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Oral Manifestations of Pemphigus Vulgaris: Clinical Presentation, Differential Diagnosis and Management

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Abstract

Pemphigus vulgaris is a chronic autoimmune mucocutaneous disease characterized by the formation of intraepithelial blisters. It results from an autoimmune process in which antibodies are produced against desmoglein 1 and desmoglein 3, normal components of the cell membrane of keratinocytes. The first manifestations of pemphigus vulgaris appear in the oral mucosa in the majority of patients, followed at a later date by cutaneous lesions. The diagnosis is based on clinical findings and laboratory analyses, and it is usually treated by the combined administration of corticosteroids and immunosuppressants. Detection of the oral lesions can result in an earlier diagnosis. We review the oral manifestations of pemphigus vulgaris as well as the differential diagnosis, treatment, and prognosis of oral lesions in this uncommon disease.

Keywords: Pemphigus; Oral mucosa; Autoimmune bullous disease

Introduction

Pemphigus vulgaris (PV) is the most frequently observed member of a group of chronic autoimmune mucocutaneous diseases characterized by the formation of intraepithelial blisters. It is a rare disease (0.1-0.5 cases/100,000 inhabitants/yr), with onset in the fifth or sixth decade of life [1-3]. PV is infrequent in children and adolescents but some cases have been reported, therefore it should be taken into account in the differential diagnosis at these ages [4,5].

As in some other diseases, there is a higher incidence of PV at lower than higher latitudes [6]. It has also been observed more frequently in certain peoples, e.g., Ashkenazi Jews, Mediterranean populations and Asians (especially Indians and Japanese) [4-6], who show some genetic predisposition. A relationship has been found with HLA, especially with certain HLA class II alleles, with implication of HLA-DR4 (DRB1*0402) in Ashkenazi Jews and of HLA-DRw14 (DRB1*1041) and HLA-DQB1*0503 in Mediterranean and Asiatic peoples [1,3,7-9]. HLA class II alleles are critical for antigen recognition by T lymphocytes. HLA class I alleles may also play a role in the development of PV [3]. Nevertheless, PV can appear in individuals with different HLA types and cannot be considered a hereditary disease [10].

The morbidity and mortality of PV is related to the extent of the disease, the drug dose required to eradicate lesions, the age of the patient, the antibody titer, and the presence of comorbidities [2, 7]. Before the introduction of corticosteroids, around 75% of patients died within the first year. Currently, less than 10% of patients die, usually due to secondary effects of the treatment [3,9,11,12].

Etiology

PV results from an autoimmune process in which IgG serum antibodies are produced against normal desmosomal adhesion molecules on the cell membrane of keratinocytes [1].The serum antibodies responsible for PV are always IgG type, and IgG4 ê, ë has been associated with the active phase of the disease and IgG1 ê, ë with the remission phase [6, 10]. However, although the antibodies found in intercellular spaces of the epithelial tissue are usually IgG type, they can also be IgM or Ig A types, and complement protein C3 can even be observed [10]. The normal epithelial adhesion molecules implicated are desmoglein 3 and, to a lesser extent, desmoglein 1 (Dsg3 and Dsg1), which belong to the cadherin supergene family and have a molecular weight of 130 and 160 KDa, respectively [1,7,9,13]. The binding of antibodies to desmoglein at mucosal or cutaneous level gives rise to the loss of cell adhesion, with separation of epithelial layers (acantholysis) and the consequent appearance of blisters on skin or mucosae [1,3]. The presence of antibodies against Dsg3 is associated with an initial pemphigus that predominantly appears in mucosae, whereas the presence of antibodies against both Dsg1 and Dsg3 is associated with a more advanced pemphigus with both cutaneous and oral manifestations [1,3]. This is because the oral mucosa mainly expresses Dsg3, whereas skin expresses Dsg3 and Dsg1. Only mucosal lesions are found at the onset of PV, due to the expression of anti-Dsg3 antibodies. However, as the disease progresses, anti-Dsg1 antibodies are also expressed and cutaneous lesions appear [3,7]. Dsg is the most widely studied autoantigen, but others have been found in patients with PV, including á9-acetylcholine receptor and pemphaxin [3,5,14].

