Oral Pemphigus Vulgaris: A Case Report

Desai Rajiv S¹, Wadekar Mansi¹, Bansal Shivani P¹, Shirsat Pankaj M¹, Pooja Prasad¹
¹Department of Oral Pathology and Microbiology

Abstract:
Pemphigus vulgaris is a chronic inflammatory autoimmune, intraepithelial blistering potentially life threatening disease. It initially manifests in the form of intraoral lesions, which may spread to mucous membrane and skin. It is characterized by the production of autoantibodies against intercellular substances. Eighty to ninety percent of patients with pemphigus vulgaris develop oral lesions and in 60% of cases oral lesions are the first sign therefore a dentist must be familiar with clinical manifestations of pemphigus vulgaris for early diagnosis and treatment.

Keywords: Pemphigus vulgaris; autoimmune disease; vesiculobullous disease.

Introduction:
Pemphigus is derived from Greek word pemphix meaning bubble or blister. It is described as a group of chronic bullous diseases, originally named by Wichman in 1791. There are 0.5 to 3.2 cases reported each year per 100,000 population, with the highest incidence in the 5th and 6th decade of life, with male to female ratio of 1:2. More common in Ashkenazi Jews and those of Mediterranean origin. Pemphigus is a group of autoimmune blistering disease of skin and mucous membrane characterized histologically by intradermal blisters, immunologically by circulating IgG antibody directed against cadherin-type epithelial cell adhesion molecules particularly desmoglein 3. Cadherins are calcium-dependent intercellular adhesion molecules that are essential for tissue integrity. The disease usually occurs in the patients with certain HLA genotypes [HLA class II allele associations are found with HLA-DR4 (DRB1*0402), DRw14 (DRB1*1041) and DQB1*0503] which generates B-cells responsible for the specific auto antibodies. The activation of these B-cells require a complex interaction with CD4 + T-helper 2 (Th2) cells and it is the Th2 cell over activation that leads to the auto antibody production that is necessary for pemphigus vulgaris and pemphigus foliaceus.

The primary subset of pemphigus are pemphigus vulgaris (PV), pemphigus vegetans, pemphigus foliaceus (PF), pemphigus erythematosus, paraneoplastic pemphigus (PNP) and drug related pemphigus. PV is the most common form of pemphigus, accounting for over 80% of cases. Lesions can occur anywhere on the oral mucosa, but most commonly affects buccal mucosa followed by involvement of the palatal, lingual and labial mucosa.

Case Report
A 59-year-old male reported to the Department of Oral Pathology and Microbiology with chief complaint of painful ulcers and burning sensation in mouth since 5-6 months. Extra-orally there was no sign of any skin or mucosal lesion (Figure 1). The introduction of corticosteroids, reduced mortality rate from 75% to less than 10%. We report an interesting case of PV in 59-year-old male complaining of painful ulcers and burning sensation in mouth since 5-6 months.

Figure 1: Extra-oral photograph of patient showing no skin lesions.
Intra-orally, multiple ulcerative lesions with yellow pseudomembrane surrounded by erythematous borders were seen on hard palate, ventral and lateral aspect of tongue, lower labial mucosa, vestibule, bilateral buccal mucosa and floor of the mouth. (Figure 2) Erosive bleeding spots were seen on scraping pseudomembrane. Nikolysky’s sign was positive. The presence of numerous chronic oral ulcers, flaccid bullae and positive Nikolysky sign led to the differential diagnosis of various vesiculo-bullous lesion affecting the oral cavity, including PV, mucous membrane pemphigoid, bullous lichen planus, para neoplastic pemphigus, chronic ulcerative stomatitis, recurrent herpes virus infection, erythema multiforme.

Incisional biopsy from right buccal mucosa and gingiva was obtained. Histopathological examination observed the presence of supra-basilar blister formation with an intact basement membrane. The dense layer of fibrinous exudate containing inflammatory cells covered the split area. (Figure 3) Few giant cells (Tzanck cells) were noticed in the split area. In the subepithelial and perivascular regions, there was a chronic inflammatory cell infiltration. A diagnosis of PV was provided on the basis of clinico-pathological correlation. Evaluation of the circulating autoantibody titers to Dsg 1 and Dsg 3 was conducted by enzyme immunoassay. The ELISA test provides diagnostic criteria for the presence of absence of circulating autoantibodies, that is if the observed value is more than 20 then the result is positive and if it is less than 20 then the result is negative. For this case the observed value of both Dsg 1 and Dsg 3 was more than 20.

Direct immunofluorescence (DIF) study was positive and revealed IgG and C3 deposits in intercellular spaces throughout the epithelium and exhibited a characteristic fish-net pattern in PV patients. A final diagnosis of oral PV was rendered, and the patient was sent to the dermatology department for further treatment.

