Case Report

Oral Pemphigus Vulgaris: A Case Report and Literature Update

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Abstract

Introduction: Pemphigus vulgaris is a rare cause of oral mucosal ulceration. Clinical Picture: A 47-year-old Chinese man presented with a 3-month history of oral ulceration. There were no lesions on the skin or other mucosal sites. Histology and immunostaining were consistent with pemphigus vulgaris. Treatment: Systemic and topical corticosteroids were instituted, together with topical antifungals. Conventional periodontal therapy was carried out to improve gingival/oral health. Outcome: Control of oral ulceration was achieved with re-establishment of normal oral function. No other sites to date have been involved. Conclusions: Chronic oral ulceration can be the sole manifestation of pemphigus vulgaris, at least initially. Early recognition of this lesion may prevent delayed diagnosis and inappropriate treatment of a potentially chronic dermatological condition.

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Key words: Desmoglein, Desmosomes, Gingivitis, Oral ulceration, Pemphigus, Vesiculobullous

Introduction

Autoimmune blistering conditions are an uncommon cause of chronic ulceration of the oral mucosa. Nevertheless, it is important to diagnose these conditions early and institute treatment as soon as possible, as they can lead to serious involvement in other mucosal and cutaneous sites and even death. The more common autoimmune blistering conditions affecting the oral mucosa are pemphigus and mucous membrane pemphigoid. We describe a case of oral pemphigus vulgaris and its management. This will be followed by a review of the current literature.

Case Report

A 47-year-old Chinese man was referred to the Oral Medicine Clinic of the Department of Oral and Maxillofacial Surgery, National University Hospital (NUH), with a 3-month history of chronic oral ulceration. The oral ulceration caused the patient considerable discomfort and significantly affected his normal oral function. His medical history was significant for essential hypertension and hyperlipidaemia. His daily medication included adalat, losartan and lovastatin. He was never on captopril.

This well-built gentleman, a hawker's assistant, showed no signs of cutaneous involvement at presentation. He had several red-based superficial erosions on the mucosal side of his lower lip (Fig. 1). Intra-orally, there were multiple small, irregular, fibrin-covered erosions and areas of intense erythema involving particularly the gingivae (Figs. 2 and 3). The left cheek mucosa and the soft palate had localised areas of mild erythema. The patient rendered the observation that at least some of the erosions, particularly of the posterior buccal mucosa, started initially as flaccid blood-filled blisters. Indeed, on initial presentation, 2 clear fluid-filled blisters were observed on the posterior aspect of the left cheek mucosa (Fig. 4). The hard palate and tongue were uninvolved. The site which was most severely affected was the lingual marginal and attached gingivae of the lower right quadrant. The considerable pain and discomfort which the patient felt hindered him from carrying out effective oral hygiene measures and this in turn contributed further

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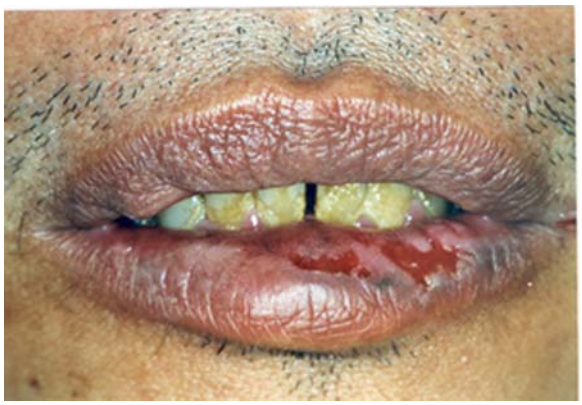

Fig. 1. Lower lip at initial presentation.

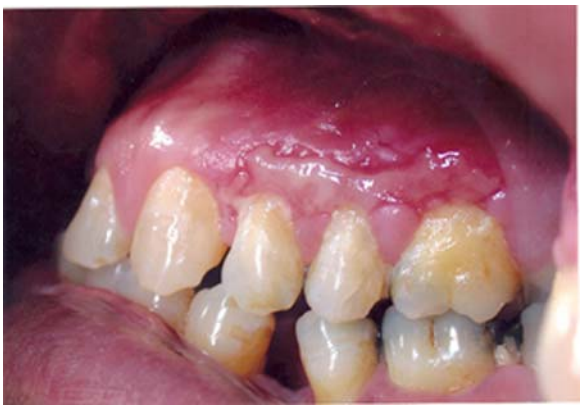

Fig. 2. Fibrin-covered erosive lesion on the gingiva.

