

Dermatologic and Oral Manifestations of Pemphigus Vulgaris: A Case Report with Review

Sudeshna Bagchi¹, Rudra P Chatterjee², Sanjeet K Das³, Sheikh A Mahmud⁴

ABSTRACT

Introduction: Pemphigus vulgaris is a chronic, autoimmune, mucocutaneous disorder characterized by a rapid appearance of a thin-walled vesicle and/or bulla, which ruptures eventually, resulting in painful erosions. The global occurrence is 0.1–0.5 cases/1 lakh population/year. Although a higher incidence in women has been reported, many suggest an equal sex predilection.

Case description: A 72-year-old male patient reported to our department with painful ulcerations in his mouth and a severe dysphagia for 15 days followed by the appearance of similar lesions in the back, legs, and genital areas. The ulcerations were extremely tender, superficial, and ragged, showing a positive Nikolsky's sign. A provisional diagnosis of the vesiculobullous disease was made. A cytological smear, a routine histopathological examination, and a direct immunofluorescence test confirmed the diagnosis as pemphigus vulgaris.

Management and prognosis: The patient was on corticosteroids in tapering doses along with azathioprine and antibiotics. By 6 weeks, the lesions had healed and no recurrence was noted afterwards.

Conclusion: Pemphigus vulgaris is a serious disease that can turn lethal if early diagnosis and immediate treatment are not provided. Systemic corticosteroids remain the mainstay of treatment, which markedly reduces the clinical course with a favorable outcome.

Keywords: Direct immunofluorescence, Nikolsky's sign, Pemphigus, Pemphigus vulgaris.

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INTRODUCTION

The name pemphigus, originally introduced by Boissier de Sauvages in the 1750s, comes from the Greek "pemphix", which means a blister or bubble.¹ It is a chronic, potentially life-threatening, autoimmune, intraepithelial, blistering disease affecting the skin and mucous membrane. The clinical variants of the pemphigus include pemphigus vulgaris, pemphigus erythematosus, pemphigus vegetans, pemphigus foliaceus, paraneoplastic pemphigus, and IgA pemphigus, of which pemphigus vulgaris (PV) is the commonest (70%).^{1,2} Cutaneous lesions are characterized by flaccid blisters and crusted erosions mainly seen in the head, upper trunk, and groin. Intraorally, flaccid bullae are noted, which would rupture soon, resulting in ill-defined, shallow painful ulcerations.³ With the help of a clinical diagnosis, a histopathologic evaluation, and an immunofluorescence test, a final diagnosis was made, and the patient responded well with systemic corticosteroids.

CASE DESCRIPTION

A 72-year-old male patient of a semiurban area reported with the chief complaint of mouth ulcers for last 15 days. His history revealed that the patient had similar episodes of ulcerations from the last 5–6 months, which regressed without any medication. At the time of presentation, the patient had severe dysphagia and similar ulcerations on the thigh for the last 3–4 days. The medical history revealed that he was hypertensive and under medication.

Moist multiple erosions with hemorrhagic crusts were found on the femoral aspects of both legs. Intraorally, the presence of extremely tender multiple superficial ragged ulcerations showing a positive Nikolsky's sign distributed haphazardly on the buccal mucosa, palate, alveolar mucosa, labial mucosa, and tongue were found (Fig. 1). These led to a provisional diagnosis of a vesiculobullous lesion affecting the oral cavity.

