



DENTAL PERSPECTIVE OF PEMPHIGUS VULGARIS – A CLINICAL CASE WITH DIAGNOSTIC AND TREATMENT GUIDELINES.

Elena Firkova

Department of Periodontology and Oral Diseases, Faculty of Dental Medicine, Medical University – Plovdiv, Bulgaria.

ABSTRACT

Pemphigus vulgaris (PV), a rare autoimmune mucocutaneous blistering disorder, has been reported with an incidence of 0.1-0.5 cases per 100,000 individuals worldwide per year. It is slightly more common in women and occurs primarily in adults during the 5th or 6th decade of life. The etiology of PV is uncertain but is supposed to be mediated by circulating immunoglobulin G autoantibodies against the desmosomal cadherins, desmoglein 1 and 3. Biopsy, light microscopic examination, and additional adjuvant tests, such as immunofluorescence studies can be used to establish the diagnosis. In most cases (70-90%), the first signs of disease appear on the oral mucosa, but most patients with oral lesions are initially misdiagnosed and treated improperly for months or years. If these patients are misdiagnosed or left untreated, PV may be fatal with a mortality rate ranging from 60% to 90%. Therefore, here we discuss the basics of diagnosing and treating patients with PV and oral lesions.

Keywords: pemphigus, oral lesions, oral diagnosis, dental treatment

INTRODUCTION

Pemphigus refers to a group of potentially life-threatening autoimmune mucocutaneous diseases, characterized by the formation of intraepithelial oral and skin blisters. Pemphigus can involve other mucosae besides the oral mucosa, including conjunctive, nasal, pharyngeal, laryngeal, esophageal, genital, and anal mucosae.

The word “pemphigus” comes from the greek *pemphix*, which means blister or bubble. It is a rare disease, which affects 0.1 – 0.5 people/100 000 inhabitants per year. The peak of incidence occurs between the fourth and six decades of life, with the male to female ratio of 1:2.

Pemphigus is classified into 6 major groups: Pemphigus Vulgaris (PV), Pemphigus Foliaceus, Pemphigus Vegetans, Pemphigus Erythematosus, paraneoplastic pemphigus and IgA pemphigus [1].

The exact cause for this disease is still not clear, but it is widely accepted, that it is a result of an autoimmune process, in which serum IgG antibodies are produced against normal desmosomal adhesion molecules (desmogleins) of the cell membranes of keratinocytes.

Desmoglein-1 is expressed in all layers of the epidermis, with higher concentration in the more superficial layers, whereas Desmoglein-3 is expressed in the basal and parabasal layers. The binding of antibodies to desmoglein at mucosal or cutaneous level leads to loss of cellular adhesion, acantholysis in stratum spinosum and the consequent formation of blisters [2].

Although PV is considered an idiopathic autoimmune disease, some environmental factors are discussed as possible to initiate the autoimmune reaction. Such factors could be medicines with thiol group-like angiotensin-converting inhibitors, penicillamine, rifampicin and others [3]; viruses, even nutritional like garlic [4]. There is a strong genetic background to pemphigus with linkage to HLA class II alleles and ethnic groups such as Ashkenazi Jews and those of Mediterranean origin, are especially liable [5].

PV is the main variant and the one that most affects the mouth. Oral lesions are the first manifestation of the disease in 50-90% of cases. They can be the only clinical symptom for a period of 2-6 months until the appearance of skin lesions, which means that recognizing oral manifestations should be extremely important for both dentists and dermatologists. Clinically, the oral blisters have a very thin wall and rapidly rupture due to oral traumas, resulting in painful and hemorrhagic erosions. The ulcers and erosions bleed easily, do not heal for a long period of time which leads to worse life quality. The patients complain from constant pain, burning sensations and general discomfort. While any area in the oral cavity can be involved, the soft palate, buccal mucosa, and lips are predominantly affected. Among these locations, blisters are most common found in areas, subjected to frictional trauma [6].

The diagnosis is based on a set of 3 criteria:

1. Clinical signs – persistent desquamative gingivitis with multiple painful erosions; positive Nikolsky sign (although not sensitive, this seems to be highly specific technique for oral blisters [7]);

2. Histological assessment of biopsy samples – acantholysis, Tzanck acantholytic cells;

3. Immunological tests – immunofluorescent techniques. Direct immunofluorescence shows positive intercellular signals for IgG deposits in keratinocytes. Indirect immunofluorescence proves pemphigus antibodies in the

serum. ELISA test – with recombinant desmoglein 1 and 3 to measure anti-desmoglein antibodies in serum. When all of the above is still uncertain – immunoprecipitation and immunoblotting techniques [8].

