Pemphigus vulgaris and mucous membrane pemphigoid: Update on etiopathogenesis, oral manifestations and management

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Received: 17/01/2011
Accepted: 28/02/2011

Abstract

Introduction: The treatment of oral mucosal disorders must be based on an early and correct diagnosis. Pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) are among the diseases that pose the greatest diagnostic difficulties for dentists, with scores of 7.35 and 8.03, respectively, on a scale from 0-10.

Objective: To conduct a literature review on PV and MMP, and to summarize the case series involving more than two patients with these diseases.

Material and Methods: A PubMed – Medline search was carried out, using the key words “pemphigus vulgaris” and “oral mucous membrane pemphigoid”. The search was limited to “case reports” and “dental journals”, and yielded a total of 122 articles on PV and 68 on MMP. The review considered only those accessible publications involving series of over two patients.

Results: Seven articles on PV and 5 on MMP, involving series of over two patients, were finally included.

Conclusions: A review has been made of the most recent literature on PV and MMP, documenting those series reporting over two patients.

Key words: Oral, pemphigus vulgaris, mucous membrane pemphigoid, treatment, autoimmune.
### Introduction

The treatment of oral mucosal disorders must be based on an early and correct diagnosis. Pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) are among the diseases that pose the greatest diagnostic difficulties for dentists, with scores of 7.35 and 8.03, respectively, on a scale from 0-10 (1). Both PV and MMP are chronic, autoimmune mucocutaneous diseases affecting the oral mucosa and which can generate doubts regarding their initial diagnosis. The present study offers a literature review on PV and MMP, and summarizes the case series involving more than two patients with these diseases. A PubMed – Medline search was carried out, using the key words “pemphigus vulgaris” and “oral mucous membrane pemphigoid”. Seven articles were published in 2010. The search was limited to “case reports” and “dental journals”, and yielded a total of 122 articles on PV and 68 on MMP. The review considered only those accessible publications involving series of over two patients. Seven articles on PV and 5 on MMP were finally included (Tables 1 and 2).

<table>
<thead>
<tr>
<th>Article</th>
<th>No. patients</th>
<th>Mean age (range)</th>
<th>Gender (F/M)</th>
<th>Evolution (months)</th>
<th>Location</th>
<th>Skin/mucosa lesions (Yes/No)</th>
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<tbody>
<tr>
<td>Sirois et al. 2000 (2)</td>
<td>42</td>
<td>56.1 (27-68)</td>
<td>30/12</td>
<td>-</td>
<td>Oral mucosa, gums and palate</td>
<td>-</td>
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<tr>
<td>Davenport et al. 2001(3)</td>
<td>33</td>
<td>56.5 (27-79)</td>
<td>25/8</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Camacho-Alonso et al. 2005 (4)</td>
<td>14</td>
<td>44.78 (21-87)</td>
<td>10/4</td>
<td>0.75-72 (mean 11.66)</td>
<td>Cheek mucosa, lip, gums and palate</td>
<td>6/8</td>
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<tr>
<td>Iamaroon et al. 2006 (5)</td>
<td>18</td>
<td>37.7 (18-55)</td>
<td>12/6</td>
<td>1-98 (mean 12)</td>
<td>Gums, oral mucosa and palate</td>
<td>-</td>
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<tr>
<td>Shamim et al. 2007 (6)</td>
<td>20</td>
<td>42.3 (20-69)</td>
<td>12/8</td>
<td>1-12 (mean 8)</td>
<td>Oral mucosa, palate and lip</td>
<td>-</td>
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<tr>
<td>Shamim et al. 2008 (7)</td>
<td>71</td>
<td>42.73 (15-70)</td>
<td>45/26</td>
<td>1-12 (mean 5.5)</td>
<td>Oral mucosa, palate, lip and tongue</td>
<td>38/33</td>
</tr>
<tr>
<td>Arisawa et al. 2008 (8)</td>
<td>4</td>
<td>4th decade of life</td>
<td>2/2</td>
<td>1-12</td>
<td>Oral mucosa, alveolar mucosa, soft palate</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 1. Summary of the case series published in the literature, involving more than two patients with pemphigus vulgaris (PV).**