Although PV is considered an idiopathic disease, a series of environmental factors that trigger the disease have been identified, including medicines (especially thiol-containing drugs, e.g., penicillamine and angiotensin-converting enzyme inhibitors), diet (garlic), and physical or viral agents [1, 3, 10, 15, 16]. Although these are infrequent causes, they should be investigated in patients with a recent diagnosis of PV [10]. No relationship has been reported with previous exposure to the antigen, which is found in mucosal pemphigoid and some other diseases. Numerous studies have demonstrated the contribution of genetic factors to the development of this disease, with reports of its relationship with MHC genes, and

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research is ongoing into other candidate genes [6]. There have also been reports on the prevalence of PV in specific populations and on cases of pemphigus familiaris [6].

Oral Clinical Presentation

Oral lesions are the first manifestation of the disease in 50-90% of cases [1,2,4,5,8,9,14]. However, they are the first manifestation in only 18% of outpatients at dermatology clinics [3]. In patients with early onset of oral lesions, these remain the sole symptoms of the disease for a period of 2-6 months until the appearance of cutaneous lesions, accounting for the importance of oral manifestations for dermatologists [1,2,9,13,17]. Some studies have found major differences in the prevalence of oral lesions as first manifestation of of PV among distinct geographic areas, e.g., 66% in Bulgaria, 83% in Italia, and 92% in Israel [3]. Oral blisters have a very thin roof and readily rupture due to oral traumas, giving rise to multiple chronic painful bleeding ulcers and erosions that heal with difficulty [5,7,8,13]. Patients report pain in the oral cavity and a burning sensation, especially when consuming spicy or acidic food [5,9,17]. Blisters can appear at any localization of the oral mucosa, although the most frequent sites are those subject to friction, such as the soft palate, buccal mucosa (Figure 1), ventral tongue (Figure 2), gingiva, and lower lip (Figure 3) [1,2,8,13].

Multiple and persistent erosions appear on the oral mucosa during early stages of PV. Infrequently, they are localized on the gingiva (Figure 4), especially the free gingiva, where they are difficult to identify as blister lesions. In more advanced stages of PV, desquamative or erosive gingivitis can be observed [3,7]. Other oral manifestations include sialorrhea, halitosis, and the continuous formation of brown or blackish crusts at the vermillion border [1,18].

PV can involve other mucosae besides the oral mucosa, including conjunctive, nasal, pharyngeal, laryngeal, esophageal, genital, and anal mucosae [2,8,13]. Blisters subsequently or sometimes simultaneously appear on the skin, although they may be asymptomatic and are not usually pruritic. Blisters are more likely to be found intact on the skin than on mucosae (due to trauma) [1,2].

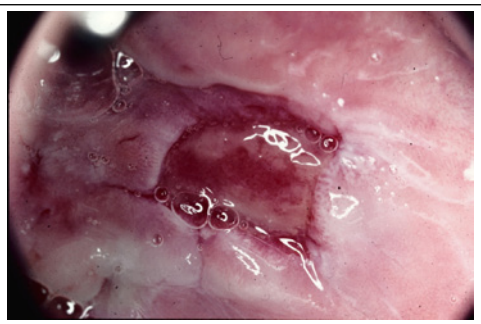

Figure 1: Erosion of buccal mucosa after rupture of blister roof.

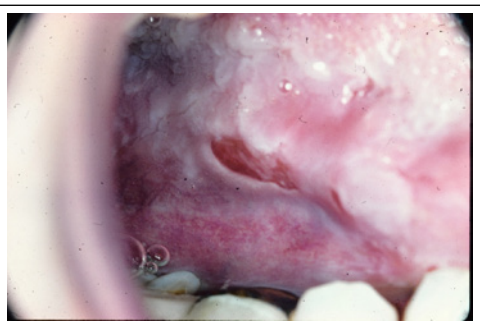

Figure 2: Involvement of ventral tongue in PV.

