Pemphigus Vulgaris: A Case-Based Update

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ABSTRACT

Pemphigus vulgaris (PV) is an autoimmune disease accounting for 80% of all cases of pemphigus. Before the advent of corticosteroid therapy, pemphigus was fatal, with a mortality rate of up to 75% in the first year. It is still a serious disorder, but the 5% to 10% mortality rate is now primarily due to the side effects of therapy. In 75% to 80% of cases, PV lesions first appear in the oral cavity. Dentists are therefore in a unique position to recognize the oral manifestations of the disease, allowing early diagnosis and initiation of treatment. The diagnosis is based on pathological examination and immunofluorescence testing. Systemic corticosteriods and steroid-sparing agents are the mainstays of treatment; topical corticosteroids may also be used to accelerate healing of persistent oral lesions. This article describes a 71-year-old woman with multiple chronic ulcers in the oral cavity, in whom PV was diagnosed 4 months after the symptoms first appeared. The article also reviews the current literature on diagnosis and treatment of the condition.

MeSH Key Words: case study; oral ulcer/etiology; pemphigus/drug therapy; pemphigus/immunology

The autoimmune bullous dermatoses fall into 2 main groups: diseases of the dermo-epidermal junction, which are due to abnormalities at the interface between the dermis and the epidermis (of which pemphigoid is one example) and intraepithelial dermatoses, which include the various forms of pemphigus. Pemphigus results from circulating immunoglobulin G (IgG) antibodies directed against desmosomes; these antibodies interfere with keratinocyte adhesion (**Fig. 1**). Acantholysis occurs, resulting in the formation of bullae.[1] There are 6 main types of pemphigus and their classification is based on the anatomic features of the lesion and the target antigens recognized by the autoantibodies (**Table 1**).[2,3]

Eighty percent of patients with pemphigus have pemphigus vulgaris (PV).[1] The annual incidence is estimated as one case per million population, but the condition is more common among Ashkenazi Jews and people of Mediterranean descent because of an association with certain human leukocyte antigen haplotypes.[4]

Before the advent of corticosteroid therapy, pemphigus was fatal, with a mortality rate of up to 75% in the first year. It is still a serious disorder, but the 5% to 10% mortality rate is now primarily due to the side effects of therapy.[5] The prognostic factors are age, time between onset of symptoms and initiation of treatment, extent of the lesions and the dose of corticosteroids required to initially control the disease.

This article describes a patient with multiple chronic ulcers in the oral cavity, in whom PV was diagnosed 4 months after the symptoms first appeared. The case study is followed by a review of the literature on the clinical diagnosis and differential diagnosis of PV, as well as the laboratory tests used to confirm the diagnosis and the therapeutic options.

Case Report

A 71-year-old woman presented with debilitating pain in the mouth as well as mouth ulcers that had appeared 4 months previously. She had initially seen her general practitioner for throat irritation, for which bacitracin and

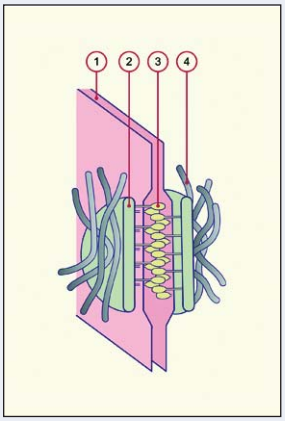

Figure 1: Drawing of a desmosome. Each desmosome attaches to a cell, and its cytoskeleton attaches to the neighbouring cell. 1 = intercellular space, 2 = cytoplasmic plaque made of desmoplakin, 3 = desmoglein (of which there are various kinds, based on cell type), 4 = keratin filaments anchored to the cytoplasmic plaque.

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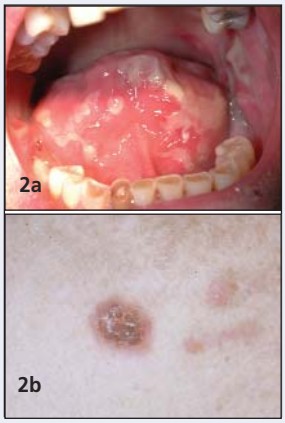

Figure 2: Large aphthoid mucosal lesions (with erosions and abrasion rings in the loosened epithelium) covering the entire oral mucosa. The lesions affected the linea alba of both cheeks and the ventral side of the tongue (2a). The patient also had crusted, erosive lesions on the shoulders and back (2b).

