

The Importance of a Multidisciplinary Team to Management the Manifestations of Pemphigus Vulgaris: Eight Case Reports

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Abstract

Pemphigus Vulgaris is a chronic autoimmune mucocutaneous disease, in which oral lesions could be the first site observed, although skin and other mucous membranes may also be affected. Clinically, the lesions are characterized by many painful blisters that rapidly rupture resulting in erosions and/or multiple ulcers in the oral mucosa and skin, which can be difficult to differentiate from other vesiculobullous or ulcerative disorders. Many patients may be misdiagnosed and improperly treated for a long time. It is considered a serious chronic disease and its treatment represents a real therapeutic challenge. We present 8 case reports of pemphigus vulgaris, in which a thorough evaluation was made, recording patient age and sex, the location and extent of the lesions, their signs, symptoms and treatment, with emphasis on the difficulty of the diagnosis and clinical management of these patients.

Key Words: Pemphigus vulgaris, autoimmune diseases, clinical manifestations, treatment

Introduction

Pemphigus Vulgaris (PV) is a chronic autoimmune mucocutaneous disease characterized by the production of autoantibodies directed against desmosome-associated protein antigens found in epithelial and epidermal intercellular substance, resulting in loss of coherence of the epidermal and mucosal epithelial structures, with subsequent blister formation [1,2].

PV is a rare disease, with a reported incidence of 0.1-0.5 cases per 100.000 individuals worldwide per year. It affects both sexes equally, though some authors have reported a greater incidence among women, and that is primarily manifests in adults during the fifth or sixth decade of the life [3-6].

Clinically, the lesions are characterized by many blisters that rapidly rupture resulting in very painful erosions and/or multiple ulcers in the oral mucosa and skin. Other mucous membranes such as the conjunctiva, nasal, and genital mucosa can also be affected. In most cases, the first signs of disease appear in the oral mucosa and precede the cutaneous manifestation [3,7].

The diagnosis of PV is based on the combination of clinical and histopathological findings. The most common symptoms that prompted patients to seek medical attention were pain and local discomfort, in addition to dysphagia and quick weight loss caused by lesions. The state of the patient's general health is seriously impaired by the disease, in some cases requiring admission to hospital [6].

The morphological view analyzed by the hematoxylin-eosine method shows the presence of intraepithelial blisters, acantholysis, and Tzanck's cells. The direct immunofluorescence evaluation of fresh lesion specimens reveals IgG or IgM antibodies and complement fragments in the intercellular space located between epithelium cells [1,4,8].

PV was considered a fatal disease before the discovery of systemic corticosteroids. The mortality rate was 75% and most patients died within 5 years of disease onset. The systemic

high-potency corticosteroids (Prednisone 40 to 80 mg/ daily) are the main drugs used in the treatment of PV. Other immunosuppressive agents (e.g.: Azathioprine, Cyclosporin, Mycophenolate Mofetil and intravenous Immunoglobulin infusion) are frequently used as adjuvant therapy and the choice of treatment depends on the disease severity [2,9,10]. All treatment has side effects, such as Cushing's Syndrome, gastrointestinal disorders, hepatotoxicity, cataracts, osteoporosis, myopathy and renal toxicity. The treatment of PV is based on controlling the disease and not on curing the patient [6].

Thus, a multidisciplinary approach is needed, including dentists trained in the areas of the stomatology, oral pathology and medical professionals in the areas such as dermatology, gynecology, ophthalmology, psychologists and others. The treatment is long term requiring constant monitoring of the patient [6].

The aim of this study was to describe 08 case reports of Pemphigus Vulgaris, with emphasis on the difficulty of the diagnosis and clinical management of the patients.

Case Reports

Eight Caucasian patients (6 women and 2 men), with ages ranging from 37 to 74 years, were diagnosed with Pemphigus Vulgaris at the Stomatology Clinic of the University Hospital of the Federal University of Santa Catarina, State of Santa Catarina, Brazil. All patients gave their informed consent prior to their inclusion in the study. In no case had the lesions been present for more than six months at the time of the first visit. The patients' main complaint was the oral pain, discomfort, and impairment of their normal oral functions.