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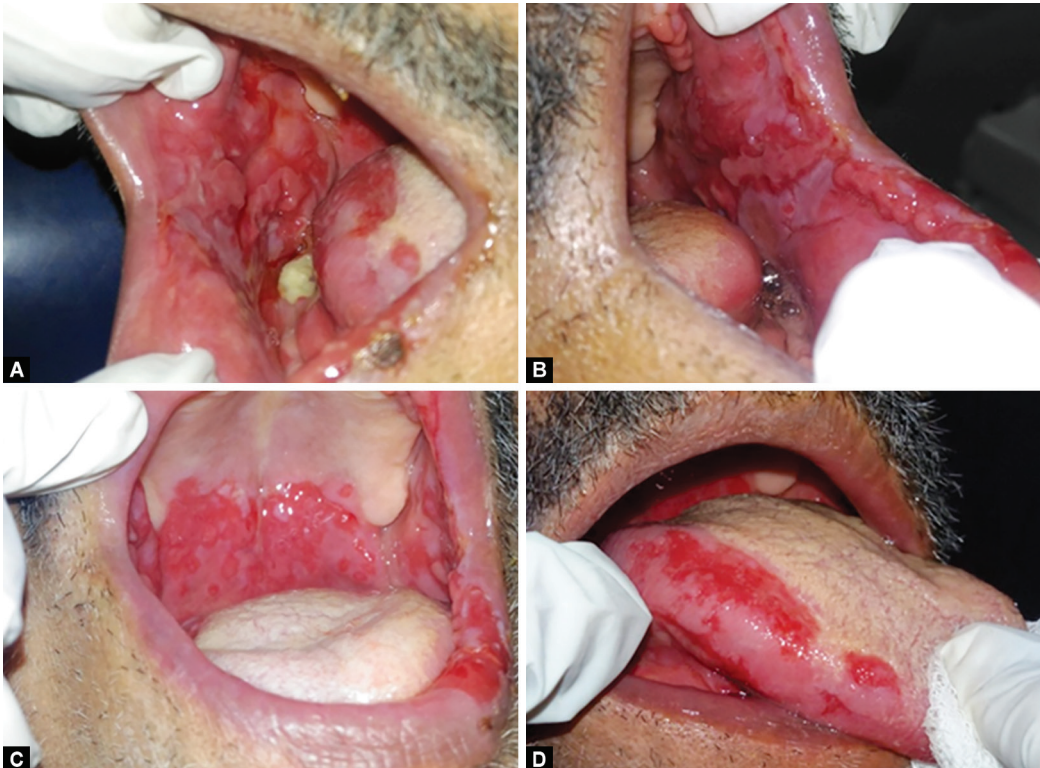
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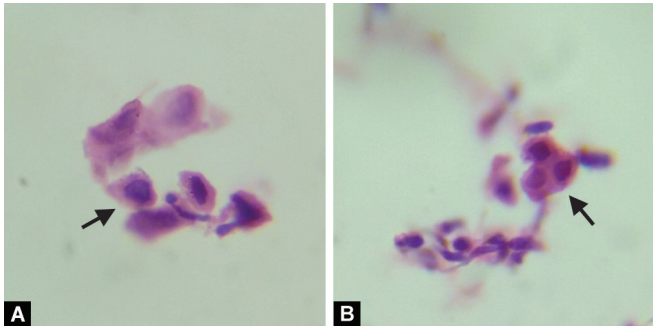
The patient was advised to undergo routine hematological and biochemical investigations and to report early. But when he reported after 20 days, the lesion had increased in severity with an involvement of the back and genital areas of the patient. However, the hematological and biochemical investigations were all within normal limits, except the ESR level, which was high (38 mm/hour).

A cytological smear obtained from oral lesions stained with hematoxylin and eosin (H and E) revealed the presence of clusters of or individual polygonal to round cells, having a basophilic cytoplasm showing a perinuclear halo and large oval nuclei having an irregularly arranged chromatin and hazy nucleoli (Fig. 2).

A biopsy was obtained from a perilesional site on the right buccal mucosa under local anesthesia and submitted for routine histopathological examinations in buffered formalin. Sections stained with H and E revealed the presence of areas of spongiosis and intraepithelial clefting above the basal cell layer with acantholysis, resulting in free-floating Tzanck cells. The deeper connective tissue showed vascular channels and scattered chronic inflammatory cells (Fig. 3). The light microscopic features were suggestive of pemphigus vulgaris.



Figs 1A to D: Intraoral photographs of the patient on the first appointment showing lesions on the bilateral buccal mucosa, palate and tongue



Figs 2A and B: Tzanck cells seen in a cytological smear

To confirm the diagnosis, direct immunofluorescence (DIF) was advised. A repeat biopsy was taken from a perilesional site for the DIF testing directly in Michel's medium, which revealed positive IgG and C3 in an intraepidermal intercellular (fish net) pattern and negative IgA, IgM, and fibrinogen (Fig. 4). The overall clinical, cytological, and histopathological features and immunofluorescence study were consistent with pemphigus vulgaris.

Considering the health status of the patient (mild hypertensive), initially dexamethasone (60 mg OD) I.M. was started with doxycycline (100 mg OD), azathioprine (50 mg OD), levocetirizine, and chlorhexidine mouthwash. After 7 days, a dexamethasone injection was given on alternate days for 1 week, followed by an oral prednisolone (10 mg BD) for 2 weeks and 10 mg OD for 2 weeks and then stopped. By 6 weeks, all the lesions had healed (Fig. 5).