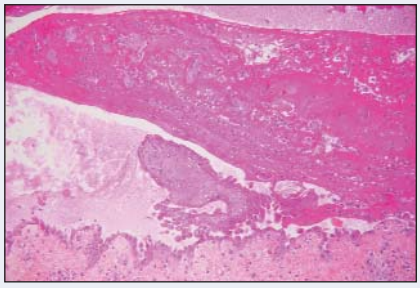

Figure 3: Cutaneous biopsy sample revealed an intraepidermal bulla of pemphigus vulgaris, which has caused cleavage of the suprabasal intraepidermal layer accompanied by acantholysis.

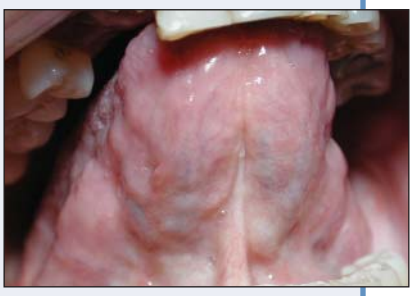

Figure 4: Clinical appearance after 9 months of treatment. All lesions in the oral cavity have resolved.

fusafungine (a topical antibacterial anti-inflammatory nasal spray) were prescribed. The symptoms worsened, and she consulted several other practitioners, who prescribed antibiotics, antifungals and topical anti-inflammatory agents. However, she experienced no improvement, and no diagnosis was ever made. The lesions caused odynophagia, which led to a 7% weight loss (6 kg). Her medical history was significant for hypothyroidism, which had been treated for the previous 7 years with levothyroxine sodium, hypertension treated with spironolactone and altizide, glaucoma treated with a collyrium, and recent-onset type 2 diabetes mellitus treated with benfluorex. The patient's outward appearance was normal, but she was depressed because the pain in her mouth had not subsided despite the various treatments. She had no fever, and her blood pressure was normal. An oral examination revealed large aphthoid lesions, with erosions and abrasion rings in the loosened epithelium, covering the entire oral mucosa. The lesions affected the linea alba of both cheeks, the gums, the border between the hard and soft palate and the ventral side of the tongue (**Fig. 2a**). There were 3 crusted erosive lesions on the shoulders and 5 on the lower back (**Fig. 2b**). Light pressure on the intact skin did not provoke the formation of bullae (negative Nikolsky's sign). A tentative diagnosis of PV was made, and the patient was referred to an internal medicine specialist because of the extent of the lesions and the presence of cutaneous lesions.

The results of blood tests and hepatic and lipid screening tests were normal. Perilesional cutaneous biopsy of the healthy tissue was carried out by the dermatology department. Pathological examination with hematoxylin and eosin dye revealed cleavage of the suprabasal intraepithelial layer, acantholysis and cell infiltration into the underlying connective tissue (**Fig. 3**). Direct immunofluorescence revealed an IgG deposit and a fraction of C3 complement in the intercellular zones of the epithelium. These elements confirmed the diagnosis of PV.

Initial treatment consisted of a "low Lever scheme" (see explanation below): 0.5 mg/kg prednisone daily (i.e., 40 mg/day for this patient)[1] and 15 mg methotrexate weekly.[5] After 2 months of treatment, the cutaneous lesions had almost vanished, but the oral lesions had not changed much. The methotrexate was increased to 20 mg/week and local corticosteroid therapy with beclomethasone was prescribed. After 6 months of treatment, the patient suffered a stress fracture in the neck of her femur probably brought on by the corticosteroid treatment. Prophylactic treatment with bisphosphonate and calcium base had been prescribed at the beginning of the PV therapy, but was stopped after 2 months because the patient could not swallow all of the medications. Once the fracture had healed, treatment of the oral lesions was resumed. By 9 months after the initial diagnosis, the corticosteroid therapy had been reduced to 30 mg/day and the methotrexate to 10 mg/week, and all lesions had disappeared (**Fig. 4**). Between the ninth and twelfth months of treatment, the corticosteroid therapy was further reduced, first to 20 mg/day and then to 10 mg/day; the dose of methotrexate was maintained at 10 mg/week.