In the intraoral examination, all patients presented erosions and/or ulcers in the oral mucosa (*Figure 1*). A sensitive but nonspecific clinical sign, Nikolsky's sign, in which the separation of the superficial epithelial layers from the basal layer occurs on exertion of tangential pressure on the

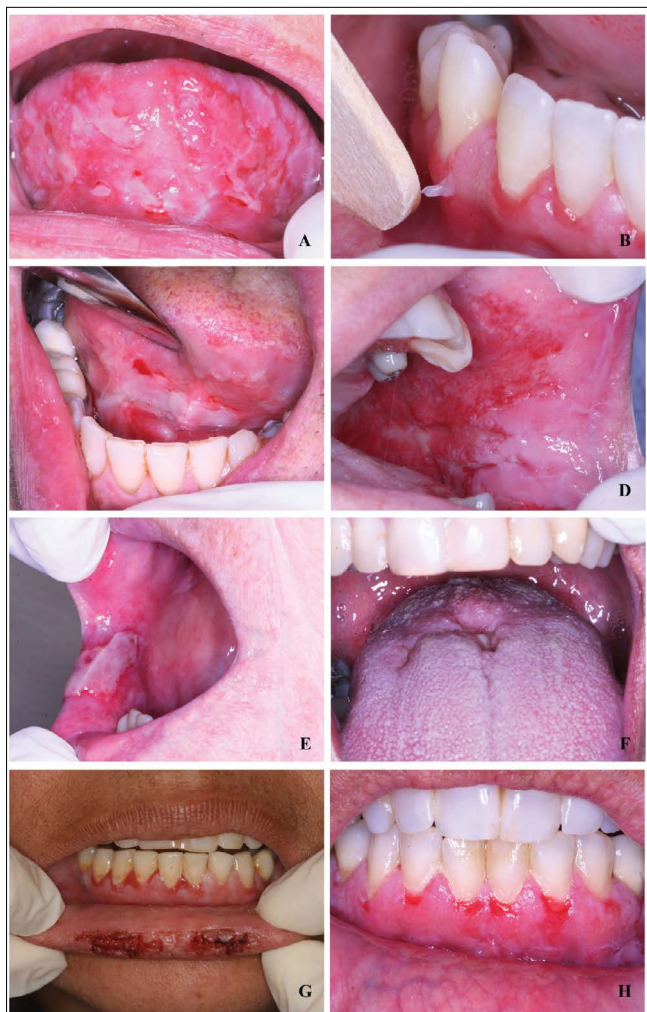


Figure 1: Oral Lesions in different sites in patients with PV. **A:**Ulcers in the tongue of patient 1. **B:**Positive Nikolsky Sign in the gingival lesions of patient 2. **C:**Ulcer in the floor mouth of patient 3. **D:**Extensive ulceration in the buccal mucosa of patient 4. **E:**Ulcer covered by pseudomembrane in the retrocomissural mucosa. **F:**Ulcer in the tongue dorsum of patient 6. **G:**Ulcers in the lower lip and erosions in the buccal gingiva of patient 7. **H:**Erosions in the buccal gingiva of patient 8.

perilesional mucosa, was positive in most cases (Figure 1B). The clinical features of the eight PV cases are summarized in Table 1.

The involvement of skin and/or other mucosal membranes such as lesions in the conjunctiva, trunk, face and extremities were observed in most cases (Figure 2 A, B, C and D). Hospitalization was required in 2 cases to control the disease or treatment-related complication.

Diagnosis was initially based on clinical findings and subsequently confirmed by histopathologic examination and direct immunofluorescence in some cases. The histological findings were characterized by acantholysis in the suprabasal region and Tzanck cells. Connective tissue of lamina propria showed mixed inflammatory cell infiltrate (Figure 2 E and F).

After appropriate hematologic and metabolic evaluation, topical corticosteroid (0.05% to 0.1% clobetasol propionate) was administered. Since all cases presented lesions in different location within the oral cavity, we decided to administer the corticosteroid oral suspension mouthrinse, three times a day. Low level lasertherapy (LLLT) is usually used to decrease the oral lesions pain. In some cases, there were localized lesions in the gingiva. For these cases, the use of a tray with the topical corticosteroid in gel presentation (0.05% to 0.1% clobetasol propionate) was managed. Some patients developed candidosis as a side effect of use of clobetasol propionate. These patients were treated with a topical antifungal agent (nystatin in oral suspension) without interrupting the use of clobetasol. The association between 0.05 or 0.1% clobetasol

propionate with oral solutions of nistatin 100.000UI could be obtained by magistral manipulation to avoid oral candidiasis as a side effect in the patient.

