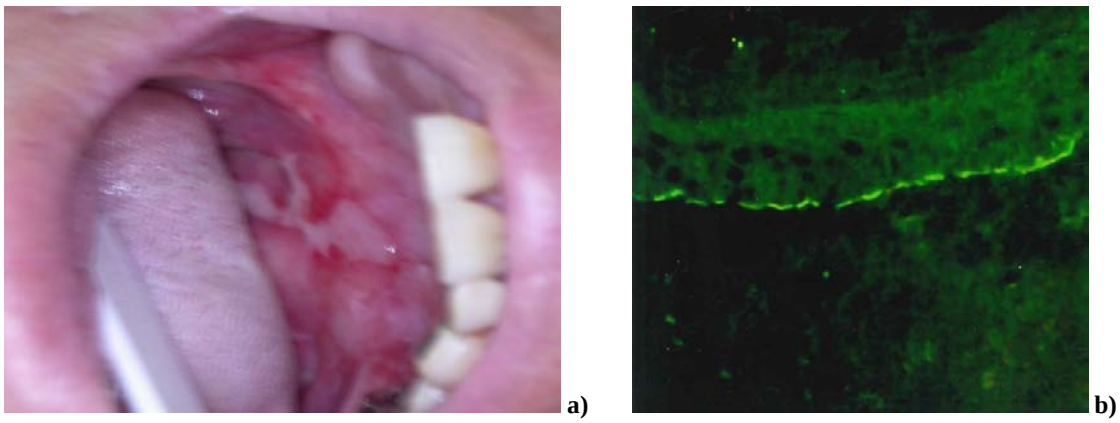


Fig. 3 – a) Multiple erosions of the buccal mucosae and sublingual; b) Indirect split skin: IgG –Linear basement membrane zone (Roof).

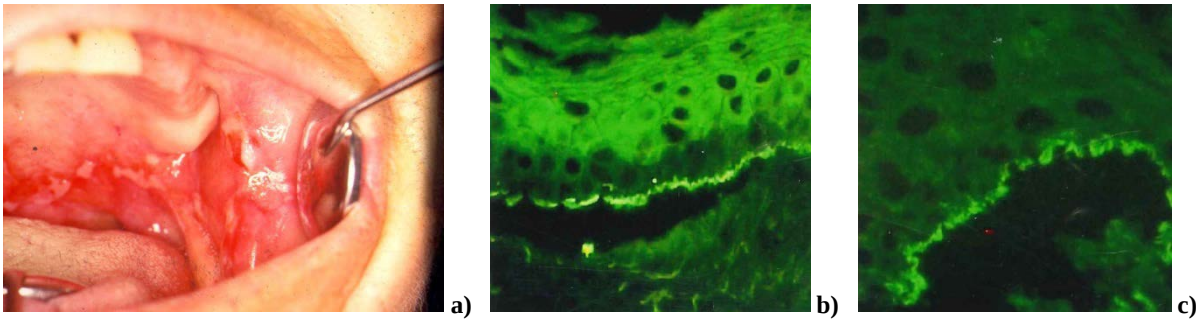


Fig. 4 – a) Diffuse irregular erosions and ulceration with pseudomembranes on the buccal mucosae and hard palate; b) and c) Indirect split skin: IgG – Linear basement membrane zone (BMZ) (Roof) and IgA – Linear BMZ (Roof).

Case 3

A 71-year-old woman presented with a one-year history of lesions on the epiglottis, buccal and palatal mucosa (Figure 3a). The DIF test detected continuous linear IgG in the BZM. IIF testing of the patient's serum showed circulating IgG anti-BMZ antibodies detected to a titer of 1 : 100. The ssIIF test demonstrated that there was IgG binding to the roof of the separated skin (Figure 3b). ELISA test showed positive BP180. The patient was treated with methylprednisolone 0.5 mg/kg and topical triamcinolone.

Case 4

A 70-year-old woman presented with a three-month history of lesions on the gingival and buccal mucosa (Figure 4a), as well as on the umbilicus. The DIF revealed continuous linear IgG deposition and discontinuous IgA and C3 depositions in the BMZ. The ssIIF test demonstrated that the immunoglobulins were bound to the epidermal side of the separated skin (Figures 4b and 4c). IIF detected circulating IgG (titer 1 : 200) and IgA (titer 1 : 10) anti-BMZ antibodies. ELISA test was negative. She was treated with methylprednisolone (40 mg/d) and topical triamcinolone.

Discussion

The first case of MMP was reported by Wickmanns [9] in 1794 in a female patient. MMP is more commonly observed in women than men, with a male-to-female ratio of nearly 1 : 2 [1, 4]. The elderly population is most commonly affected by the disease; the majority of patients were in the age range of 60 to 80 years [5].