<table>
<thead>
<tr>
<th>Article</th>
<th>No. patients</th>
<th>Age (mean/ range)</th>
<th>Gender (F/M)</th>
<th>Evolution (months)</th>
<th>Location</th>
<th>Extent</th>
<th>Skin/mucosa lesions (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farrel et al. 1998 (9)</td>
<td>3</td>
<td>11.66 (8-14)</td>
<td>3/0</td>
<td>3</td>
<td>Gums and lips</td>
<td>2</td>
<td>3/0</td>
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<td>Assman et al. 2004 (10)</td>
<td>2</td>
<td>66.5 (66-67)</td>
<td>1/1</td>
<td>84</td>
<td>Oral mucosa and gums</td>
<td>2</td>
<td>0/2</td>
</tr>
<tr>
<td>España et al. 2005 (11)</td>
<td>5</td>
<td>55.8 (41-69)</td>
<td>2/3</td>
<td>66</td>
<td>Oral mucosa, cheek mucosa, gums and palate</td>
<td>1</td>
<td>4/1</td>
</tr>
<tr>
<td>Freitas et al. 2008 (12)</td>
<td>2</td>
<td>65 (52-78)</td>
<td>-</td>
<td>-</td>
<td>Cheek mucosa, hard and soft palate</td>
<td>2</td>
<td>2/0</td>
</tr>
<tr>
<td>Arisawa et al. 2008 (8)</td>
<td>6</td>
<td>(20-80)</td>
<td>3/3</td>
<td>11</td>
<td>Alveolar mucosa, lips, oral mucosa</td>
<td>1</td>
<td>1/5</td>
</tr>
</tbody>
</table>

**Table 2. Summary of the case series published in the literature, involving more than two patients with mucous membrane pemphigoid (MMP).**
Pemphigus Vulgaris (PV)
PV is a serious autoimmune disorder with mucocutaneous manifestations characterized by the development of blisters on the skin and/or mucosal membranes (13). Six types of pemphigus have been established: vulgaris, vegetans, erythematous, foliaceus, paraneoplastic pemphigus, and pemphigus IgA (14).

PV usually manifests between the fourth and fifth decades of life, and affects both males and females equally (15). The reported incidence is 0.1-0.5 cases per 100,000 inhabitants and year (16).

The disease is characterized by the production of IgG and IgM antibodies within the intercellular space, targeted against desmosomal cell adhesion molecules such as desmoglein 3 and (in 50% of all cases) desmoglein 1 (16). The presence of HLA class I (HLA-A10, HLA-A26) and HLA class II genes (DR4, DR14) has been associated with a certain predisposition to develop the disease (17).

In 60% of all cases the symptoms initially manifest in the oral cavity (3), though according to some authors the proportion reaches 90% (16). Clinically, the lesions consist of small and asymptomatic blisters that rupture easily, giving rise to painful and bleeding erosions.

While any part of the oral cavity can be affected, the most common locations are the friction zones such as the cheek mucosa, tongue, palate, lower lip and gums. The lesions typically develop over several months in the oral cavity before spreading to the skin and other mucosal zones such as the pharynx, larynx, esophagus or genital mucosa (3,4).

A direct relationship has been reported between PV and periodontal tissue involvement in the form of increased plaque accumulation, increased pocket depth, and attachment loss (18).

The tentative clinical diagnosis must be confirmed by means of complementary tests such as exfoliative cytology, histopathological study, direct and indirect immunofluorescence, and immunoprecipitation tests. Exfoliative cytology in the blister or vesicle phase of the disease reveals Tzanck acantholytic cells with Papanicolaou staining (19). The histological study of PV initially identifies intercellular edema in the suprabasal portion of the stratum spinosum, with the formation of clefts and acantholysis, leading to the formation of blisters.

The identification of acantholytic cells floating in the stratum spinosum is useful, though direct immunofluorescence (DIF) is required to confirm the diagnosis (20).