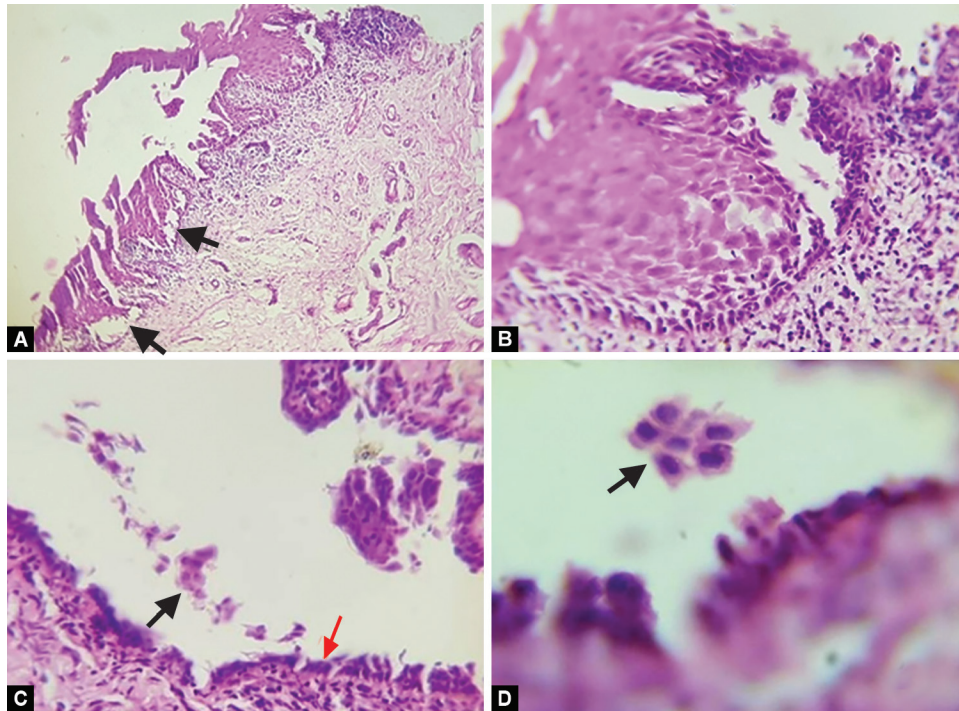
DISCUSSION

In pemphigus, the desmosomes (the specific adhesive component for secured cell-to-cell connections) are disrupted. The three subtypes of the PV are:

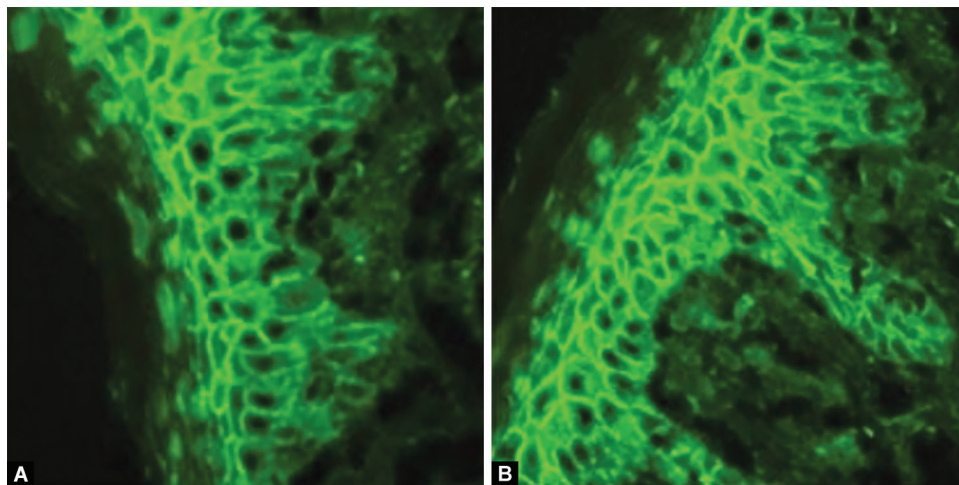
- Mucosal-dominant type—by antidesmoglein 3 IgG autoantibodies
- Mucocutaneous type—by antidesmoglein 3 and antidesmoglein 1 IgG autoantibodies
- Cutaneous type—by antidesmoglein 1 and pathogenically weak anti-desmoglein 3 autoantibodies.³

