

CASE STUDIES

Oral pemphigus vulgaris: A case-based rheumatological and immunological perspectives on a rare autoimmune mucocutaneous disease

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Abstract

A 52-year-old female patient was referred for suspected rheumatic or connective tissue disease due to one-year history of recurrent oral ulcers along with recent history of nasal ulcers, erythematous rash, puffy fingers, raised erythrocyte sedimentation rate, raised c-reactive protein, and acute inflammatory exudates on biopsy of buccal mucosal ulcers. Her intra-oral examination revealed ulcerative lesions in the mouth. Her anti-nuclear antibody (ANA) by indirect immunofluorescence showed intensity of +2 and cytoplasmic pattern. The repeat deep biopsy from oral lesions was done in view of multiple recurrent inflammatory oral ulcers, non-supportive ANA test, and bleeding with peeling of mucosal surface from oral ulcers on manipulation (Nikolsky's sign). The histopathological examination showed acantholysis. Her test for anti-desmoglein3 antibody was strongly positive and was diagnosed with oral pemphigus vulgaris (PV). Most of the times, PV is encountered by a dermatologist, but patients with only oral involvement may end up consulting a physician or rheumatologist as a suspected rheumatic or connective tissue disease due to the underlying inflammatory or autoimmune nature. The present case-based review revisits this rare chronic inflammatory autoimmune mucocutaneous disease and provides a recent review of literature based on rheumatological and immunological perspectives.

Keywords: Acantholysis, anti-desmoglein3 antibody, rheumatic disease, recurrent oral ulcers

Introduction

Pemphigus is a group of autoimmune diseases of skin and mucous membranes, in which the keratinocyte antigens (desmogleins (Dsgs), that is, desmosomal glycoproteins expressed on the epithelial cells of the skin and mucosa) are the target of the autoantibodies, leading to acantholysis and blister formation.¹ In India, the epidemiological trend of pemphigus is different and prevalence is reported to be between 0.09 and 1.8%. A significant number of patients are found to be <40 years of age. Overall, it affects all races with an equal gender predisposition.² The major variants of pemphigus are pemphigus vulgaris (PV, including its variant pemphigus vegetans) and pemphigus foliaceus (including its variant pemphigus erythematousus). Other recently described variants are pemphigus herpeticiformis, paraneoplastic pemphigus, drug-related pemphigus and immunoglobulin-A pemphigus. PV is the most common form of pemphigus.² In majority of the cases with PV, the oral cavity may be the only site of involvement for years, which may lead to delayed diagnosis and inappropriate treatment for this potentially fatal disorder, resulting in its progression and skin involvement.^{3, 4} Hence oral PV is considered as

one of the important differentials of suspected rheumatic diseases in which one of the common extra-articular manifestations is the involvement of oral mucosa.

Case report

A 52-year-old female presented with a history of recurrent painful mouth ulcers associated with difficulty in eating for 1-year, puffy fingers and swelling of face, especially in morning for 3 months, and erythematous rashes over upper limbs occasionally for 1 month. She was under treatment for diabetes for the last 1 year. Her intra-oral examination revealed ulcerative lesions present on left buccal mucosa, mandibular labial vestibule, and left lateral border of tongue (Fig. 1). Rest of the general, systemic and musculoskeletal examinations were unremarkable.

The patient had been investigated elsewhere during last 3-4 months and was found to have unexplained mouth and nasal ulcers (observed by otolaryngologist). On investigation, her previous buccal mucosal ulcer biopsy showed acute inflammatory exudates and a few degenerative squamous cells. She had no history of genital

ulcers, other cutaneous or ocular lesions on presentation.

Further investigation revealed her random blood sugar as 139 mg/dl (80-140 mg/dl), and urine examination and complete blood count were within normal limits. Her renal thyroid and liver function tests were also normal. Erythrocyte sedimentation rate (ESR) was 36 mm/hour (0-20 mm/hour) and c-reactive protein (CRP) was 18.8 mg/L (<3.0 mg/L). Her serum vitamin B12 was 339 pg/ ml (211-911 pg/ ml). Human immunodeficiency virus and hepatitis B and C virus markers were negative.

After reviewing history and investigation results, the patient was suspected to have autoimmune connective tissue disease (AICTD) due to the presence of recurrent mouth ulcers, nasal ulcers, erythematous rash, puffy fingers, raised ESR-CRP, and acute inflammatory exudates on biopsy from buccal mucosal ulcers. Her anti-nuclear antibody by indirect immunofluorescence showed intensity of +2 and cytoplasmic pattern. The bedside pathergy test was negative. Repeat deep biopsy from oral mucosal ulcers was planned in view of multiple recurrent inflammatory mouth ulcers, non-supportive ANA test, and bleeding from mouth ulcers on manipulation with peeling

of mucosal surface, possibility of positive Nikolsky's sign (Fig. 2). Nikolsky's sign is dislodgement of intact superficial layer by a shearing force, indicating a plane of cleavage in the skin or mucosa. It occurs due to pre-vesicular edema that weakens the dermal-epidermal junction.⁵

The repeat biopsy showed hyperplastic stratified squamous epithelium showing intraepithelial split where base was formed by basal cells and roof by cells of stratum spinosum. Loss of cohesion was noted at various sites at level of suprabasal cells. These findings are suggestive of acantholysis of PV (Fig. 3).