DIF reveals marking of the epithelial cell surface, indicating the presence of immunoglobulin deposits on the keratinocyte membrane (intercellular space). In 100% of the cases IgG deposits are observed in the epithelial intercellular spaces, while the presence of IgM deposits is much less frequent (17). Indirect immunofluorescence (IIF) in turn detects circulating antibodies targeted to the epithelial cell surface (anti-intercellular substance) - fundamentally IgG4 and IgG1, and less commonly IgG3 (17,21). At present, immunoprecipitation is regarded as the technique of choice for identifying the patient autoantibody target antigens. In this context, desmoglein 3 is targeted in PV, while desmoglein 1 is targeted in pemphigus foliaceus (in skin)(22).

The objective of treatment is to deal with the activity flare-ups as early as possible (23). In patients with non-progressing oral lesions, moderate to high potency topical corticosteroids are recommended, applied 2-3 times a day, such as 0.05% fluocinolone acetonide or 0.05% clobetasol propionate (24,25). In these patients it also may be useful to prescribe dapsone (125-150 mg daily) or tetracycline (2 g/day) and nicotinamide (1.5 g/day) (21).

In patients with severe disease and spreading of the lesions to skin surfaces, corticosteroids are the treatment of choice, at a dose of 1-3 mg/kg/day during 6-10 weeks, with gradual reduction of the applied dose. In order to reduce the corticosteroid dose, such treatment is combined with immune suppressors such as cyclophosphamide 100 mg/day (23), though doses of up to 200 mg/day have also been used (21), or azathioprine 1-2 mg/kg/day. In relation to the latter, it is important to evaluate thiopurine methyltransferase, since the treatment efficacy and side effects are dependent upon the activity of this enzyme (23). Other options are chlorambucil 0.1-0.15 mg/kg/day, cyclosporine A 5-8 mg/kg/day, mycophenolate mofetil (MMF) 35-45 mg/kg/day, and methotrexate 10-17.5 mg/week. In refractory cases it is advisable to prescribe rituximab, plasmapheresis to reduce the presence of antibodies in serum (26), or pulse therapy comprising intravenous cyclophosphamide combined with dexamethasone at high doses (15,21,23).

Although much less frequent than PV, paraneoplastic pemphigus is a variant in which the pemphigus lesions are secondary to a neoplastic process. This presentation is most often associated to hematological neoplasms (84% of all cases), particularly non-Hodgkin lymphomas (42%), chronic lymphocytic leukemia (29%), Castleman’s disease (10%), and others – though cases have also been documented in non-hematological neoplastic processes (16% of all cases)(27,28).

Mucous Membrane Pemphigoid (MMP)
MMP is a chronic autoimmune disease of unknown etiology that manifests in the form of subepithelial blisters. Classically, the variants of MMP are bullous pemphigoid and mucous membrane or cicatricial pemphigoid – the latter being the most common presentation. It is more common in females, and the mean age at onset of the disease is in the fifth or sixth decade of life (29,30).

Presentations in children have also been described (31). The epidemiological characteristics of MMP are unclear,
Pemphigus vulgaris and mucous membrane pemphigoid.

MMP is characterized by the production of autoantibodies (mainly IgG) (97%), C3 complement factor (78%) and, to a lesser degree, IgA (27%) and IgM (12%), targeted to certain components of the basal lamina of the epithelium. An accumulation of IgG has been documented between laminin 5 and type IV collagen present at the dermal-epidermal junction (32). Different forms of MMP exhibit autoantibodies against different elements of this zone of the basal lamina: laminin 5 and 6, antigen 180, and antigens BPAg 1 and BPAg 2 (21, 32).

Depending on the autoantibodies detected by immunoassay techniques, MMP can be classified into 6 subgroups: oral pemphigoid, anti-epiligrin pemphigoid, anti-BP Ag mucosal pemphigoid, ocular pemphigoid, a fifth group consists of patients with antibodies directed against more than one antigen, and anti-p200 pemphigoid (32). The oral, ocular and genital mucosas are the most commonly affected mucosal membranes, followed in decreasing order of frequency by the pharyngeal, laryngeal, nasal and esophageal mucosas. Within the oral cavity, the most frequently affected locations are the gums, followed by the soft and hard palate, the oral mucosa and the tongue. Clinically, the affected patients show blisters occupying the full thickness of the epithelium, and which can develop for hours or days before rupturing. When these blisters finally rupture, they leave pseudomembranes with irregularly shaped yellowish ulcerations surrounded by an erythematous halo. A positive Nikolsky sign is a common finding. The patients usually suffer bleeding, pain and desquamation of the oral mucosa. Occasionally, gingival inflammation in the absence of bacterial plaque can be observed, in the form of chronic desquamative gingivitis (29, 30), though pocket depth and attachment loss have not been found to be statistically significant (33).