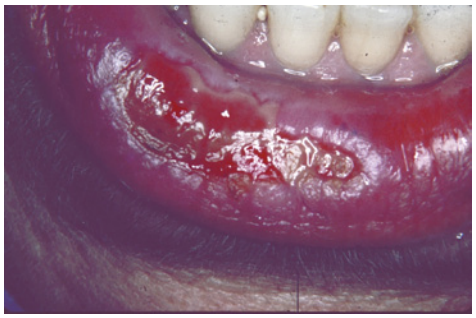

Figure 3: Erosions on lower lip after disappearance of blister roofs.

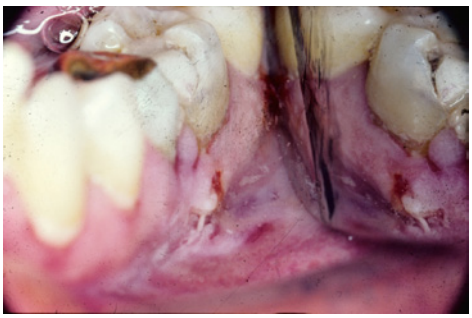

Figure 4: Involvement of free and attached gingiva in PV.

Virtually all (99%) associated cutaneous lesions are diagnosed within six months compared with only 57% of oral lesions. Detection of oral lesions at the onset of the disease would allow an earlier diagnosis and treatment, improving the prognosis of patients [9,17]. PV is frequently chronic, with a progressive increase in severity; it is life-threatening if not treated, due to dehydration, protein loss, and opportunistic infections [1,3].

Diagnosis

The diagnosis of PV is based on three independent set of criteria: clinical features, histology, and immunological tests [5,10]. Presence of this disease must be suspected in cases of persistent gingivostomatitis; persistent multiple oral erosions, or severe desquamative or erosive gingivitis [1,7]. One diagnostic approach has been to press with the finger on the skin to test for the appearance of a new blister (Nikolsky's sign). Although questions have been raised about its sensitivity and specificity [1,7], it appears to be a highly specific technique in the oral setting (96.3%) and may be very useful in the preliminary diagnosis of oral blistering diseases [19].

Laboratory examinations include: Tzanck smear to detect acantholytic cells, useful in lesions of the oral mucosa; standard histology of fresh blister specimens to detect suprabasal acantholysis; direct immunofluorescence to detect intercellular deposits of immunoglobulin G, M, A and C3 protein on epidermis and perilesional skin, offering 100% sensitivity; indirect immunofluorescence to detect pemphigus antibodies in serum; ELISA test using recombinant Dsg1 and Dsg3 to measure anti-Dsg1 and anti-Dsg3 antibodies in serum; and, when the diagnosis remains uncertain, immunoprecipitation and immunoblotting techniques [1,2,7,14,20].