Tests for anti-Dsg 1 and 3 antibodies were done by enzyme-linked immunosorbent assay (ELISA). The results showed anti-Dsg1 antibody negative at 9.5 U/ML (>20 U/ML-positive), while anti-Dsg3 antibody was strongly positive at 205.5 U/ML (>20 U/ML-positive). Dsg1 is expressed in all layers of the epidermis, with a higher concentration in the more superficial layers, whereas Dsg3 is expressed in the parabasal and basal layers. The presence of a suprabasilar split reflects the expression of Dsg3 and relative lack of Dsg1 in the oral mucosa. The presence of antibodies to both, Dsg1 and Dsg3, are seen in patients who develop

Fig. 1: Ulcerative lesions present on buccal mucosa, mandibular labial vestibule, and lateral border of tongue



Fig. 2: Bleeding from mouth ulcers on manipulation with peeling of mucosal surface, possible positive Nikolsky's sign

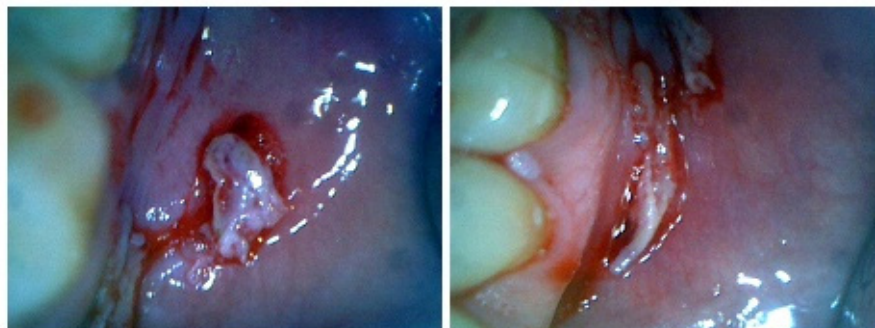
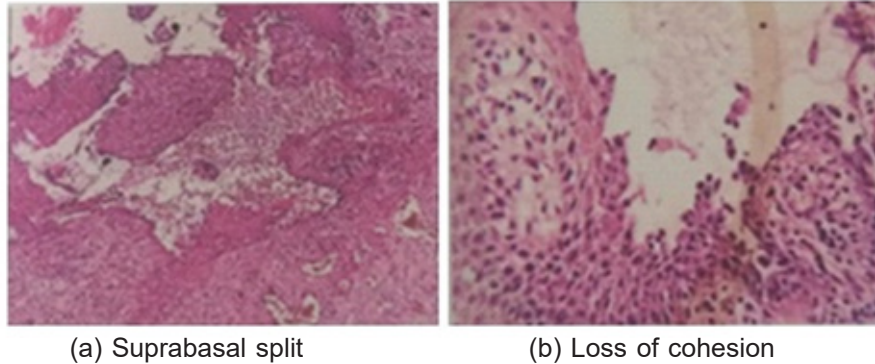


Fig. 3: Histopathology examination after repeat biopsy suggestive of acantholysis



skin lesions.¹

Based on the aforementioned clinical investigations, history, immunologic and histopathology features, the diagnosis was concluded as oral PV. The patient was treated with prednisolone and azathioprine (according to weight) along with diabetes medications. She showed complete resolution of all the symptoms within one and a half month, including mouth ulcers and systemic complaints.

Discussion

There is no uniformly accepted method to differentiate oral ulcerative lesions, because significant numbers of entities are still not well understood. However, many of the ulcers are clinically differentiated on the bases of their presentation (acute, chronic or recurrent), frequency (single or multiple), site (buccal mucosa, lips or tongue) or presence of other associated features.

Recurrent oral aphthosis or recurrent aphthous stomatitis is the occurrence of recurrent oral ulcers in the absence of any systemic cause.^{6, 7} Oral aphthous ulcers most commonly occur on non-keratinized mucosa in healthy, but can be seen on the keratinized mucosa in immunodeficient subjects. They typically occur as painful, symmetrically round fibrin-covered mucosal defects with an erythematous border. Three clinical types of aphthous ulcers have been identified.