Autoantibodies (mainly IgG4) becomes reactive against the components of epithelial desmosome-specific proteins such as desmoglein 1 and desmoglein 3 by a direct/singular effect and causes disruption and dissolution of intercellular junctions and loss of cell-to-cell adhesion, leading to apoptolysis, through a type II hypersensitivity reaction.^{4,5} In contrast, Grando observed that the desmosomes remain intact till the late stages of acantholysis, which contradicts the previous concept of acantholysis by steric hindrance. A “multiple-hit” hypothesis was suggested where antigens such as desmosomal cadherins, adhesion molecules, cell membrane receptors, mitochondrial proteins, and pemphaxin are involved. Activation of multiple signaling pathways was noted. Cell membrane receptor antigens are first targeted by the autoantibodies followed by an intracellular signaling by Src, epidermal growth factor receptor kinase, protein kinases A and C, phospholipase C, mTOR, p38 MAPK, JNK, other tyrosine kinases, and calmodulin.^{6,7} As the PV might have a genetic predisposition to the human leukocyte antigen (HLA class II), it is common within certain families and ethnic groups, such as Ashkenazi Jews (HLA-DRB1) and people having a Mediterranean origin.⁸ Despite pemphigus being an autoimmune disease, several trigger factors have been noted, which include different drugs, diseases, vaccines, genetic factors, nutrients, micronutrients, pregnancy, and stress.⁹

Though PV has a global incidence of 0.1–0.5/1 lakh people/year,¹ it varies from 0.17 per million/year (France) to a higher range



Figs 3A to D: (A) A lesion showing suprabasal epithelial split (H and E; 10×); (B) Spongiosis and areas of suprabasilar split in the epithelium (H and E; 40×); (C) Black arrow—Tzanck cells; red arrow—“row of tombstone” appearance (H and E; 40×); (D) Round to oval keratinocytes having hyperchromatic nuclei and a perinuclear halo (H and E; 100×)



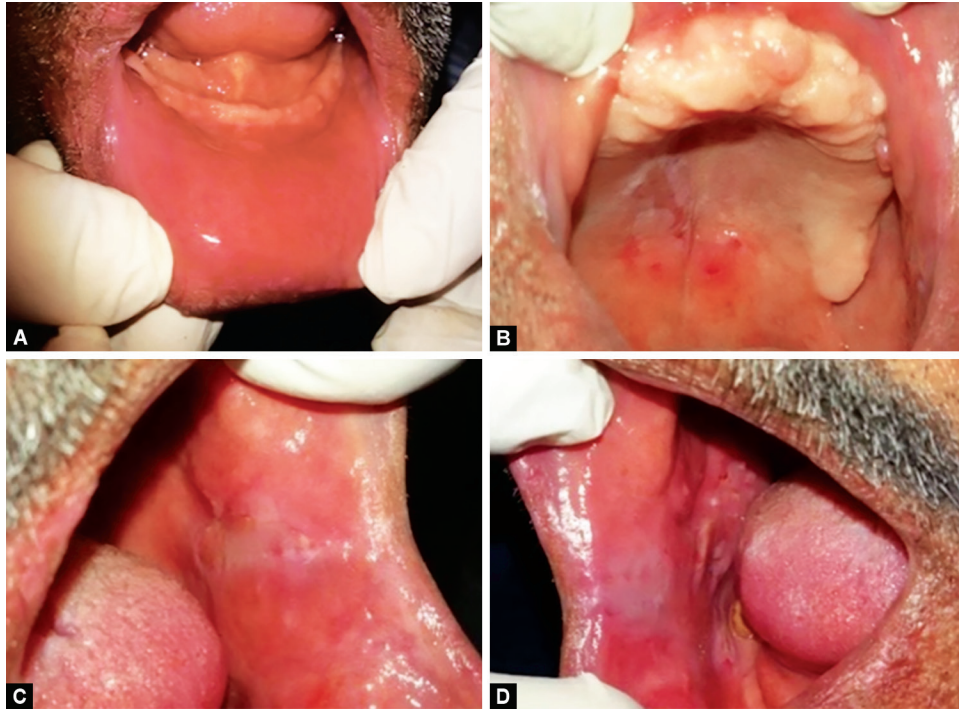
Figs 4A and B: (A) DIF showing a positive IgG in an intraepidermal intercellular (fish net) pattern; (B) DIF showing positive C3 in an intraepidermal intercellular (fish net) pattern

of 6.8 per million/year (United Kingdom).¹⁰ Incidence ranges from 0.09 to 1.8% in India.¹¹ The mean age of onset is 4th–6th decade.¹² In the present case, the patient was a 72-year-old male. Although, a higher incidence in women has been reported, many suggest an equal sex predilection.^{13–18}