Table 1 Classification of pemphigus[3]

Type	Anatomic features	Associated antibody	Target antigens
Pemphigus vulgarus (PV)	Persistent, painful oral lesions;		
Mucosal PV	skinfolds are affected;	IgG	Desmoglein 3
Cutaneous–mucosal PV	vegetans-like; fetid,	IgG	Desmogleins 1 and 3
Pemphigus vegetans	reddish plaques	IgG	Desmogleins 1 and 3
Superficial pemphigus	Characterized by mainly		
Pemphigus foliaceus	cutaneous lesions	IgG	Desmoglein 1
Pemphigus erythematosus		IgG	Desmoglein 1
Endemic pemphigus			
Brazil		IgG	Desmoglein 1, desmocollin 1
Tunisia		IgG	Desmogleins 1 and 3
Colombia		IgG	Desmoglein 1
Paraneoplastic pemphigus	Characterized by proliferation of various types of tumours, particularly lymphoid hemopathies	IgG	Desmoplakin I/II, desmogleins 1 and 3, envoplakin, periplakin, antigen 170 and 230 kilodalton
IgA pemphigus	Exudative lesions with vesicopustules	IgA	Desmocollin 1 and another unidentified antigen
Herpetiform pemphigus	Rosette-like lesions	IgG	Desmogleins 1 and 3
Drug-induced pemphigus	Mainly cutaneous lesions	IgG	Heterogeneous

Discussion

This case report describes a patient who presented with oral and cutaneous lesions of PV, which was not diagnosed until later in the course of the disease. In 75% to 80% of cases, PV lesions appear first in the oral cavity. Cutaneous lesions are diagnosed within 6 months in 99% of cases, whereas for oral lesions diagnosis within the first 6 months occurs in only 57% of cases. Furthermore, 70% of patients see more than 4 practitioners before the diagnosis is confirmed.[1,2,6]

Pemphigus is a rare autoimmune disorder with intraepidermal bullous lesions which affect in particular the oral, genital or ocular mucosa and the epidermis. This condition typically affects people between the ages of 50 and 60 and is generally evenly distributed between the sexes. PV, the most common form of pemphigus in Europe, represents 80% of all cases.[6] The incidence of PV is 0.1–0.5 per 100,000 population in the United States.[7] The initial lesions are often insidious and localized. The mouth is affected by persistent, painful ulcers and a burning sensation, which affects the appetite. The skin becomes affected several weeks or months after the mucosal lesions appear, with the appearance of flaccid blisters filled with clear fluid. These fragile blisters are easily broken, which leaves behind erosions surrounded by epidermal rings. Putting pressure on healthy skin causes either a bulla or an erosion; this effect is known as Nikolsky's sign.[1,2,8] This sign, although highly suggestive of pemphigus, is not specific and may be absent, as in the patient described here. Histologically, PV is characterized by intraepidermal cleavage, with a basal cellular layer forming the base of the blister. Direct immunofluorescence reveals a homogeneous deposit of IgG and C3 in the intercellular substance.[4]

The differential diagnosis of PV includes certain chronic mucodermatoses, which appear as bullous, ulcerous or erosive lesions (**Table 2**). In rare cases, pemphigus lesions may be confused with the ulcerative lesions of Crohn's disease or hemorrhagic rectal colitis or ulcerative lesions due to dietary deficiencies, such as iron (hypochromic iron deficiency), zinc (enteropathic acrodermatitis), folic acid or vitamin B_{12} (pernicious anemia).[1,2,8–10]

Pemphigoid can be diagnosed using the "clip sign,"[1] which involves using forceps to detach a flap of epithelium from around a gingival erosion. In erosive lichen planus, the "clip sign" is negative (i.e., it is not possible to detach an epithelial flap), and the associated reticular appearance