Minor-type is usually 2-3 mm in diameter, heals spontaneously in two weeks and constitutes 80–90% of the ulcers. Major type is usually 1–3 cm in size, lasts for 10 days to 6 weeks or even longer, may heal with scarring and accounts for about 10% of the lesions. Herpetiform apthae appears as 1-2mm small, extremely painful, and numerous (up to 100) lesions.⁸

In the rheumatology or clinical immunology practice, it is not uncommon to find mouth ulcers secondary to some drugs or in certain diseases with joint manifestations.⁶ The common differentials of oral ulcers, other than recurrent oral aphthosis and systemic AICTDs, are trauma, infections (herpes simplex, syphilis, HIV, and hand-foot-mouth disease), drugs, radiotherapy, haematinic/nutritional deficiencies (iron, vitamin B12, folic acid, coeliac disease), mucocutaneous disease (PV, lichen planus, erythema multiforme), squamous cell carcinoma, and haematological diseases (cyclic neutropenia, lymphoma).⁶

The differentiating characteristics of few of the common encounters, other than aphthous ulcers, are as follows. Acute inflammation of the oral mucosa following systemic chemotherapy and/or radiation therapy is called oral mucositis. Clinical presentation varies from erythema to patchy or confluent ulceration with a superficial pseudo-membrane or even rarely overt necrosis. Lesions are often very painful, may compromise nutrition and oral hygiene, and can predispose to risk of local as well as systemic infection.⁹ Oral ulcers in PV are found on buccal mucosa, palate or gingivae. They are irregular, multiple, shallow ulcer with peripheral extension and positive Nikolsky's sign and desquamative gingivitis.⁸ Squamous cell carcinoma represents about 95% of all oral malignancies and may present as a red, white, red-white, exophytic, or ulcerative lesion. The classic ulcer is described as a crater-like lesion having a rolled, indurated border and a velvety base. The most common sites affected in the oral cavity are floor of the mouth, ventral and lateral borders of the tongue, and lower lip. Lesions are usually solitary, but in rare cases multifocal.⁸

The differentials of “aphthous-like” oral ulcers with

rheumatological perspectives that may or may not have joint involvement are mentioned in table 1.⁶

Out of all these, PV with sole oral mucosal involvement becomes one of the important differentials for suspected AICTDs due to its underlying inflammatory or autoimmune nature. Therefore, it should be expected to have clear-

cut diagnostic criteria for pemphigus. This is relevant in individual patients and it makes easier for results of different clinical studies to be compared. One of the articles selected in the review used a set of diagnostic criteria, which appears to be appealing. These Japanese diagnostic criteria are mentioned in table 2.^{13, 14}

Table 1: The clinical presentation of the oral ulcers in rheumatological (autoimmune or autoinflammatory) systemic diseases

Rheumatological systemic diseases	Clinical characteristics of oral ulcers
A. Diseases having oral ulcers among their classification criteria⁶	
Systemic lupus erythematosus	Oral mucosal haemorrhages, erosions, shallow painless ulcerations with surrounding erythema at soft & hard palate and gingivitis occur commonly. ⁷ Concomitant nasal ulcers.
Behcet's disease	Recurrent oral ulcers (minor, major, herpetiform aphthosis) having occurred at least three times in a period of 12 months. Oral lesions occur on the lips, tongue, buccal mucosa, soft and hard palate, tonsils and even in the pharynx and nasal cavity. The lesions are single or multiple, 2 to 10 mm or more in diameter, and are sharply circumscribed with a dirty grey base and a surrounding bright red halo. Usually the ulcers heal spontaneously without scarring but recur. ⁷
Granulomatosis with polyangiitis	Granulomatous nodules occur in the nose, larynx, trachea, bronchi and mouth. The nodules in the mouth ulcerate, the alveolar ridges become necrotic and ulceration of the tongue and perforated ulcers of the palate develop. The 'strawberry gums' appearance of hypertrophic gingivitis is a rare but characteristic. The commonest presentations are rhinorrhoea (purulent or bloody nasal discharge), severe sinusitis and nasal mucosal ulceration. ⁷
Crohn's disease	Typical lesions in the mouth include diffuse oral swelling, focal mucosal hypertrophy and fissuring, persistent ulceration, polypoidal lesions including fissuring of the lower lip, angular and granulomatous cheilitis. ⁷
PFAPA syndrome	The clinical appearance is suggestive of minor aphthous ulceration or stomatitis. ¹⁰
B. Diseases not having oral ulcers among their classification criteria⁶	
Reactive arthritis	The buccal, palatal and lingual mucosa may show painless, shallow, red erosions and severe stomatitis may ensue. ⁷
Sjögren's syndrome	Dry oral mucosa often presents with ulcers.
Amyloidosis ⁷	The mucosa is involved only in primary systemic amyloidosis. Glossitis with macroglossia occurs in about 20% of cases and may be an early sign. Furrows develop and necrotic purulent patches appear. The mucous membranes of the cheek and lips have a similar hypertrophic appearance. ⁷
Discoid lupus erythematosus ⁷	On the lips or in the mouth the patches are greyish and hyperkeratotic. They may be eroded and are usually surrounded by a narrow red inflammatory zone. On the mucosa the typical lesion is a plaque of depressed dull red epithelium sometimes with puncta or striae, surrounded by a white elevated zone 2 to 4 mm wide fading into white parallel lines at the outer margin. ⁷
Sweet syndrome	Oral ulcers with acute febrile neutrophilic dermatosis ¹¹
C. Others⁶	
MAGIC syndrome	It has no established diagnostic criteria, but is manifested by an overlap between Behcet's syndrome in which recurrent ulcers are a diagnostic criterion and Relapsing polychondritis. ¹²