Oral lesions appear in 80–90% of the patients and the disease starts with oral lesions in 53.52%.¹⁹ Again, a simultaneous occurrence of lesions in the skin and mucosa has also been reported in 23.94% of the cases.²⁰ Cutaneous lesions are mainly seen in the head, upper trunk and groin.¹⁷ Intraorally, the lesions show a positive Nikolsky’s sign due to a perivascular edema disrupting the dermal–epidermal junction.²¹ Sometimes, if the bullae are smaller

and tense, an Asboe-Hansen sign/indirect Nikolsky sign/Nikolsky II sign can also be found.²² The lesions gradually begin as flaccid bullae, which rupture soon, forming ill-defined, shallow ulcerations covered by a collapsed roof as a whitish superficial slough.⁸ Areas commonly involved are the bilateral buccal mucosa, hard palate, tongue, lower lip, soft palate, floor of the mouth, upper lip, gingiva, and oropharynx.²³ Undetected bullae may still be found in the hard palate sometimes. Gingival margins and lateral borders of tongue receiving a toothbrush trauma and frictional activities suffer from larger and tenderer lesions.²⁴

A cytological smear of the PV shows clusters of or singly scattered Tzanck cells, which are large, polygonal to round



Figs 5A to D: Posttreatment after 6 weeks

keratinocytes having a basophilic cytoplasm showing a perinuclear halo. These cells have large hyperchromatic nuclei, containing an irregularly arranged chromatin and hazy/absent nuclei.²⁵ Histopathologically, pemphigus may initially present as spongiosis and intraepithelial eosinophilia. The PV is mainly characterized by acantholysis and an intraepithelial vesicle or bullae formation just above the basal layer, creating the “suprabasillar split”.²¹ Sometimes, only the basal cells remain projecting into the blister cavity, giving a “row of tombstone” appearance. Tzanck cells, which are detached keratinocytes from the basal and lower prickle cell layers, are present as single or a cluster of cells. The histologic features are more prominent in oral lesions, as secondary infections mask the cutaneous lesions. A relative scarcity of inflammatory cells helps distinguish this from other bullous diseases, where profuse inflammatory cell infiltration is seen.²⁵

Immunofluorescence (direct and indirect) is an established technique used to detect an array of antigens in cells and tissues. Primary antihuman antibodies conjugated to FITC fluorescein (anti-IgA, anti-IgG, anti-IgM, and anti-C3) are applied to the tissue sections and studied under fluorescence microscopy.²⁶ The IgG antibodies targeting the desmoglein are deposited in the intercellular space, resembling a “chicken-wire” or “fish-net” appearance.²⁷ The DIF test can remain positive for many years even after the disease has regressed.²⁸ The indirect immunofluorescence (IIF) uses patient’s serum to identify the circulating autoantibodies directed against Dsg1 and Dsg3.⁴ This simple nontraumatic procedure can also be done nowadays using the blister fluids.¹¹ The sensitivity of DIF varies from 90 to 100% in patients with active disease; in the case of IIF, it varies from 75 to 100% (for IgG type).^{26,27} A specialized enzyme-linked immune sorbent assay (ELISA), having 96–100% specificity for pemphigus, can also be used to analyze the circulating autoantibodies. This is more specific and sensitive compared to IIF.³

The differential diagnoses commonly included are mucous membrane pemphigoid, erythema multiformi, linear IgA bullous

dermatosis, primary herpetic gingivostomatitis, pemphigus vegetans, erosive lichen planus, and lupus erythematosus. Careful correlation of the clinical findings, histopathological features and DIF has led to the diagnosis as pemphigus vulgaris.¹

In the present case, rapid and accurate diagnosis led to a fast initiation of treatment, without which the disease could have turned fatal, as there is a loss of the epidermal barrier, a loss of body fluids, and there are chances of a secondary infection. He responded well with systemic corticosteroids and other adjuvants with successful remission. Corticosteroids have reduced the mortality rate from 75% to 30%.²⁹ Death in pemphigus occurs mostly as a result of septicemia, peptic ulcer disease, pneumonia, and cardiovascular disease.¹⁰

CONCLUSION

Pemphigus vulgaris is a serious and potentially life-threatening disease. An early and accurate diagnosis is a prerequisite for an immediate therapy to prevent any fatal outcome. Clinical diagnosis must be confirmed by a histopathological evaluation as well as DIF. Systemic corticosteroids remains the mainstay of the treatment, which markedly reduces the clinical course with a favorable outcome.

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