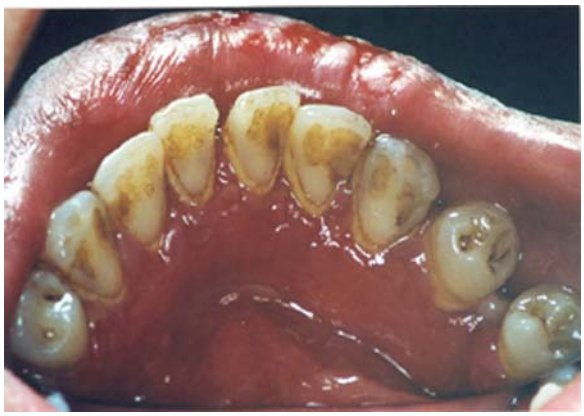

Fig. 3. Intensely erythematous gingivae with multiple small erosions.

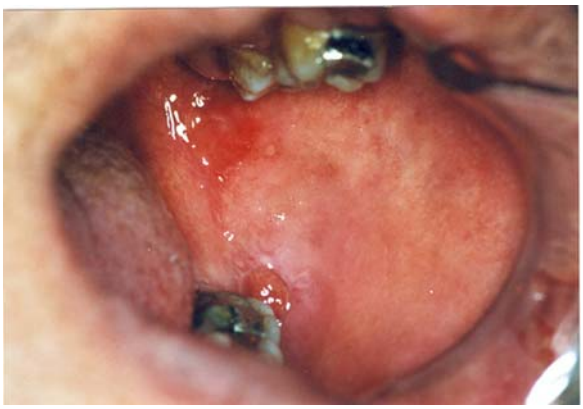

Fig. 4. Bulla formation on the left cheek mucosa.

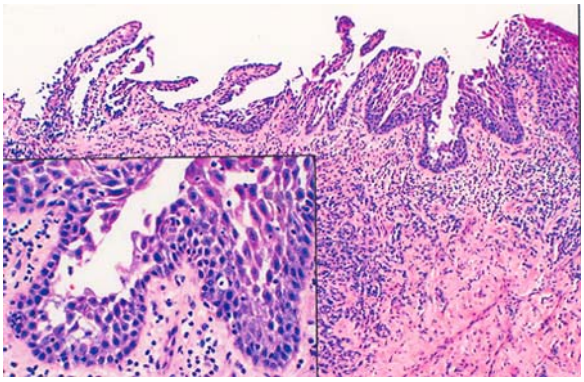

Fig. 5. Section shows oral mucosa with acantholysis of the epidermis, suprabasal blister formation and inflammatory cellular infiltration in the upper dermis (Haematoxylin-eosin x55).
The insert shows prominent acantholysis of the keratinocytes with blister formation (Haematoxylin-eosin x275).

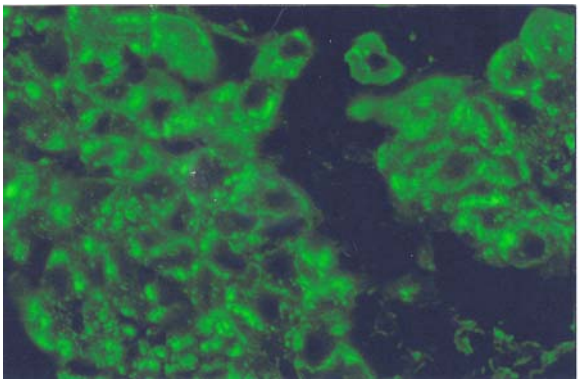

Fig. 6. Section shows granular deposition of immunoglobulin IgG in the intercellular space of the keratinocytes of the epidermis (Immunofluorescence x550).

to the severity of the gingival inflammation. A dermatologist confirmed the absence of any cutaneous lesions. Other sites such as the conjunctival, nasal, genital and oesophageal mucosae were free of lesions as well.

A vesiculobullous disorder was suspected based on the history of bullae formation, multiple chronic ulcerations and the apparent fragility of the oral mucosa experienced during examination. The main provisional diagnosis was pemphigus and mucous membrane pemphigoid, although the former was thought more likely as the latter tends to affect an older age group (that is, the elderly in pemphigoid and the middle-aged in pemphigus). The other common conditions that can present with chronic oral ulceration are oral lichen planus or a drug-induced lichenoid lesion. An

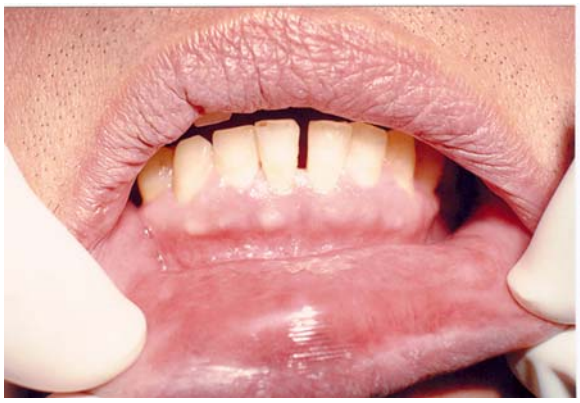

Fig. 7. Healed lip lesions (without scarring) after systemic corticosteroids.

