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Pemphigus Vulgaris Unveiled: From Nikolsky's Sign to Immunofluorescence

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Abstract

Oral pemphigus vulgaris (PV) is a rare, chronic, autoimmune, mucocutaneous disorder characterized by the formation of flaccid blisters and painful erosions, predominantly affecting the oral mucosa. This case report describes a 52-year-old female presenting with ulcerations in the buccal mucosa as well as alveolar mucosa, accompanied by a positive Nikolsky's sign. Diagnostic investigations including cytology, histopathology, and direct immunofluorescence, confirmed the diagnosis of PV, revealing characteristic features such as suprabasilar split, Tzanck cells, and a "fish-net" pattern of IgG deposition. Early diagnosis and initiation of systemic corticosteroids and immunosuppressive therapy are crucial in reducing morbidity and preventing complications. This report, emphasizes the importance of early recognition, particularly by dental professionals, and highlight the advances in treatment strategies including the role of therapeutic agents like rituximab, in improving patient outcomes.

Keywords: Pemphigus Vulgaris, Autoimmune disorder, Blisters, Nikolsky's sign, suprabasilar split, Tzanck cells, Direct immunofluorescence, "fish-net" pattern

Introduction

The term pemphigus originates from the Greek word "pemphix," meaning blister or bubble, and was first introduced by Boissier de Sauvages in 1750s. Dr. Wichman in 1791, officially introduced the term pemphigus to describe a chronic blistering condition,

which is now classified among the autoimmune bullous diseases.[1].

Pemphigus is a rare, potentially life-threatening autoimmune disease affecting the skin and mucous membranes. Its global incidence is 0.5–3.2 cases per million annually, with a female predominance (2:1) and peak onset in the 5th to 6th decade. In India, prevalence ranges from 0.09% to 1.8%, varying by region and ethnicity[2,3].

Pemphigus includes several variants, with Pemphigus Vulgaris (PV) and Pemphigus Foliaceus (PF) being the most common. PV involves suprabasilar clefting, while PF shows subcorneal separation. PV accounts for over 80% of cases, often presenting with oral mucosal lesions [3].

Pemphigus vulgaris (PV) is caused by autoantibodies against desmoglein-3 (and sometimes desmoglein-1), leading to acantholysis and intraepithelial blistering. Genetic predisposition is linked to HLA-DR4 and HLA-DR14, particularly in Ashkenazi Jews, Mediterranean, and Japanese populations [1,2,6].

Oral lesions are often the first sign of Pemphigus Vulgaris, presenting as flaccid bullae that rupture into painful ulcers, mainly on the buccal mucosa. Desquamative gingivitis may occur but is less common. Skin involvement includes flaccid blisters and crusted erosions, typically on the scalp, face, chest, and groin [7,8].

Histologically, PV shows suprabasilar acantholysis with a “row of tombstones” appearance. Diagnosis is confirmed by DIF revealing intercellular IgG and C3, while IIF and ELISA detect circulating desmoglein-3 autoantibodies[9].

Early diagnosis is essential, as delayed recognition, especially in mucosal-only presentations, can lead to progression to skin lesions and increased morbidity. Advanced diagnostic techniques such as Enzyme-Linked Immunosorbent Assays (ELISA) and biochip mosaic assays have improved diagnostic accuracy together with monitoring of disease activity[10].

Systemic corticosteroids remain the cornerstone of treatment. They are often combined with immunosuppressive agents like azathioprine, mycophenolate mofetil, or rituximab, a monoclonal anti-CD20 antibody that has shown excellent results in refractory cases[11]. Prompt initiation of therapy can significantly improve the prognosis and prevent life-threatening complications.

Case Report

A 52-year-old female patient presented with complaints of pain and ulceration on both cheeks, persisting for 20 days. She experienced discomfort that interfered with eating, speaking, and maintaining oral hygiene. She also gave a history of prior skin involvement on forearm, though no active lesions were observed at the time of examination. Her medical history was also non-contributory.

Intraoral examination revealed well-defined, erythematous areas of denudation on both buccal mucosae, retromolar regions, and alveolar mucosa with respect to 43, 44, and 45. The patient reported with the history of vesicle formation followed by spontaneous rupture. A positive Nikolsky’s sign was noted intraorally, with gentle pressure causing epithelial detachment, raising clinical suspicion of Pemphigus Vulgaris. Cytological smears from the oral lesions, stained with hematoxylin and eosin (H&E), showed the presence of clusters and individual polygonal or round keratinocytes having basophilic cytoplasm with perinuclear halo, suggestive of Tzanck cells.