Four patients (case numbers 1, 2, 4 and 7) were referred to the dermatology clinic for treatment of the skin lesions. The patients with ocular involvement (case numbers 1, 2, 3, 4, 6, 7 and 8) were referred to the Ophthalmology Clinic of the same hospital for the treatment of these lesions. The combination of topical treatment and systemic corticosteroids (Prednisone) and immunosuppressive therapy (Azathioprine) was necessary. The topical and systemic treatment is shown in Table 1. All patients responded to treatment, with important lesion improvement (Figure 3), but different doses of the corticosteroids and immunosuppressive agents were necessary in each case. As side-effects of the systemic corticosteroid therapy, some patients presented Cushing's Syndrome, acneiform eruptions, arthritis, ocular irritation, conjunctivitis, hormonal alteration, joint pain, stretch marks on the skin, vascular disorders and secondary infection. These effects were monitored carefully by the physician. After improvement and stabilization of the lesions, corticosteroids were gradually tapered off until the minimum dose necessary to avoid the recurrence and appearance of new lesions.

In spite of the oral and systemic lesions having been stabilized, since pemphigus vulgaris is a chronic autoimmune disease, these patients continue to be followed-up by a multidisciplinary team.

Table 1. Summary of the main clinical characteristics and treatment of the patients.

Case	Age	Sex	Location of Oral lesions	Systemic manifestation	Hospitalization	Treatment
1	58	F	Multiple painful ulcers in the Hard and soft palate, tongue, labial mucosa	Skin and ocular lesion, dysphagia, hyperglycemia, hormonal alteration	No	0.1% clobetazol proprionate solution, LLLT, Prednisone 20mg + Azathioprine 150mg and 50 mg
2	37	F	Erosion and/or painful ulcers in the buccal gingiva, soft palate, buccal mucosa, retromolar region	Skin and ocular lesion erythema and conjunctivitis	No	0.05% clobetazol proprionate gel and solution, LLLT
3	59	M	Multiple painful ulcers in the soft palate, floor of the mouth, tongue, upper and lower bottom of groove	Ocular lesion, dysphagia, dysphonia, dehydration	Yes	0.05% clobetazol proprionate solution, LLLT, Prednisone 30 mg + Azathioprine 50 mg
4	43	F	Multiple painful ulcers in the soft palate, floor mouth, tongue, oropharynx, bilateral buccal mucosa, labial mucosa, buccal gingiva	Ocular and skin lesion, dysphagia, dysphonia, dehydration	Yes	0.1% clobetazol proprionate solution, LLLT, Prednisone 80 mg + Azathioprine 100mg
5	74	F	Multiple ulcers in the lower labial mucosa, tongue, floor of the mouth	none	No	0.05% clobetazol proprionate solution
6	48	M	Multiple ulcers in the Labial mucosa, buccal mucosa, floor of the mouth, tongue, buccal gingiva	Ocular and genital mucosal lesions	No	0.05% clobetazol proprionate solution, LLLT, Azathioprine 50mg, prednisone 5mg
7	30	F	Multiple painful ulcers in the lower labial mucosa, bilateral buccal mucosa, buccal gingival, floor of the mouth	Skin and ocular lesion	No	0.1% clobetazol proprionate solution, LLLT, Prednisone 50mg + Azathioprine 150mg + Dapsone 100mg
8	55	F	Multiple painful ulcers in the buccal gingiva, floor of the mouth, buccal mucosa	Ocular lesion	No	0.05% clobetazol proprionate solution, prednisone 40mg



Figure 2: Multiple lesions and histopathological aspects of PV. **A:**Crusts overlying ulcers in the lower lip and face. **B:**Ulcers on the trunk. **C:**A big blister on the arm. **D:**Ocular irritation. **E and F:**Acantholysis in the suprabasal region of the surface epithelium.

Discussion

Pemphigus vulgaris (PV) may be seen across a wide age spectrum, but most cases have been noted to occur in middle-aged to elderly adults [3,6,7,11,12]. This is in agreement with our cases, in which the lesions most frequently occurred in patients in the fifth and sixth decades of life. Females were more frequently affected (4 out of 5 cases), which is consistent with the previous reports of Shamin et al. [7] and Camacho-Alonso et al. [3].

PV represents one of several mucocutaneous blistering diseases in which oral lesions are commonly observed [12],

and in most cases (70 to 90%), the first signs of disease appear in the oral mucosa [4]. Onset is usually insidious, often masquerading as nonspecific ulcerations that heal within a few weeks with new lesions appearing elsewhere [12]. Blisters, which rapidly lead to chronic painful erosions and ulcers, are seen mainly in areas subjected to frictional trauma, such as the buccal mucosa, palate, ventrum of tongue and lips [13] and gingival involvement is often desquamative or erosive in nature.