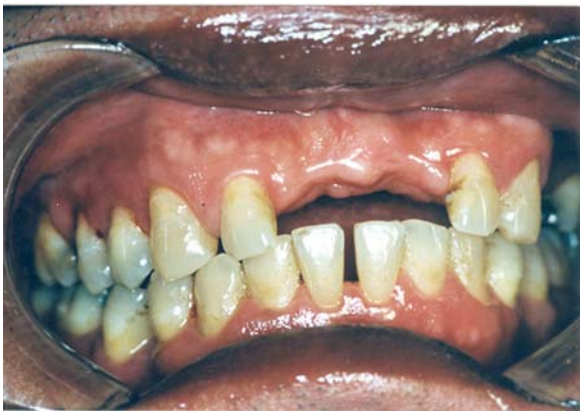

Fig. 8. Healthy gingivae after topical/systemic corticosteroids and periodontal treatment.

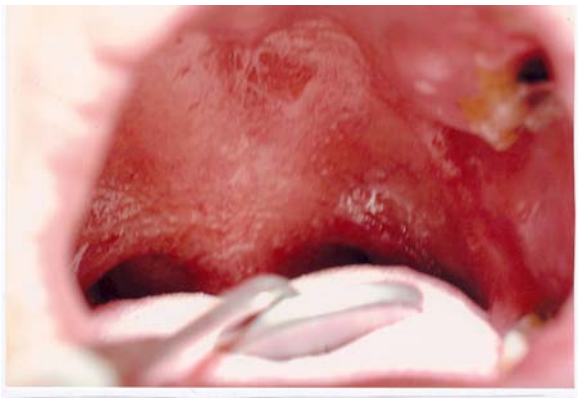

Fig. 9. Oropharyngeal thrush developed during high-dose corticosteroid therapy.

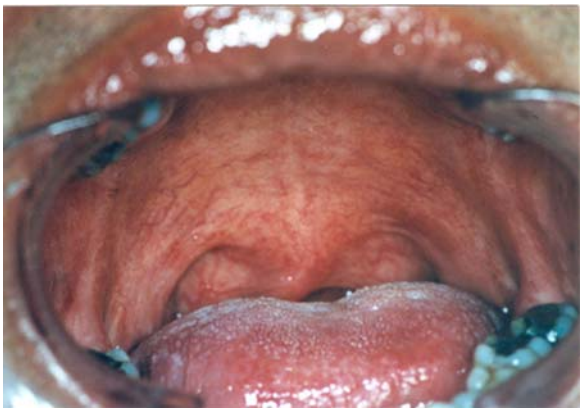

Fig.10. Complete resolution of thrush after use of topical nystatin.

incisional biopsy was performed on perilesional sites of the lower lip and the left cheek mucosa. These specimens were submitted for direct immunofluorescence studies (fresh specimen) and conventional histology.

Histopathological examination revealed suprabasal blister formation associated with extensive acantholysis of keratinocytes (Fig. 5). Direct immunofluorescence studies showed granular deposits of IgG and C3 in the intercellular spaces between the keratinocytes (Fig. 6). A final diagnosis of oral pemphigus vulgaris was made. Indirect immunofluorescence was not done as it is, unfortunately, not available at our centre.

The patient was commenced on systemic corticosteroids (prednisolone) at an initial dose of 0.5 mg/kg/day (40 mg). Calcium supplements and cimetidine were also prescribed concomitantly. This initial dose failed to control the disease but after stepping up to 1 mg/kg/day (80 mg), there was marked improvement in 2 weeks (Figs.7 and 8). A lower gingival soft splint was constructed to aid in the application of topical corticosteroids to the severely affected gingivae as well.[1] The patient was instructed to apply the paste, initially Oral Cort E (0.1% triamcinolone acetonide and lignocaine) and then Dexaltin oral paste (dexamethasone), because of lack of response to the former, onto the gingival splint and to wear it 3 times a day after meals for about an hour each time. In addition, the patient was given nystatin to be used as a mouthwash to prevent secondary candidal infection. The patient was put through periodontal sessions, which include oral hygiene instructions and quadrant scaling/root planning, with the latter performed only some time after the commencement of corticosteroid therapy when the gingivae was less friable and painful. During the above period of systemic corticosteroids (third month at a dose of 40 mg/day of prednisolone), the patient developed thrush on the posterior palate/pharyngeal area (Fig. 9). This was controlled with more aggressive use of topical nystatin (Fig. 10).