A perilesional biopsy was performed under local anesthesia, soft tissue sample received and divided into two halves. Histopathological evaluation was carried out

with one half of the tissue sections while the other was send for Direct Immunofluorescence studies.

Light microscopic histopathological evaluation revealed suprabasilar clefting in the surface epithelium with intraepithelial acantholysis. Basal keratinocytes exhibited tombstones appearance. Spongiosis and free-floating Tzanck cells were also observed, supporting the diagnosis of Pemphigus Vulgaris.

Direct Immunofluorescence studies demonstrated intercellular deposition of IgG in a "fishnet" pattern along the spinous layer of the epithelium, confirming the autoimmune etiology of this disease.

Based on clinical features and light microscopic evaluation(cytological evidence, histopathological analysis and Direct Immunofluorescence findings) a confirmatory diagnosis of Pemphigus Vulgaris was established.

After a confirmatory diagnosis, systemic corticosteroids were administered using Prednisolone at a dose of 30 mg per day in divided doses for 10 days, followed by 20 mg and 10mg daily for 10 days respectively. In addition, Cephalexin 500 mg was prescribed three times daily for 7 days to prevent any secondary infection. Micronutrient supplements were also administered as supportive therapy.

Discussion

Pemphigus encompasses several clinical variants, including Pemphigus Vulgaris (PV), Pemphigus Vegetans, Pemphigus Foliaceus, Pemphigus Erythematosus, Paraneoplastic Pemphigus (PNP), drug-induced Pemphigus**,** and Immunoglobulin A (IgA) Pemphigus**.** Pemphigus vulgaris is the most prevalent form**,** responsible for over 80% of all pemphigus cases**,** particularly those presenting with oral mucosal lesions**.**

The etiopathogenesis of PV involves autoantibodies directed against desmoglein-3 (and sometimes desmoglein-1), critical adhesion molecules in desmosomes of epithelial cells. This autoantibody-mediated attack leads to acantholysis, the loss of intercellular connections, causing intraepithelial blister formation [1,2]. The pathogenesis is further explained by the "desmoglein compensation theory" and the "multiple-hit hypothesis," suggesting the involvement of non-desmosomal proteins and multiple signaling pathways including p38 MAPK, SRC, and EGFR kinase[4]. Moreover, genetic predisposition,(particularly the presence of HLA-DR4 and HLA-DRB1 alleles), environmental triggers, certain medications (e.g., Penicillamine, Captopril), viral infections, and stress may act as precipitating factors[5].

Pemphigus vulgaris (PV) is a chronic, potentially life-threatening autoimmune disorder characterized by intraepithelial vesicle formation .It primarily affects the mucous membranes and skin, with oral manifestations often serving as the first clinical indicator[1,2]. In the present case, the patient exhibited classic oral findings of PV, including painful ulcerations on the buccal mucosa and alveolar ridge, preceded by vesicle formation and a positive Nikolsky's sign, all of which are aligned with typical early presentations [3].

Cytological smear revealed Tzanck cells—acantholytic keratinocytes characterized by a perinuclear halo and hyperchromatic nuclei—which are supportive but not pathognomonic of PV[7], in present case too clusters and individual polygonal or round keratinocytes having basophilic cytoplasm with perinuclear halo were noticed under light microscope with hematoxillin and eosin staining.

Histopathology, being the cornerstone for diagnosis of PV, revealed the presence of suprabasilar clefting, a "row of tombstones" appearance of basal keratinocytes, and floating Tzanck cells. These findings are consistent with

intraepithelial acantholysis specific to PV and help to differentiate it from subepithelial blistering diseases such as mucous membrane pemphigoid and bullous lichen planus[8].

Direct immunofluorescence (DIF) of perilesional tissue remains the gold standard for confirming PV. In this case, DIF demonstrated intercellular IgG deposition in a characteristic "fishnet" or "chicken-wire" pattern throughout the epithelium, confirming the autoimmune nature of the disease.