Skin lesions are uncommon and are located on the face, neck, scalp, trunk and extremities (32). Ocular lesions are observed in approximately 40% of all patients with MMP, and tend to initially manifest as chronic conjunctivitis with burning sensation, irritation, photosensitivity and excessive tearing (lacrimation). The subsequent course can be characterized by symblepharon, ankyloblepharon and cicatricial bridles that can lead to blindness (29, 34).

The definitive diagnosis can only be established based on the histopathological data and immunofluorescence studies (30). Histologically, the disease is characterized by separation at basal membrane level, giving rise to a subepithelial blister (29, 35). The lamina propria shows a chronic inflammatory infiltrate composed of eosinophils, lymphocytes and neutrophils (32). Direct immunofluorescent techniques (DIF) are useful, since they reveal the presence of homogeneous IgG and C3 complement deposits along the junction between the connective tissue and epithelium.

Indirect immunofluorescence (IIF) in turn is able to detect circulating antibodies in the serum of the patient (34). However, in application to MMP, the sensitivity of this technique is very low in comparison with other diseases such as PV for example. Nevertheless, in some cases the IIF findings have been shown to be positive in patients with negative DIF results (11, 32). The factors to be taken into account in treating MMP are its location, severity and progression rate. In low risk patients with lesions confined to the oral mucosa and/or skin, topical corticosteroids are advised, such as 0.1% triamcinolone acetonide, 0.05% fluocinolone acetonide, or 0.05% clobetasol propionate in ointment, applied 3-4 times a day during 9-24 weeks. In patients with isolated erosions, intralesional corticosteroid injections (triamcinolone in 5-10 mg/ml solution) can be used. In subjects presenting gingival lesions in the form of desquamative gingivitis, 0.05% clobetasol propionate is recommended, with nystatin 100,000 IU to avoid candidiasis overinfection (32, 34). When MMP affects the palate, esophagus or nasal mucosa, beclomethasone dipropionate or budesonide (50-200 µg) can be prescribed (32). Topical 0.1% tacrolimus in pomade, associated to prednisone 40 mg/day via the oral route has been reported to offer good results, with resolution of the lesions after three months of treatment, and offering a preventive effect against the disease (36). Depending on the patient response, other alternatives can be considered, such as 100 mg of doxycycline a day for 8 weeks, or minocycline 50-100 mg/day during 3-39 months, and nicotinamide 2-3 g/day (32, 34).

In high risk patients with multiple oral lesions, rapidly progressing spread of the disease to other mucosal membranes such as the eyes, genital, esophagus or nasopharyngeal zone, or recurrent lesions, the administration of prednisone 1-2 mg/kg/day, with gradual dose reduction, and immune suppressors such as cyclophosphamide (0.5-2 mg/kg/day), azathioprine 1-2 mg/kg/day, or mycophenolate mofetil 2-2.5 g/day has been described (21, 23, 32, 34).

Another treatment option is dapsone (50-200 mg/day) for 12 weeks (23). Treatment is started with 25 mg during three days, followed by 25 mg increments every three days until reaching a dose of 100 mg, followed by boosting of the dosage to 150 mg (34). Blood test monitoring is important in order to avoid the appearance of side effects (23). Other drugs that have been used include methotrexate, which at low doses prevents the progression of conjunctival cicatrization in 72% of all patients, tumor necrosis factor-alpha, leflunomide or sulfonamide (regarded as an alternative to dapsone, administered at a dose of 1.5-3 g/day). Less commonly used options in turn are intravenous immunoglobulins (1-2 g/kg/cycle),

with a reported incidence of 1.5-9.5 cases per 100,000 inhabitants and year (29).
plasmapheresis in patients with eye lesions refractory to corticosteroids and immune suppressors and, as a last option, surgery to avoid complications such as blindness, esophageal strictures or upper airway stenosis (32).

References