Over the past 8 months, the prednisolone has been tapered down to 10 mg/day. The patient is currently still on this daily low-dose systemic corticosteroid therapy and, to date, no other sites are involved. Two attempts at reducing the prednisolone to below 10 mg/day have resulted in a

flare-up of his condition (appearance of new gingival ulcers). The plan is to wean the patient off the corticosteroids gradually while maintaining clinical remission. If the patient develops significant and intolerable side-effects from systemic corticosteroids, an adjuvant second-line steroid-sparing immunosuppressant will be considered.

Discussion

Pemphigus vulgaris (PV) is a chronic autoimmune intraepithelial blistering disease. PV almost always affects the mouth and it can be the initial site of presentation in 50% of cases, before skin and other mucosal sites (oesophagus, pharynx, larynx, nasal, genital) become involved. Skin lesions present as flaccid fluid-filled blisters on sites exposed to trauma. The blisters break to form large denuded areas of skin which can prove fatal if extensive areas are involved.[2,3]

PV is an uncommon condition affecting males and females in the 4th to 5th decade of life. Over a 3-year period at the National Skin Centre (NSC), a tertiary dermatological referral centre in Singapore, 50 cases of pemphigus were reported.[4] Of these, 31 patients were diagnosed with pemphigus vulgaris, 16 with pemphigus foliaceus, 2 with paraneoplastic pemphigus and 1 with IgA pemphigus. Of those patients with pemphigus vulgaris, nearly half were Chinese, 5 Indians and 1 Malay. The average age at the time of diagnosis was 49 years.

In our department of Oral and Maxillofacial Surgery, NUH, pemphigus vulgaris is an uncommon cause of chronic oral mucosal ulceration. During the period 1981 to end 2003, there were only 3 histologically confirmed cases of oral pemphigus vulgaris.

The aetiology of pemphigus vulgaris is uncertain. In some cases it may have a strong genetic basis as it has been reported more frequently in certain racial groups, for example, the Ashkenazi Jews and those of Mediterranean descent. Strong associations with certain HLA Class II alleles (DRBI*0402 and DQBI*0503) have been demonstrated in PV, as well. Other initiating factors reported include certain foods (garlic), infections, neoplasms and drugs.[3] The drugs commonly implicated are those in the thiol group, in particular captopril, penicillamine and others such as rifamipicin.[5,6] In the patient reported here, careful enquiry was made as to the possibility of drugs initiating PV. However, as stated earlier, captopril was not prescribed to the patient and the other medication that the patient was on (including losartan, a newer ACE II antagonist) has, to date, not been associated with the formation of PV. Furthermore, the onset of ulceration did not coincide with the commencement of the current drugs that the patient had been consuming, which was some time before the oral ulceration.

In PV, autoantibodies are produced against desmosomes (adhesion proteins), specifically demoglein 3 (Dsg 3). Another important component of desmosomes is termed desmoglein 1 (Dsg 1). The latter is the target of autoantibody formation in pemphigus foliaceus that affects cutaneous sites only. Dsg 3 is predominantly expressed in oral epithelium while both Dsg 1 and Dsg 3 are expressed in skin (although Dsg 1 is expressed more intensely in the superficial layers while Dsg 3 is found more abundantly in basal and suprabasal layers). Dsg1 and Dsg 3 are components of desmosomal cadherin responsible for holding the cells of the epithelium together. The loss of adhesive function among the spinous cells due to anti-Dsg 3 antibodies results in bulla formation immediately suprabasal in pemphigus vulgaris. Skin integrity in this case in maintained by Dsg 1. In pemphigus foliaceus, anti-Dsg 1 antibodies cause blister formation in the superficial epidermis. No mucosal involvement is seen as mucosal integrity is achieved through Dsg 3.[7-10]

The circulating autoantibodies in patients with PV have been shown to be pathogenic as injection of auto-anti DsG3 antibodies into neonatal mice produce suprabasal blisters found typically in PV.[11] Recently also, Dsg 3 knockout mouse were produced and they had developed spontaneous acantholysis of the oral mucous membranes, further supporting the importance of Dsg 3 in PV.[12] The levels of circulating antibody titre has traditionally been used as a correlation of disease activity and as a guide to the effectiveness of the therapy instituted. These antibodies are detected by indirect immunofluorescence, whereby the patient's sera are incubated with a suitable substrate like normal human skin and/or monkey oesophagus. Autoantibodies, if present, are detected by fluorescence-labelled human antibodies as in direct immuno-fluorescence.[13,14]