PV is mediated by IgG autoantibodies, predominantly of the IgG4 subclass, targeting desmoglein 3 (Dsg3) and/or desmoglein 1 (Dsg1), which are cadherin-type adhesion molecules found in desmosomes of mucosal and epidermal cells[9,10]. Mucosal-dominant PV is typically associated with anti-Dsg3 antibodies, while mucocutaneous forms show both anti-Dsg1 and anti-Dsg3 reactivity[11].

Management of PV requires early and aggressive intervention to prevent complications such as secondary infections, electrolyte imbalance, and sepsis, which can be fatal if untreated. The standard of care includes systemic corticosteroids, often combined with immunosuppressive agents like azathioprine or mycophenolate mofetil as steroid-sparing agents[12]. In refractory cases, biologics such as rituximab (anti-CD20 monoclonal antibody) or intravenous immunoglobulin (IVIG) have shown promising results due to their targeted immunomodulatory actions[10,11] In the present case Prednisolone with tapering dose along with broad spectrum antibiotic like Cephalexin and micronutrient supplements give a promising result.

In this case, prompt diagnosis through a combination of clinical signs, cytopathology, histopathology, and immunofluorescence allowed for early therapeutic intervention, likely contributing to a favorable clinical outcome. The present case stated the importance of considering PV in the differential diagnosis of chronic, non-healing oral ulcers, particularly when accompanied by a positive Nikolsky's sign and vesiculobullous history.

Conclusion

Oral pemphigus vulgaris is a potentially debilitating condition that requires early recognition and prompt treatment to prevent complications and improve the patient's quality of life. Since the disease starts with oral lesions in 53.52% cases, the dental surgeons play a crucial role for diagnosis of the lesion in at early stage. Given its chronic nature, PV demands careful, long-term management with a combination of systemic therapies and local treatments. Advances in therapeutic options, particularly biologic agents like rituximab, offer hope for patients who do not respond to traditional treatments.

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Legend Figures

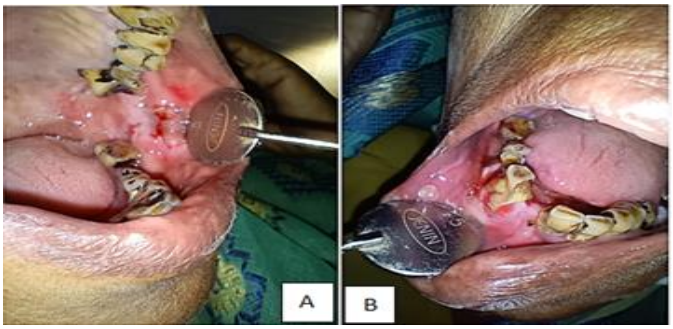

Figure A and B: intraoral examination revealed a relatively well defined erythematous area of denuded mucosa with history of vesiculation and spontaneous rupture of the vesicles in relation to both buccal mucosa and retromolar area and also over the alveolar mucosa with respect to 43, 44 and 45.

Figure C and D: Extra oral examination revealed skin manifestation with respect to forearm.

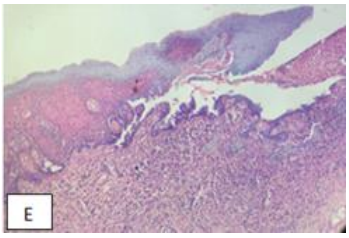

Figure E: The histopathological evaluation of the biopsied tissue revealed suprabasilar split, intraepithelial separation (acantholysis), "row of tombstone" apperaence of the basal cell layer .

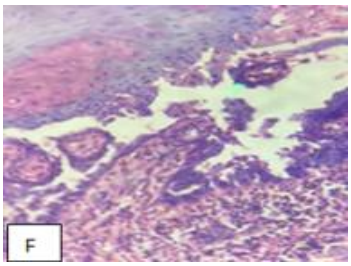

Figure F: Areas of spongiosis and free floting Tzank cell.

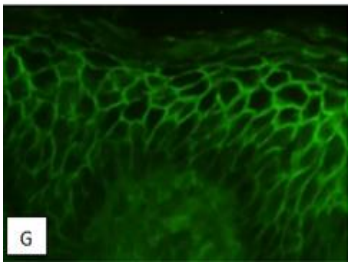

Figure G: A direct immunofluorescence study of the biopsied specimen demonstrated intercellular deposition of IgG antibodies appears as "fish net" pattern