The treatment should be organized by the dermatologist, in close cooperation with a periodontologist for oral treatment. Standard therapy consists of a combined use administration of systemic corticosteroids and immunosuppressants [9]. After achieving a remission, the dose is minimized to levels, able to control the active course of the disease but to avoid the side effects of these drugs. Additional therapeutic arsenal includes pulse therapy (intravenous infusion of very high doses of immunosuppressants for a short time period); high doses of intravenous immunoglobulin; plasmapheresis; extracorporeal photopheresis with exposure of serum to psoralens and UVA; antagonists of tumor necrosis factor α (infliximab, etanercept); antiCD20 monoclonal antibodies (rituximab) [10]. The morbidity and mortality of PV are 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 [11]. Before the introduction of corticosteroids, around 75% of patients died within the first year. Currently, less than 10% of patients die, usually due to the secondary effects of the treatment [12].

CASE REPORT

A 68-years female was referred to the department of periodontology and oral diseases, Faculty of Dental Medicine – Plovdiv from an ear-nose-throat specialist with chief complain of multiple “aphthae” in the oral cavity and throat, causing severe pain. The history revealed that lesions appeared almost 3 months before the visit. The patient actively sought help from her dentist since the beginning, but the diagnosis was “recurrent aphthous stomatitis” and it was treated with antiseptic dyes (Granofurin, Vagothyl) and herbal rinses. 2 months after the appearance of first oral blisters, skin blisters appeared on the hands and legs. Anyway, the patient neglected the blisters, considering them as a food allergy or trauma. The main reason she continued looking for help was the inability to swallow because of the constant pain in the mouth and throat.

Intraoral examination revealed clinical signs, characteristic for desquamative gingivitis and advanced periodontal disease (fig.1). There were multiple and persistent areas of erosions on the soft palate (fig.2), buccal mucosa (fig. 3) and ventral surface of the tongue (fig.4). Some of the erosions located on the distal attached maxillar gingiva were covered by thin superficial membrane (fig. 5a, b). The gingival mucosa exhibited a positive Nikolsky sign. The patient reported a spontaneous bleeding from the gums; severe bleeding was observed under slight provocation with a periodontal probe. Halitosis and formation of dark crusts at the vermillion were noticed, result of healed blisters. Extraoral examination revealed few blisters on the palmar surfaces of both arms; the decollete and very big crusts from blisters on the legs (fig.6 a, b). The patient used to punch the blisters for the liquid to flow out and then put an antibiotic dressing on top.

Fig. 1. Clinical signs of desquamative gingivitis. Bleeding on slight provocation. A ruptured blister in the attached gingiva in maxillar right premolars. Ulcerated gingival margins and papillae in the lower canines and premolars.



Fig. 2. Painful palatal lesions



Fig. 3. Buccal erosion, next to tooth #37.

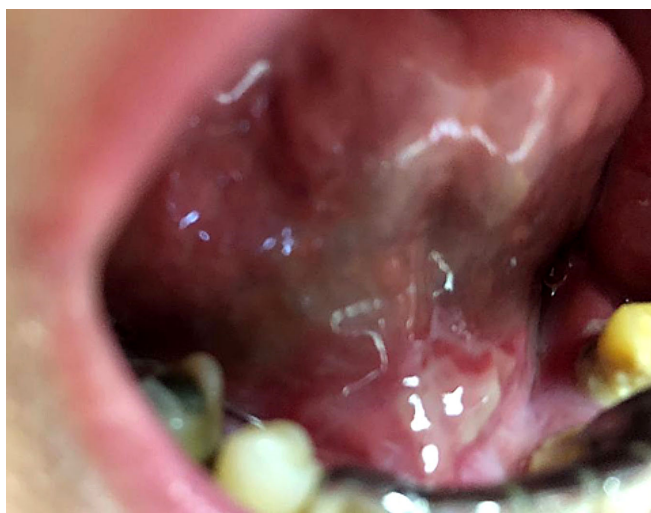


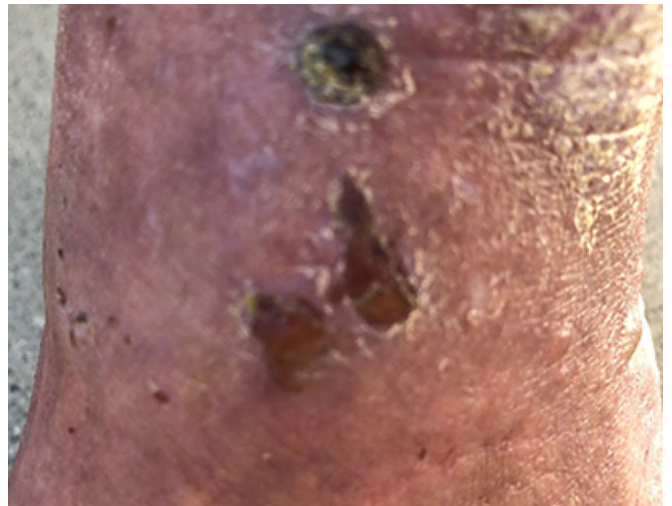
Fig. 4. Erosion on the ventral surface of the tongue