Specific enzyme-linked immunosorbent assays (ELISA) are now available for detecting Dsg 3 and Dsg 1 autoantibodies.[15] As stated earlier, all patients with PV, especially with mucosal involvement, have antibodies against Dsg 3. In fact, it has been shown that at least 50% of patients with oral PV have antibodies against Dsg 1 as well and these patients suffer a more severe disease.[16,17] In those patients with Dsg 3 autoantibodies only (early PV), the appearance of antibodies against Dsg 1 heralds the development of more severe disease and involvement of cutaneous sites.[18] A recent study confirms that antibody levels of Dsg 1 and Dsg 3, detected by ELISA, correlate well with disease severity at cutaneous and oral sites respectively.[19] In future, the diagnosis and long-term follow-up of patients with pemphigus would rely on detecting and quantifying antibodies against desmoglein proteins using ELISA.

The mainstay of treatment with PV, even if confined to the oral mucosa, is systemic corticosteroids. The oral lesions of PV may respond partially to topical corticosteroids (creams, pastes, intralesional injections), but some form of systemic immunosuppression is needed to control the level of circulating autoantibodies.[20,21] Before the advent of steroids, the mortality of PV was about 30% as a result of electrolyte loss and sepsis. Currently, the mortality of pemphigus is 6% and is due to the effects of immunosuppressive therapy.[3,22] The initial dose of corticosteroids (prednisolone) is typically about 0.75 to 1 mg/kg/day. If this is insufficient in controlling the disease, the dose is increased by 25% to 50% every 5 to 7 days. If more than 1 mg/kg/day of prednisolone is needed, adjuvant immunosuppressives are added for their "steroid-sparing" effect. They are instituted also if there are frequent relapses of the disease when doses of prednisolone are tapered or if significant side-effects are experienced with the steroids. The immunosuppressants that are used include azathioprine, cyclophosphamide and mycophenolate mofetil. If the disease is very severe, progresses rapidly and is unresponsive to standard corticosteroids and oral immunosuppression, pulse therapy with megadoses of methylprednisolone or cyclophosphamide given intravenously may be required.[23-25] Plasmapheresis or high-dose intravenous immunoglobulins (IVIG) may also be considered. Guidelines on the use of IVIG therapy have recently been published.[26] In the local study of 31 patients with pemphigus vulgaris at NSC,[4] the average dose of oral prednisolone required to control the disease was 62 mg/day (range, 15 to 120 mg/day). Twenty-seven of these patients who were on oral prednisolone were given adjuvant therapy: 20 patients were put on dapsone (50 to 100 mg/day), 5 on azathioprine (50 to 100 mg/day) and 2 were put on cyclophosphamide (50 and 150 mg/day). Further details of standard therapeutic regimens for pemphigus vulgaris are found in the NSC Dermatology Bulletin, 2001.[27]

The duration of systemic immunosuppression needed is very variable and unclear. In the NSC study,[4] the average time required to achieve complete remission (no lesions after stopping all therapy for at least 1 month) in 11 of 31 patients (31%) was 32 months. A recent American study provides more data. Forty patients with PV were followed up for an average duration of 7.7 years. Twenty-five per cent of patients achieved complete and long-lasting remission (no lesions without systemic therapy for at least 6 months) after 2 years, 50% after 5 years and by 10 years, nearly 75% of this cohort of patients could discontinue therapy safely. It was also shown that the chances of achieving complete remission were higher if the disease at presentation was mild and if there was rapid and early response to treatment.[28]

Conclusion

PV is a rare cause of chronic ulceration of the oral mucosa. The mouth may be the only site of involvement for a year or so and this can lead to delayed diagnosis and inappropriate treatment of a potentially fatal disorder.[29,30] Newer diagnostic tests and better monitoring of the disease process can be achieved now with a clearer understanding of the role of anti-Dsg antibody-keratinocyte binding in blister formation. Treatment goals remain the same: the suppression of circulating autoantibodies, with the use of systemic corticosteroids and safer adjuvants. In future, antigen-specific immunotherapy may be an alternative to current conventional treatment modalities. Recent data shed light on the long-term prognosis of the disease, suggesting that lasting remission may be achievable more frequently in patients with PV than was thought.

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