The ulcerations may affect other mucous membranes, including the conjunctiva, nasal mucosa, pharynx, larynx,

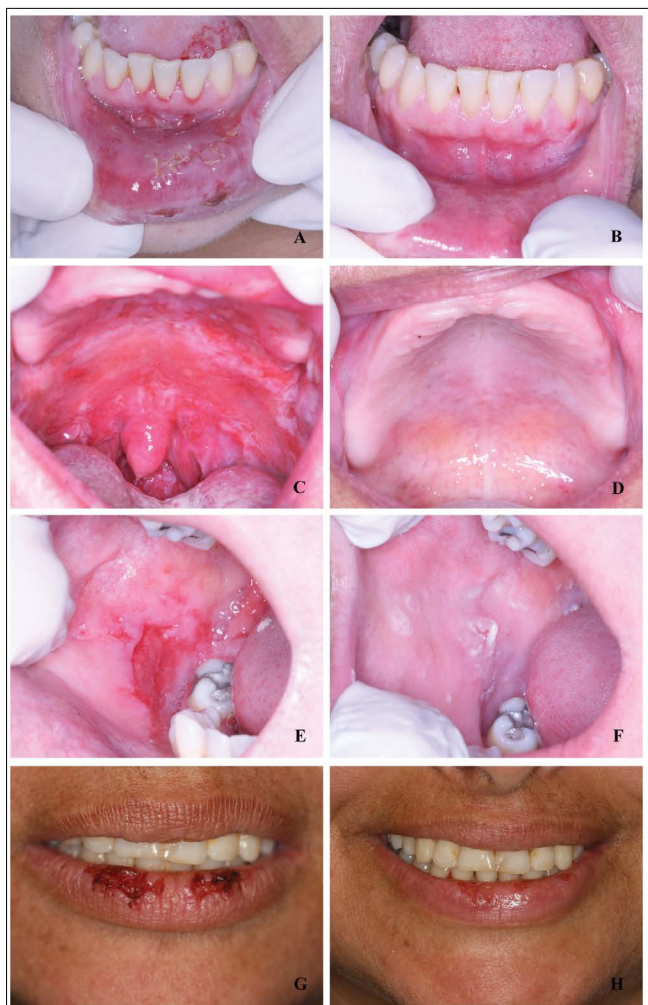


Figure 3: Aspects of oral mucosa in the first consultation and after topical and systemic treatment. **A and B:** Great improvement in the ulcers in the patient's lower lip 4. **C and D:** Remission of the extensive ulceration in the patient's palate 1. **E and F:** Significant reduction of the ulcer in the patient's buccal mucosa 2. **G and H:** Diminution of the ulcers in the patient's lower lip.

esophagus and genital mucosa, as well as the skin where intact blisters are commonly seen [4]. Cutaneous lesions begin as flaccid blisters that usually arise on skin of otherwise normal appearance, but blisters may be found on erythematous skin, particularly in injured sites. Affected skin is often painful, but rarely pruritic [13].

In our cases, at the time of the first consultation, most patients presented only oral lesions or simultaneous involvement of skin and the oral mucosa, and the main complaints were pain and discomfort during mastication. Three patients were severely impaired, presenting dehydration and malnutrition and they needed to be admitted to hospital. Some oral complications of PV lesions include oral pain, bleeding, limited oral function and impaired oral intake of food. The association of lesions and pain can impair oral hygiene and increase susceptibility to caries and periodontal disease [1].

PV is considered a very rare condition in which an acantholytic process characterizes the skin and oral mucosal lesions [12]. The pathologic process is mediated by autoantibodies produced against desmosomes (adhesion proteins), especially desmoglein 3 (Dsg 3), and to a much lesser extent, desmoglein 1 (Dsg 1). They are components of desmosomal cadherin responsible for holding the cells of the epithelium together above the basal cell layer. The loss of the adhesive function among the spinous cells due to anti-Dsg 3 antibodies results in an intraepithelial separation immediately above the intact basal layer of cells that remains adherent to the underlying basement membrane zone [12,14].

Vesiculobullous, erosive or ulcerative disorders that affect the oral mucosa or gingiva can be difficult to differentiate clinically. Data about the oral signs are few and delays in diagnosis are common [13]. A sensitive but nonspecific clinical sign, Nikolsky's sign, can be useful to differentiate PV from other autoimmune disease such as erosive lichen planus, nevertheless, it does not differentiate PV from other vesiculobullous diseases, such as mucous membrane pemphigoid.

Most patients could initially be misdiagnosed, usually with diagnoses such as aphthous stomatitis, gingivostomatitis, erythema multiform, and other diseases, and may be improperly treated for months or even years [4].