In all our patients, the disease occurred with equal frequency among the sexes, but the sample size is too small to draw a conclusion. All patients had between seventy and eighty years, which mainly correlates with those described in the literature [5]. Cutaneous lesions on the head and upper trunk can be seen in a quarter of patients with MMP [1]. The oral and conjunctival mucosae are most frequently affected in MMP, followed by involvement of nasal, oropharyngeal, laryngeal, esophageal, and anogenital mucosa [1]. The gingiva is generally one of the oral sites with the greatest incidence after the palate and the buccal mucosa [10]. In the study of Arduino et al. [10], almost 83% of patients suffered from gingival lesions (both upper and lower), followed by the palate (34%), buccal mucosa (25.3%), alveolar ridge (11%), tongue (7.7%), and labial mucosa (7.7%). The eyes are affected in about 70% of all MMP cases 8.

Interestingly, in our patients, there was an exclusive oral presentation with no evidence of other mucosal involvement, which is similar to the case reports of Di Zenzo et al. [11]. Only one patient had a lesion on the skin in the region of the umbilicus.

In the study of La Placa et al. [5], which included 22 patients affected by MMP, 18% of the patients were found to have, as remarked, an associated cancer. We performed all

necessary clinical and laboratory tests, but no evidence of malignancies was found.

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 [12]. "High-risk" patients were defined as having the involvement of the ocular, genital, nasopharyngeal, esophageal, and/or laryngeal mucosae, and they required more aggressive treatment [13]. According to this view, our patients belong to the "low-risk" group.

The exact etiology of MMP is unknown. However, there are a few reports of MMP triggered by medications (methyldopa, clonidine, indomethacin, and D-penicillamine), viruses, ultraviolet light, and genetic predisposition such as HLA DQB1*0301 [14].

Bullous pemphigoid antigen (BPAG) 1, 230 kd, BPAG2, 180 kd, laminin 5, laminin 6, α_6-integrin subunit, β_4-integrin subunit, collagen VII, and also other basement membrane zone components such as proteins of unknown origin and function have been identified as MMP autoantibody targets [13, 15]. Egan et al. [16] demonstrated a positive association between the presence of anti-laminin 5 antibodies and underlying solid neoplasm in 29% of cases. DIF investigations showed characteristic continuous linear deposits of IgG, C3, and IgA in the epithelial BMZ [5]. Arduino et al. [10] found linear deposits of IgG in 93.4%, C3 in 82.8%, and IgA in 12.9% of cases.

IIF test performed on 1 M salt-split normal human skin substrate provides the highest sensitivity for autoantibodies in pemphigoid diseases [17, 18]. The epidermal ("roof") or dermal ("floor") sides of the artificial blister are the places where the antibodies bind [18]. "Roof"-binding antibodies target BP180 and BP230 are observed in BP, linear IgA-disease, pemphigoid gestationis, and anti-BP180-type MMP. Sensitivities for BP range between 73 and 84% [18]. All of our four patients had IgG depositions, and one of them had IgA deposition to the epidermal side of the artificial blister, and 3 out of 4 patients were BP180 positive.

The main criteria in choosing a therapy depend on the patient's risk status, high or low. It is recommended that those with "low-risk" MMP (involvement of oral mucosae and skin) be initially treated by topical corticosteroids, tacrolimus, or cyclosporine, with the addition of systemic treatment, which includes tetracycline hydrochloride along with niacinamide, if needed [12, 17]. Those with "high-risk" MMP (involvement of the eyes, esophagus, larynx, and urogenital region) should be treated with systemic corticosteroids as the first choice, in combination with immunosuppressive and/or anti-inflammatory agents such as dapsone, azathioprine, cyclophosphamide or mycophenolate mofetil [12, 15]. Treatment strategies also vary according to several factors, such as the age of the patient, severity of the lesions, and the involved sites [7].

As third-line therapy, according to the European guideline for the management and treatment of bullous pemphigoid, rituximab was recommended if conventional immunosuppressive drugs were ineffective, contraindicated, or showed unacceptable side effects [19]. There is also a small study in which three patients with oral involvement MMP were successfully treated with subcutaneous injections of etanercept 25 mg twice a week [11].

However, most of the reported cases consisted only of small patient numbers, and the true benefit of such treatments is, therefore, not yet clear [20].

It is important to note that good oral hygiene is a very important addition to standard therapy, and patients should be constantly motivated to carry out standard hygiene procedures.

Based on the above, the clinical presentation, and the response to therapy, we started the treatment of the first patient with oral nicotinamide and tetracycline hydrochloride, then we added methylprednisolone. The second patient was treated with oral nicotinamide and tetracycline hydrochloride. In all patients, topical corticosteroids were added to the therapy. The third and fourth patients were treated with systemic and topical corticosteroid therapy from the beginning. Complete remission was achieved in all patients.

Conclusion

We have reported on four patients with an oral manifestation of MMP who have shown an uncommon clinical presentation of this rare disease. All patients are unique for having only the oral mucosa affected by the lesions, without the involvement of other mucous membranes. Only one patient had a few lesions on the skin. MMP should be suspected when changes in the oral cavity occur in people, especially those over 60 years of age. Early diagnosis and an adequate therapeutic approach are necessary for the MMP treatment in long-term disease control and reduction of disease-related complications.

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