Table 2 Differential diagnosis of pemphigus vulgaris[1,2]

Disease or condition	Signs and symptoms
Mucosa pemphigoid	Positive "clip sign"; linear deposits at the dermo-epidermal junction (demonstrated by direct immunofluorescence)
Erosive lichen planus	Whickham's striae near erosions
Bullous pemphigoid	Tense bullae or vesicles with clear fluid, which may develop in erythematous or normal skin; intense pruritis; lesions symmetric and tending to appear on the flexion sides and roots of limbs, the anterior-internal side of thighs and the abdomen; rare on mucosa
Linear IgA dermatosis	Symmetric blisters and pruritic lesions; rosettes common
Dermatitis herpetiformis	Starts in adolescence or young adulthood, developing in spurts with spontaneous remissions; symmetric bullae and/or pruriginous vesicles on the elbows, knees and buttocks
Acquired epidermolysis bullosa	Development of bullae at the slightest friction; atrophic scar ring on the extension sides of limbs and joints
Behçet's aphthosis	Ulcers with regular borders, surrounded by a red halo with a flat fibrinous background
Erythema multiforme	Cutaneous rosette-like lesions (3 concentric areas with an inconsistent bullous centre); persistent flaps forming pseudomembranes or crusts on the lips
Disseminated lupus erythematosus	Systemic signs (e.g., fever, asthenia) often accompanied by petechiae, dry mouth and edema
Crohn's disease and hemorrhagic rectal colitis	Cutaneous–mucosal signs accompanied by abdominal pain, buccal aphthosis, asthenia, weight loss, anorexia
Bullous toxidermia (pigmented, fixed and bullous erythema from Stevens-Johnson's syndrome and toxic epidermal necrolysis)	Intense onset, rapid development, frequency of mucosal problems and general signs necessitate emergency admission to hospital
Chronic ulcerative stomatitis	Presence of erosive lesions of the oral mucosa
Folic acid or vitamin B_{12} deficiency (pernicious anemia)	Oral pain, erythematous tongue, asthenia and anemia; numbness in extremities and psychic troubles
Hypochromic iron deficiency	Paleness; fatigue; headaches; vertigo; buzzing in the ears; irritability; insomnia; problems with concentration; sensitivity to cold; anorexia and nausea
Enteropathic acrodermatitis	Impairment or loss of taste and smell; problems with sight; heavy diarrhea; alopecia; hypertension

facilitates the diagnosis. Herpes in both its acute form and its "crusted" chronic form can be readily diagnosed, especially if the patient is immunodepressed. Herpes lesions usually appear on the lips. Erythema multiforme is diagnosed on the basis of cutaneous lesions, which appear as "rosettes" (round maculopapular lesions made up of several concentric parts). Behçet's aphthosis is characterized by recurrent aphthoid ulcerations with possible associated genital and/or ocular ulcerations (uveitis, retinal vasculitis).[1,8,9]

In all cases of suspected pemphigus, a pathological examination must be carried out along with an immunofluorescence test.[1,9,10]

The treatment depends on the prognostic elements of the condition, such as the extent of the lesions and antibody levels. Treatment is administered in 2 phases: a loading phase, to control the disease, and a maintenance phase, which is further divided into consolidation and treatment tapering. The basic treatment for pemphigus consists of either local or systemic corticosteroid therapy (**Table 3**).[7] Local corticosteroid therapy is used in cases

Table 3 Treatments for pemphigus[7,11,12]

Corticosteroid
Local
Topical
Intralesional
Systemic
By mouth
Parenteral
Adjuvant
Immunosuppressors
Azathioprine
Cyclophosphamide
Methotrexate
Cyclosporine
Chlorambucil
Mycophenolate mofetil
Anti-inflammatory
Dapsone
Sulfamides
Tetracycline
Minocycline
Gold salts (aurothiomalate)
Colchicine
Retinoids
Thalidomide
Antimalarial
Hydroxychloroquine
Immunomodulating therapy
Plasmapheresis
Intravenous γ-globulins