The clinical features of PV are similar to benign mucous membrane pemphigoid and erosive lichen planus. The diagnostic orientation is based on the clinical oral manifestations, while confirmation is provided by the histological findings, which show the cleavage or separation of the suprabasal layer of the surface epithelium with the basal layer of cells remaining adherent to the basement region and Tzanck cells. Direct immunofluorescence evaluation of fresh lesion specimens revealed IgG or IgM and complement fragments in the intercellular space [3,4,7,12]. Assay of serum antibody titres by direct immunofluorescence may also help guide prognosis and treatment [13]. In all patients, a perilesional biopsy of the oral lesions was obtained. The specimen sections were stained with Hematoxylin-Eosin, and the principal histological characteristics were observed.

PV was considered a life-threatening disease associated with increase in morbidity and mortality, mainly before the emergence of systemic corticosteroids. Their use and immunosuppressants has greatly improved prognosis, although morbidity and mortality are still considerable (<10%), with some patients dying from treatment-related complications. Systemic corticosteroids are the mainstay of treatment, and immunosuppressants tend to be used for their corticosteroid-sparing effect (reduction in adverse effects) or when corticosteroids result in poor disease control [5,6]. As adjuvant immunosuppressive agents, azathioprine, mycophenolate mofetil, cyclophosphamide and methotrexate as well as cyclosporine and chlorambucil are used, with azathioprine being the agent of first choice [15]. In therapy-refractory pemphigus, high-dose intravenous immunoglobulins represent an adjuvant therapy option [15]. In addition, topical treatment for cutaneous and mucosal lesions is commonly used as adjuvant therapy [2] and may also be considered as a possible systemic steroid-sparing technique [12].

Some studies have reported good outcomes for patients with oral lesions treated with clobetasol propionate in a mouthwash [16]. Clobetasol propionate at 0.05% is currently the most widely used potent topical corticosteroid. It allows the disease symptoms to be controlled with a restricted number of daily applications and provides a better initial control of the symptoms and a significant lengthening of the lesion-free period [17].

Therapeutic goal in PV is to achieve control of the disease activity and long-lasting remissions [15]. Because of variable patient response, the selection, dose, and duration of medical therapy are determined based upon the individual patient's overall health status, severity of the disease, and treatment response [1].

Sometimes the treatment of oral lesions represents a real therapeutic challenge. The oral lesions of PV heal much more slowly than skin lesions and are often recalcitrant to treatment. This can be explained by trauma of mastication and occurrence of oral candidosis or herpetic stomatitis [11]. In our cases, disease control was achieved with the combined use of systemic corticosteroids (prednisone), immunosuppressants (azathioprine) and topical corticosteroids (clobetasol

propionate). One patient presented only localized gingival lesions, and did not use systemic corticosteroid. These lesions were controlled with clobetasol propionate in gel form (0.05%) administered in a tray.

The adverse effects of prolonged therapy with systemic steroids are numerous and include hypertension, hyperglycemia, osteoporosis, adrenal suppression, peptic ulcer, weight gain, fat redistribution, glaucoma, cataracts, mood change, stretch marks on the skin, vascular disorders, increased risk of infection, and delayed wound healing. Long-term application of potent topical steroids may lead to mucosal atrophy, hypopigmentation, secondary candidiasis, irritation, poor healing and systemic absorption. Typically, once the disease is controlled, steroids are gradually tapered off depending on the treatment response and relapse potential [1].

The most common adverse effect of topical corticotherapy in this study was candidosis. These patients were treated with a topical antifungal agent without interrupting the use of clobetasol. With regard to systemic corticosteroids, some patients presented side effects such as: Cushing's Syndrome, acneiform eruptions, arthritis, ocular irritation, conjunctivitis, hormonal alteration, joint pain and secondary infection, and these effects were monitored carefully by the physician. After the establishment of an acceptable treatment response, long-term follow-up is necessary [12].

Low level lasertherapy (LLLT) with red spectrum (660 nm) could be indicated to control the pain and to accelerate the healing of PV erosions and ulcers. LLLT was considered a noninvasive technique indicated as adjuvant therapy in oral and skin PV lesions [18]. When PV is located in specific area like lips, it's also possible to management the lesions with infiltrate intralesional steroids injection (triamcinolone 10 mg/ml) [19].

Thus, pemphigus vulgaris is a chronic autoimmune mucocutaneous disease, in which the oral mucosa is the first site affected in most cases and consequently dental professionals play a critical role in the early diagnosis and management of oral lesions. In addition, a multidisciplinary team is fundamental for the successful treatment of PV.

Conflict of Interest

The authors declare that they have no conflict of interest.

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