Discussion

PV is an intra-epithelial suprabasilar blistering disease affecting the skin and mucous membranes, caused by circulating autoantibodies directed against intercellular adhesion molecules resulting in acantholysis of lower layer of stratum spinosum.\(^{(1)}\)

In 70-90% cases, earliest manifestation of the disease appears on the oral mucosa. Although the lesions can develop anywhere in the oral cavity, they are most frequently encountered in tissue which are subjected to frictional damage, such as the cheek mucosa, pharynx, larynx, esophagus, genital mucosa as well as the skin where intact blisters are widespread.\(^{(2)}\)

The binding of IgG (IgG1 & IgG4) autoantibodies to Dsg 3,
an adhesion molecule which is a transmembrane glycoprotein found on desmosome. Dsg 3 is the principle mechanism responsible for causing PV. Dsg 3 is mostly found in the oral epithelium, whereas Dsg I and Dsg 3 are present in the skin. Anti-Dsg I and anti-Dsg 3 antibodies causes the cells of stratum spinosum to lose their adhesive function, resulting in bulla formation. The diagnosis of pemphigus is based on thorough clinicopathologic correlation. DIF on sections from a fresh frozen biopsy or indirect immunofluorescence (IIF) performed on patient’s serum are important for verifying the diagnosis. To rule out PV, the DIF and IIF are frequently used. The DIF is based on the in vitro antigen-antibody reaction, produced by ultraviolet-excited fluorochromes (fluorescein isothiocyanate). Patients skin or mucosa can be used to reveal intercellular distribution of IgG and C3 deposits. The perilesional or mucosal skin biopsy should be frozen in liquid nitrogen or placed in Michel’s transport medium as soon as possible in order to achieve the best result. Michel’s solution consist of ammonium sulfate, N-ethyl maleimide, and magnesium sulfate in citrate buffer, which enable specimen to preserve for up to two weeks. Dsg3, an autoantigen with increased expression in the stratum spinosum’s lower layer, is targeted by IgG autoantibodies. IIF of higher expression in lower layer of stratum spinosum. IIF is used to confirm the presence of circulating autoantibodies, however it cannot discriminate Dsg3 and DsgI antibodies. The ideal vesicles and bullae for biopsies are those that are less than 24 hours old and yet intact. The Biopsy should be taken from the lesion’s leading edge. Hematoxylin & eosin stained sections show areas of characteristic suprabasilar acantholysis. (Figure 4) Suprabasilar split distinguishes PV from other sub-epithelial blistering diseases such as mucous membrane pemphigoid, bullous lichen planus and chronic ulcerative stomatitis. ELISA, a quantitative serological test with high sensitivity and specificity, detects IgG anti-DsgI and anti-Dsg3 autoantibodies, can be used for further investigations and follow up. This life threatening condition should be urgently treated as it result in a breakdown of epidermal barrier function, which leads to a loss of bodily fluids and subsequent and bacterial infection. The principal mode of treatment is systemic corticosteroid therapy as they present potent anti-inflammatory and immunosuppressive action. Prolonged use of corticosteroids can lead to adverse effects like diabetes, hypertension and osteoporosis. To avoid side effects, It is advisable to combine systemic corticosteroids with an immunosuppressive medication. Patient undergoing corticosteroids therapy should be regularly monitored for blood sugar and hypertension. The most widely prescribed oral corticosteroid is prednisone, or prednisolone in combination with deflazacort. When prednisone dose more than 1 mg/kg/day are not an option, corticosteroids can be given as pulse therapy, which involves using methylprednisolone and dexamethasone for three successive days. Pulse therapy provides the benefit of allowing for a rapid reduction in prednisone dose while lowering its side effects. Adjuvant medicines such as azathioprine, rituximab, cyclophosphamide, dapsone, methotrexate, and others can be administered if corticosteroid alone cannot control the condition. Topical therapy of PV lesions lowers pain and prevent secondary infection when used as an adjuvant to systemic treatment. Corticosteroid and antibiotic creams can be applied topically. Antiseptic solutions such as potassium permanganate (1:10,000 or 1:20,000) or chlorhexidine may also be used in severe situations. The oral mucosa may even be treated with potent gel corticosteroids such as clobetasol dipropionate. Other immune modulating drugs such as intravenous immunoglobulins (IVIG), monoclonal antibody therapy directed against B-lymphocytes, plasmapheresis have been used for effective therapy if the condition does not respond to systemic corticosteroids. Recurrence of oral PV is possible, so patients need to be observed for a long period of time and, disease activity should be monitored using clinical or immunological parameters, it may be possible to take preventive measures in advance. Periodic follow-ups should be performed and treatment should start immediately if lesions recur.

Conclusion
PV being a potentially fatal condition, might result in death if left untreated. Usually the oral mucosa is the first involved site even before the skin and other mucosal sites, so the dentist plays an important role in diagnosing the disease.

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Reference:
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