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Owrzodzenia jamy ustnej i zmiany skórne – znak rozpoznawczy pęcherzycy zwykłej

Oral ulcer and skin lesions: a tell-tale sign of pemphigus vulgaris

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Streszczenie

Cel: Celem przedstawionego studium przypadku było zwrócenie uwagi na znaczenie świadomości istnienia dwóch różnych współwystępujących patologii, a także podkreślenie, że wczesne rozpoznanie i szybkie podjęcie leczenia są niezbędne w leczeniu pęcherzycy zwykłej. Pęcherzyca zwykła to rzadka, zagrażająca życiu choroba autoimmunologiczna, charakteryzująca się obecnością pęcherzy na powierzchni błony śluzowej jamy ustnej, wywołanych obecnością przeciwciał skierowanych przeciwko cząsteczkom adhezyjnym na powierzchni keratynocytów. Na uwagę zasługuje współistnienie omawianego zaburzenia z różnymi schorzeniami, zwłaszcza z zakażeniem wirusem opryszczki pospolitej. **Opis przypadku:** W pracy przedstawiono przypadek kobiety w średnim wieku, u której wystąpiło niegojące się owrzodzenie jamy ustnej wynikające z zakażenia wirusem opryszczki pospolitej, które z kolei stanowiło czynnik wyzwalający pęcherzycę zwykłą. Wyniki badania histopatologicznego i oznaczania metodą immunofluorescencji sugerowały pęcherzycę zwykłą, natomiast wyniki badania immunohistochemicznego i reakcji łańcuchowej polimerazy wskazywały na zakażenie wirusem opryszczki pospolitej. **Wnioski:** Współistnienie zakażenia wirusowego z pęcherzycą zwykłą stanowi wyzwanie terapeutyczne.

Słowa kluczowe: opryszczka zwykła, owrzodzenia jamy ustnej, pęcherzyca zwykła, skóra

Abstract

Aim: The aim of this case presentation was to highlight the importance of the awareness of two different coexisting pathologies, as well as emphasise that early diagnosis and prompt management are essential to manage pemphigus vulgaris. Pemphigus vulgaris is a rare, life-threatening autoimmune disease characterised by the presence of blisters on the surface of oral mucosa caused by antibodies against adhesion molecules on the cell surface of keratinocytes. Coexistence with various conditions, notably herpes simplex virus, is noteworthy. **Case report:** We report a case of a middle-aged female who presented with non-healing oral ulceration that turned out to be herpes simplex virus, consequently triggering pemphigus vulgaris. Histopathology and immunofluorescence were suggestive of pemphigus vulgaris, but immunohistochemistry and polymerase chain reaction were indicative of herpes simplex virus infection. **Conclusion:** The coexistence of a viral infection with pemphigus vulgaris poses a therapeutic challenge.

Keywords: herpes simplex, oral ulcers, pemphigus vulgaris, skin

INTRODUCTION

Pemphigus vulgaris (PV) is a rare life-threatening autoimmune condition characterised by blister formation notably over the oral mucosa. It is caused by the presence of antibodies against adhesion molecules on the cell surface of keratinocytes[1]. Despite many postulates on triggering factors, herpes simplex virus (HSV) infection remains a notable trigger[2]. Diagnosis is based on the clinical presentation along with histopathological analysis of ulceration or blister biopsy. Additionally, immunofluorescence and typing of the viruses present in the lesion can be determined by immunohistochemistry, in situ hybridization or polymerase chain reaction (PCR)[3]. Classically, patients with HSV and PV co-infection are treated successfully with long-term steroid therapy, initially with high doses until remission, followed by low doses to maintain remission. We would like to highlight that seemingly multiple skin or mucosal lesions ought to be taken seriously and coexistence of two different pathologies should be ruled out when new skin lesions appear, as early diagnosis and prompt management are essential for an excellent outcome.

CASE PRESENTATION

A 55-year-old woman with underlying hypertension presented with recurrent non-healing oral ulceration, which was progressively worsening for the past 2 months. These oral ulcerations were accompanied by odynophagia. Subsequently, the patient noticed vesicular lesions appearing over the anterior chest and arms. She denied recent upper respiratory tract infection, high-risk behaviour, family history of skin disorders, traditional medication or corrosive substance ingestion or known allergy.

Relevant clinical findings included the presence of multiple painful irregular ulcerative lesions over lower lips, dorsal and ventral tongue (Fig. 1), buccal mucosa, soft palate, and labial region. Additionally, multiple vesicles were noted over the anterior chest (Fig. 2) and the forearm. Otherwise, the patient was afebrile with stable vital signs and not in respiratory distress. Flexible nasopharyngolaryngeal scope (FNPLS) revealed ulceration over the base of the tongue, laryngeal surface of the epiglottis, arytenoids, posterior commissure and pyriform fossa. Vocal cord mobility was intact and airways were patent. Other than that, nasal and ear examinations were unremarkable. Other systemic examinations were also unremarkable.

Routine haematological and biochemical investigations as well as autoimmune and infective screening were unremarkable. Histopathological examination (HPE) of oral ulcer biopsy was suggestive of HSV, with further immunohistochemistry staining revealing the presence of HSV 1 and HSV 2. Concurrently, the HPE of the biopsy taken from the anterior chest wall showed epidermis with the presence of suprabasal blister associated with intraepidermal re-epithelialisation, as well as neutrophil, lymphocyte and eosinophil infiltration suggestive of PV (Fig. 3).

The patient was referred to and co-managed by a dermatology team and was started on oral steroid, high-dose oral prednisolone, for 6 months along with chlorhexidine gargle and analgesics. Tremendous reduction of oral ulcerations and anterior skin lesions was noticed after 1 month.