Table 2: Japanese diagnostic criteria for pemphigus¹³

Diagnosis of pemphigus is made when at least one item from each three findings or two from clinical and one from immunological findings are satisfied	
Clinical findings	Multiple, easily rupturing, flaccid blisters of the skin; subsequent progressive, refractory erosions or crusts after blisters. Non-infectious blisters or erosions of visible mucosa- including oral mucosa; or Nikolsky's sign
Histological findings	Intraepidermal blisters caused by acantholysis
Immunologic findings	IgG or complement deposition in the intercellular spaces of the lesional or normal-appearing skin and mucosa detected by direct immunofluorescence antibody assay, or anti-desmoglein antibody identified by indirect fluorescent antibody assay, or anti-desmoglein antibody identified by ELISA

In patients with mild disease, moderate to high dose corticosteroids (0.5-1 mg/kg/day) in combination with steroid sparing adjuvants are preferred. Many clinicians prefer dexamethasone-cyclophosphamide pulse (DCP) therapy in patients with moderate to severe disease or those with mild disease who fail to the conventional treatment and have no contraindication for the pulse therapy. The mainstay of literature on treatment of pemphigus from India has largely been restricted to this therapy. DCP regimen is divided into four phases. Phase 1 includes administration of 100 mg dexamethasone dissolved in 500 ml of 5% glucose (in patients with normoglycemia) as a slow intravenous drip over 2 hours and repeated on 3 consecutive days. On the second day, cyclophosphamide 500 mg is also given in the same infusion. DCP therapy is repeated at 28-day intervals. In between the DCP, the patient receives 50 mg cyclophosphamide orally daily. If the disease is very severe on presentation or early disease control is warranted, daily prednisolone or pulse in a shorter interval may be considered. The patient enters phase 2 when complete remission is achieved, but continues to receive DCP along with daily oral cyclophosphamide 50 mg for 9 cycles. Phase 3 includes continuation of only oral cyclophosphamide for 9 months followed by phase 4, which is a treatment-free follow-up period for early detection of relapse, if any.^{15, 16}

With the availability of novel targeted therapeutic agents, patients who fail conventional treatment/ DCP and those in whom they are contraindicated or cause severe adverse effects can now be offered intravenous immunoglobulin and/ or rituximab. It can also be safely used in patients with sepsis or those who are at risk of infection.¹⁶ However, a growing consensus even suggests that rituximab treatment should be offered to all pemphigus patients, irrespective of severity because most of the experiences and evidences in the literature support that treatment with rituximab

results in early remission, fewer relapses, and an overall better prognosis.¹⁷ The major limitations of this agent in the Indian scenario are cost, lack of expertise, and limited data on clinical experience.¹⁶

The autoimmune bullous skin disorder intensity score (ABSIS) and pemphigus disease area index (PDAI) are the two main validated severity scoring systems for pemphigus, which can also be used in other autoimmune bullous diseases.¹⁸ Physician's global assessment is a visual analogue scale; however, it is not a reliable and accurate marker for disease severity in comparison to the ABSIS or PDAI.¹⁹ The use of desmoglein 1 and 3 antibody levels by ELISA to monitor the severity of pemphigus is controversial.¹⁸

In summary, most of the times PV is encountered by dermatologist but, the patient with oral PV (sole oral involvement) may end up consulting rheumatologist or clinical immunologist due to its underlying inflammatory or autoimmune nature. Therefore, PV should be kept in mind as one of the differential diagnoses while dealing with a case of suspected systemic rheumatic disease involving oral mucosa.

Competing interests

The author declares that he has no competing interests.

Citation

Dalal A. Oral pemphigus vulgaris: A case-based rheumatological & immunological perspectives on a rare autoimmune mucocutaneous disease. *IJRCL*. 2021;9(1):CS3.

Submitted: 29 November 2021, **Accepted:** 18 January 2022,

Published: 1 February 2022

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