Fig. 5 a,b. Erosions in the attached gingiva of the maxilla; covered by a thin membrane (wall of the blister)



Fig. 6 a, b. Skin blister. Hemorrhagic crusts on the ankle after a big bullae rupture.



There was no history of any systemic diseases except high blood pressure for 6-7 years, which was treated successfully with calcium channel blockers.

Based on the history and clinical examination, a provisional diagnosis of PV was made. The patient was immediately referred to the dermatologic clinic in the Medical University – Plovdiv for histologic and immunologic tests and relevant systemic treatment.

DISCUSSION

This clinical case is a typical example of a patient with misdiagnosed and incorrectly treated disease, which cost a delay of a few months of adequate treatment to achieve remission. Setting the provisional diagnosis of general practitioners and dentists is not difficult if there is a knowledge of the basic clinical symptoms of the disease and the differential diagnosis of oral lesions.

Guidelines for differential diagnosis of oral lesions

The most frequent differential diagnosis in patients

with oral lesions are:

1. Recurrent aphthous stomatitis. In this case, small ulcers with white-yellowish membrane are seen, surrounded by an erythematous halo. They disappear without treatment for 10-14 days. Acute course;

2. Behcet disease. Big painful aphtae in the oral mucosa, together with genital and ocular ulcers.

3. Acute herpetic gingivostomatitis. Occurs most often in infants under 6 years. In this case there is a prodromal period, then small grayish vesicles which may occur on the gingiva, labial and buccal mucosa, soft palate, pharynx and tongue. After 24 hours vesicles rupture and reveal painful ulcers with red halo-like margins and a depressed white central portion. Heal without scarring for 7-10 days.

4. Bullous lichen planus. Characteristic reticular lesions are always found connected with bullae;

5. Mucosal or cicatricial pemphigoid. Oral lesions do not appear before skin lesions; blisters are smaller with a shorter duration than these in PV. Heal fast without scarring;

6. Erythema multiforme. Target-shaped skin lesions, multiple large shallow, painful oral ulcers with an erythematous border; hemorrhagic crusting of the vermilion border of the lips [6, 13].

Guidelines for treatment of oral lesions

The systemic treatment, prescribed by the dermatologist affects the course of oral ulceration in patients with PV, but still, their response to treatment is much slower in comparison to the cutaneous lesions. That is why a close collaboration between dermatologist and dentist is required for complete healing of oral signs.

1. Application of topical corticosteroid creams (0.1% triamcinolone acetonide in Orabase, 0.05% fluocinolone acetonide, 0.05% clobetasol propionate);

2. In refractory lesions - intralesional injection of triamcinolone acetonide 20 µg/ml every 7-15 days, but the injections must be stopped if there is no improvement after the 3^d one;

3. Optimal oral hygiene, including soft mouth rinses with diluted chlorhexidine; no mouth rinses with alcohol;

4. Proper atraumatic periodontal treatment and supportive periodontal care; a prophylactic administration of 20 mg prednisone/day is recommended for 5-7 days before any dental procedure, which is connected with trauma to the gums [14, 15, 16,17].

Minimizing oral irritations is very important in patients with PV. There is a study suggested co-enzyme Q10 as adjuvant therapy for periodontal involvement [18].

CONCLUSIONS

Most patients with oral lesions could be initially misdiagnosed, usually as aphthous stomatitis, and may be improperly treated for months. This can have crucial consequences. When diagnosed on time and treated correctly, the long-term prognosis depends on the age of the patient and the initial severity, the extent of the lesions, the drug dose, required for remission of the disease, and possible side effects of the medications. There is no consensus on the optimal treatment approaches and a lack of evidence-based treatment guidelines. For a better overall prognosis of patients with PV, a close cooperation between dermatologist and dentist and a personalized approach is necessary in order to improve their life quality.