Disease or condition	*Clinical characteristics*
Recurrent aphthous stomatitis	Appearance of ulcers (aphthae) in oral mucosa with yellowish base, surrounded by an erythematous halo and regular margins and that disappear without treatment. Acute course
Behçet's disease	Appearance of aphthae in the oral mucosa with genital and ocular ulcers
Eerythema multiforme	Target-shaped skin lesions, oral erosions, involvement of lips in the form of erosions and crusts
Erosive lichen planus	Appearance of Wickham striae and erosive lesions
Oral candidiasis	Whitish lesions that detach on scraping and atrophic erythematous areas
Acute herpetic gingivostomatitis	Prodromic symptoms followed by the onset of small yellowish vesicles that rapidly rupture, giving rise to ulcers with an erythematous halo. It affects free and attached g ingiva.
Impetigo	Bacterial infection with appearance of skin ulcers covered by a honey-colored crust. It affects face, arms and legs. It is more frequent in children.
Disease by linear IgA deposit	Symmetric blisters and pruritic lesions, target-shaped lesions
Mucosal pemphigoid or cicatricial pemphigoid	Possible manifestation of an underlying malignant disease: oral lesions do not precede skin lesions, and blisters are smaller with a shorter duration than in PV. They heal rapidly without scarring
Bullous pemphigus	Vesicles or tension blisters with clear content that develop on normal or erythematous skin; intense pruritus, symmetric lesions that appear on flexion areas, root of extremities, thighs, and abdomen; rare on mucosae.
Herpetiform dermatitis	1-3 cm erythemas that infiltrate palate and buccal mucosa; aphthae on labial mucosa. They appear months or years after the appearance of lesions on skin
Epidermolysis bullosa	Development of blisters with minimal pressure, ring-shaped atrophic scars on the inner surface of limbs and articulations
Paraneoplastic pemphigus	Autoimmune syndrome associated with lymphoproliferative neoplasm of B cells
Erythematous pemphigus	There are usually no oral lesions
Pemphigus foliaceus	There are usually no oral lesions
Chronic benign pemphigus familiaris	There are usually no oral lesions
Disseminated lupus erythematosus	Systemic signs (fever, asthenia) normally accompanied by petechiae, edemas and dry mouth
Crohn's disease and hemorrhagic rectal colitis	Mucocutaneous signs accompanied by abdominal pain, aphthae in oral mucosa, asthenia, weight loss, and anorexia
Folic acid or vitamin B12 deficiency	Oral pain, erythematous tongue, asthenia and anemia, paresthesias in limbs, and physical problems
Hypochromic iron deficiency	Pallor, fatigue, cephalalgias, vertigo, buzzing in the ears, irritability, insomnia, concentration problems, sensitivity to cold, anorexia and nausea
Enteropathic acrodermatitis	Loss of taste and smell, sight problems, intense diarrhea, alopecia, and hypertension

Table 1: Differential diagnosis of oral lesions in pemphigus vulgaris.

The first manifestations of PV are on the oral mucosa in the majority of patients
In these patients, oral manifestations are the sole symptoms of the disease until cutaneous lesions appear 2-6 months later
Oral blisters have a very thin roof and readily rupture due to trauma, giving rise to chronic painful bleeding ulcers and erosions that heal with difficulty
The most frequent sites of oral lesions are those subject to friction
PV should be suspected in cases of persistent gingivostomatitis, persistent and multiple oral erosions, or severe desquamative or erosive gingivitis
The most frequent diagnoses in cases of oral lesions are recurrent aphthous stomatitis, Behçet's disease, erythema multiforme, erosive lichen planus, and oral candidiasis
Lesions of the oral mucosa in patients with low antibody titers may be controlled with mouthwashes or topical creams containing corticosteroids
Intralesional injection of triamcinolone acetonide or paramethasone can be used in refractory oral lesions
The wellbeing of patients may be improved by: analgesics, a strict oral hygiene with diluted antiseptic mouthwashes, a soft diet without irritants, correct prosthetic restorations, and anti-candida therapy
Traumatisms may trigger or exacerbate PV, therefore some authors recommend the prophylactic use of prednisolone (20 mg/day) for 5-7 days before dental procedures involving gums

Table 2: Points of interest.

Differential Diagnosis of Oral Lesions

Many patients with PV can be initially misdiagnosed and incorrectly treated for months. The most frequent diagnoses in patients with oral lesions are recurrent aphthous stomatitis, Behçet disease, erythema multiforme, erosive lichen planus, and oral candidiasis [2]. In children and adolescents, PV should be differentiated from erythema multiforme, acute herpetic gingivostomatitis, impetigo, linear IgA disease, epidermolysis bullosa, cicatricial pemphigoid, bullous pemphigus, and paraneoplastic pemphigus [4].