where the PV is not extensive and lesions are limited to the oral cavity. Corticosteroids can be prescribed in the form of a paste, an ointment or a mouthwash administered as monotherapy or as adjunctive therapy with a systemic treatment. Intralesional corticosteroid therapy accelerates the scarring process of a lesion or is used to treat persistent lesions. This treatment, which gives inconsistent results, involves sublesional injections given every 7 to 15 days; treatment is stopped after 3 injections if there is no improvement. Scarring is accompanied by cutaneous or mucosal atrophy,[7,11] the major drawback of this treatment. Some patients may also see improvement with topical application of tacrolimus.[6,7] If the patient has extraoral lesions or if the oral damage is extensive, systemic corticosteroid therapy is initiated immediately. The initial dose depends on the chronicity of the lesions and the severity of the disease. A daily application of prednisone 0.5–2 mg/kg is recommended.[7,13] Depending on the response, the dose is gradually decreased to the minimum therapeutic dose, taken once a day in the morning to minimize side effects.

Corticosteroids taken by mouth have many long-term harmful effects, including adrenal atrophy, abnormal sensitivity to infection, high blood pressure, hypertriglyceridemia, hyperglycemia, cortisone myopathy, erosive duodenitis and stress fracture, as in the case presented here. To minimize iatrogenic effects, Lever and Schaumburg-Lever[5] recommended a treatment called the "high Lever scheme" with very high loading doses (100–175 mg taken twice daily for 5–10 weeks), followed by the "low Lever scheme," which includes a rapid reduction in dosage over a few weeks, with a maintenance dose of 40 mg every 2 days accompanied by local adjuvant treatment.[5] The lack of randomized controlled trials precludes any conclusions as to whether these protocols are superior to those using higher loading doses. An adjuvant drug is prescribed for most patients with severe PV,[12] with the objectives of reducing the cortisone dose and ensuring stable remission. However, the use of adjuvant therapy remains controversial. Therefore, it is only used in cases where corticosteroids are contraindicated, and a lower dosage of the corticosteroids is required. To date, there have been no objective data allowing determination of the best efficacy–tolerance ratio, and no prospective randomized studies have confirmed or invalidated the suitability of using these drugs immediately as an adjunct to corticosteroid therapy. Several adjuvant therapies are used (**Table 3**). Colchicine, thalidomide and retinoids can be beneficial in mild to moderate cases. Azathioprine and cyclophosphamide are the most commonly used drugs.[7,12] Azathioprine has a slow onset of action, which is appropriate in mild cases. Cyclophosphamide appears effective in maintaining remission after corticosteroid therapy is discontinued. However, its potential benefits must be weighed against the increased risk of side effects, such as hemorrhagic cystitis or hematological disorders. In a recent study, low-dose methotrexate showed some efficacy with no side effects.[12] Cyclosporine is indicated in cases of hematological abnormalities, which constitute a contraindication to other immunosuppressors. Mycophenolate mofetil is a new drug with few side effects; it has spectacular effects when used in conjunction with corticosteroids. Plasmapheresis is used to eliminate the antibodies responsible for the disease. In addition to its many side effects, the use of plasmapheresis is also limited by its complicated administration and high cost.[7,11,12] Some traditional methods should be used in association with systemic corticosteroid therapy, such as calcium and vitamin supplements, gastric protecting agents and bisphosphonate treatment (especially if osteopenia has been detected by osteodensitometry).[13] As a complement to systemic treatment, and if the oral cavity is affected, several steps must be taken to improve the patient's comfort. Strict local hygiene should be maintained with a diluted antiseptic mouthwash. The adequacy of prosthetic restorations must be checked, and a soft diet may be necessary.

Conclusions

PV is a rare chronic autoimmune cutaneous–mucosal disease that is often diagnosed late, even when oral lesions occur. If not treated promptly, the disease has a high morbidity rate, and it may be fatal in 5% to 10% of cases. The diagnosis is confirmed through pathological examination and direct immunofluorescence testing in the healthy perilesional mucosa. The therapeutic regimen, based on corticosteroid therapy as well as adjuvant treatments, helps to decrease painful symptoms. Current research is directed to finding substitutes for general corticosteroid therapy so as to lower the rates of iatrogenic morbidity.

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