REFERENCES:

1. Black M, Mignogna MD, Scully C. Number II. Pemphigus vulgaris. *Oral Dis.* 2005 May;11(3):119-30. [PubMed] [Crossref]
2. Amagai M. Autoimmune and infectious skin diseases that target desmogleins. *Proc Jpn Acad Ser B Phys Biol Sci.* 2010; 86(5):524-37 [PubMed].
3. Mutasim DF, Pelc NJ, Anhalt GJ. Drug-induced pemphigus. *Dermatol Clin.* 1993 Jul;11(3):463-71 [PubMed]
4. Brenner S, Wolf R. Possible nutritional factors in induced pemphigus. *Dermatology* 1994; 189(4):337-9 [PubMed] [Crossref]
5. Tron F, Gilbert D, Mouquet H, Joly P, Drout L, Makni S, et al. Genetic factors in pemphigus. *J Autoimmun.* 2005 Jun;24(4):319-28. [PubMed] [Crossref]
6. Bascones-Martinez A, Munoz-Corcuera M, Bascones-Ilundain C, Esparza-Gómez G. Oral Manifestations of Pemphigus Vulgaris: Clinical Presentation, Differential Diagnosis and Management. *J Clin Exp Dermatol Res.* 2010; 1:112 [Crossref]
7. Mignogna MD, Fortuna G, Leuci S, Ruoppo E, Marasca F, Matarasso S. Nikolsky's sign on the gingival mucosa: a clinical tool for oral health practitioners. *J Periodontol.* 2008 Dec;79(12):2241-6 [PubMed] [Crossref]
8. Mihai S, Sitaru C. Immunopathology and molecular diagnosis of autoimmune bullous diseases. *J Cell Mol Med* 2007 May-Jun;11(3):462-81 [PubMed] [Crossref]
9. Yeh SW, Sami N, Ahmed RA. Treatment of pemphigus vulgaris: Current and emerging options. *Am J Clin Dermatol.* 2005; 6(5):327-42 [PubMed] [Crossref]
10. Prajapati V, Mydlarski PR. Advances in pemphigus therapy. *Skin Therapy Lett.* 2008 Apr;13(3):4-7 [PubMed].
11. Scully C, Mignogna M. Oral mucosal disease: Pemphigus. *Br J Oral Maxillofac Surg.* 2008 Jun;46(4):272-7. [PubMed] [Crossref]
12. Ruocco E, Baroni A, Wolf R, Ruocco V. Life-threatening bullous dermatoses: Pemphigus vulgaris. *Clin Dermatol* 2005 May-Jun;23(3):223-6 [PubMed] [Crossref]
13. Kapoor S, Sikka P, Kaur GP. Pemphigus vulgaris of oral cavity: A case report with its treatment strategies. *Int J Nutr Pharmacol Neurol Dis.* 2013; 3(2):146-149. [Crossref]
14. Akman A, Kacaroglu H, Yilmaz E, Alpsoy E. Periodontal status in patients with pemphigus vulgaris. *Oral Diseases* 2008 Oct;14(7):640-3. [PubMed] [Crossref].
15. Arduino PG, Lopetuso E,

Carcieri P, Giacometti S, Carbone M, Tanteri C, et al. Professional oral hygiene treatment and detailed oral hygiene instructions in patients affected by mucous membrane pemphigoid with specific gingival localization: a pilot study in 12 patients. *Int J Dent Hyg.* 2012 May;10(2):138-41 [PubMed] [Crossref].

16. Gambino A, Carbone M, Arduino PG, Carcieri P, Carbone L, Broccoletti R. Conservative approach in patients with pemphigus gingival vulgaris: a pilot study of five cases. *Int J Dent.* 2014; 2014:747506 [PubMed] [Crossref].

17. Tamgadge S, Tamgadge A, Bhatt DM, Bhalerao S, Pereira T.

Pemphigus vulgaris. *Contemp Clin Dent.* 2011 2(2):134-7. [PubMed] [Crossref].

18. Prashanth J, Jesudoss Prabhakaran AC. The beneficial effect of Coenzyme Q in diabetic neuropathy: An overview. *Int J Nutr Pharmacol Neurol Dis* 2012; 2(2):80-83 [Crossref].

Please cite this article as: Firkova E. Dental Perspective of Pemphigus Vulgaris – A clinical case with Diagnostic and Treatment Guidelines. *J of IMAB.* 2019 Apr-Jun;25(2):2516-2520. DOI: <https://doi.org/10.5272/jimab.2019252.2516>

Received: 23/10/2018; Published online: 22/04/2019



Corresponding author:

Assoc. Prof. Elena Firkova, PhD, DDS
Department of Periodontology and Oral Diseases, Faculty of Dental Medicine,
Medical University – Plovdiv
e-mail: elenafirkova@yahoo.com