The differential diagnosis includes other dermatological diseases with possible manifestations on the oral mucosa, including dermatitis herpetiformis, mucosal pemphigus, erythematous pemphigus, pemphigus foliaceus, or benign chronic pemphigus familiaris [2]. The following conditions should also be considered: disseminated erythematous lupus, enteropathic acrodermatitis, Crohn's disease, hemorrhagic rectal colitis; and deficiencies in folic acid, vitamin B12, or hypochromic iron [9].

All of these differential diagnoses are summarized in Table 1.

Treatment of Oral Lesions

Oral lesions are challenging, since their response to treatment is much slower in comparison to cutaneous lesions [10]. Lesions of the oral mucosa in patients with low titers of circulating antibodies may be controlled (at least temporarily) with mouthwashes or topical creams that contain corticosteroids, e.g., 0.1% triamcinolone acetonide in orabase, 0.05% fluocinolone acetonide, 0.05% clobetasol propionate, or 0.05% halobetasol. Intralesional injection of triamcinolone acetonide (20μg/L) or paramethasone every 7-15 days can be used in refractory lesions, but the treatment must be withdrawn if symptoms do not improve after three injections [2,4,7,8,9,10,11].

As a complement to treatment with local or systemic corticosteroids, the following measures can be taken to improve the wellbeing of patients: administering analgesics, maintaining strict oral hygiene using diluted antiseptic (chlorhexidine) mouthwashes, periodontal treatment, following a soft diet without irritants, checking prosthetic restorations, and applying anti-candida therapy in patients on long-term corticosteroid treatments [3,9,10,21].

Factors that can exacerbate the disease include sun exposure, radiographs, stress, and traumas [10]. Because oral traumas can trigger or worsen PV, Bystryn et al. recommend the prophylactic administration of 20 mg prednisone/day in addition to the patient's normal requirement for 5-7 days before any dental procedure that is associated with trauma to the gums [10].

In PV patients with extensive oral lesions or skin involvement, the standard therapy consists of the combined administration of corticosteroids and systemic immunosuppressant's to remit symptoms. After achieving this objective, a maintenance regimen is started, using the minimum possible dose able to control the disease in order to minimize the side effects of these drugs [1,2,3,7,11].

There is no consensus on the optimal dose of corticosteroids to be used or on the most effective immunosuppressant [12].

Research advances have expanded the therapeutic arsenal against PV, which now includes treatments with: pulse therapy (intravenous infusion of very high doses of immunosuppressants for a short time period); high doses of intravenous immunoglobulin; plasmapheresis; immunospecific immunoadsorption; extracorporeal photopheresis with exposure of serum to psoralens and UVA; antagonists of tumor necrosis factor α (TNFα); cholinergic antagonists; and anti-CD20 monoclonal antibodies (e.g., rituximab) [1,11,22]. However, no treatment has demonstrated superiority over the others [12]. In fact, there is a lack of well-designed studies on the efficacy of the numerous new PV treatments and a shortage of evidence-based clinical guidelines. This can largely be attributed to the low frequency of the disease and a failure to establish a consensus on terms used to describe and analyze the extent, activity, severity, or healing-remission of PV or on time points for assessing the therapeutic response [11, 12,23]. In an attempt to address this issue, the American Academy of Dermatology (AAD) published a consensus declaration in 2008 on follow-up intervals and on the definition of treatment failure/success and recurrences [22].

Finally, a close collaboration between dentists and dermatologists is required to combat this disease.

Prognosis of Oral Lesions

The prognosis of untreated oral lesions is a progression that involves other mucosae, including the skin. When treated, the prognosis depends on the age of the patient, the initial severity, the extent of lesions, the interval between symptom onset and start of treatment, and the drug dose required to control the disease, among other factors [2,3,9]. The prognosis is worse when there is an elevated titer of circulating antibodies [7,10]. Various authors have reported that the oral lesions can disappear after 2 months to one year [5,9], although it remains unclear whether the PV completely remits [3], and there are no well-defined criteria for the cure/remission of this disease [11].

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