Upon subsequent follow-up after completion of 3-month steroid therapy, patient's symptoms improved and no odynophagia was observed. Repeat FNPLS showed improvement of ulceration (Fig. 4).

DISCUSSION

Pemphigus, which derives from a Greek word "pemphix" for blister, is a potentially life-threatening intraepidermal autoimmune bullous disease characterised by the loss of cell-to-cell adhesion within the epidermis and/or mucosal surfaces (acantholysis) with blister formation[4]. Anti-desmoglein circulating antibodies, which cause dysfunctional adhesion of the desmosomal protein, is the

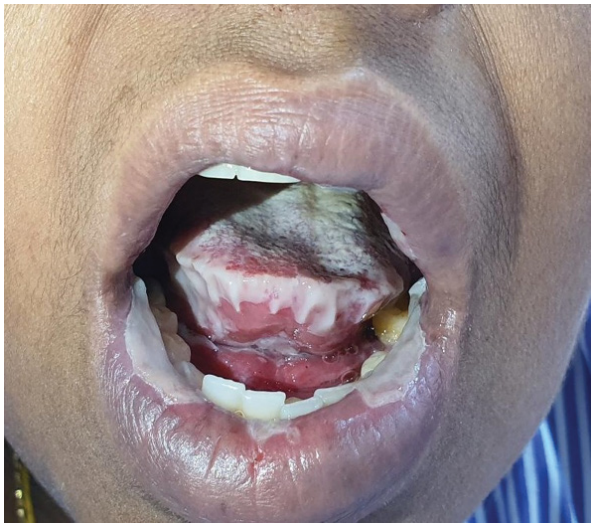

Fig. 1. Multiple painful irregular ulcerative lesions over the lower lips, as well as dorsal and ventral tongue

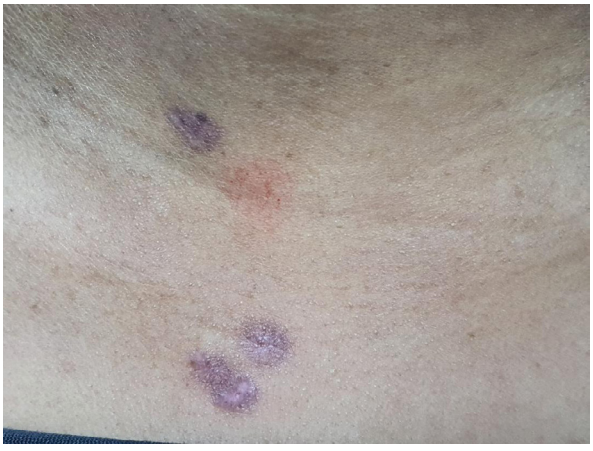

Fig. 2. Multiple vesicles are seen over the anterior chest

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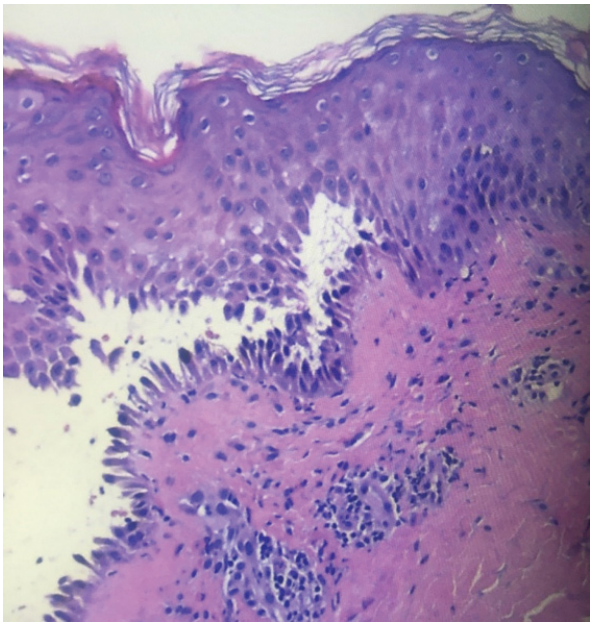

Fig. 3. HPE revealing the presence of suprabasal blister associated with intraepidermal re-epithelialisation, neutrophil, lymphocytes and eosinophils infiltration suggestive of PV

predominant pathogenesis[5]. PV generally occurs between fourth and sixth decades of life with no gender predilection[5,6]. Interestingly, only 0.5 to 3.2 cases are reported each year per 100,000 population[5,6]. PV has been sparsely reported amongst children and the elderly[6].

Several variants of pemphigus have been reported including PV, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, paraneoplastic pemphigus and drug-induced pemphigus. PV, which accounts for more than 80% of cases, is the most common form[6]. On the other hand, HSV is a DNA virus causing fever as well as cutaneous and intraoral manifestations in humans[5].

Coexistence of HSV and PV is difficult to identify purely based on oral ulceration. Oral buccal mucosal lesions are the first sign in 70–90% of cases[7]. Parallel to this, lesions are found to be more prevalent in areas which are prone to friction or trauma or regions which are more friable, particular over the palatal, lingual and labial mucosa. Other mucosal sites that may be affected by PV include oropharynx, oesophagus, conjunctiva, nasal, larynx, urethra, vulva, and cervix[6]. Additionally, shallow irregular ulcers may develop from rapidly rupturing bullae on a non-inflamed base[7]. Our patient initially presented with a shallow irregular lesion on the buccal mucosa, labial mucosa, palatal region, and lingual surface as well as skin lesions around the neck and arm.

The exact aetiology and pathogenesis of PV is still debatable and not fully established. Nevertheless, it is considered to result from an interplay between numerous endogenous (genetic predispositions) and exogenous factors, including ultraviolet radiation, X-rays, drugs (principally those containing thiol and/or phenol groups), neoplasms, pregnancy, emotional stress, vaccinations and nutritional issues.

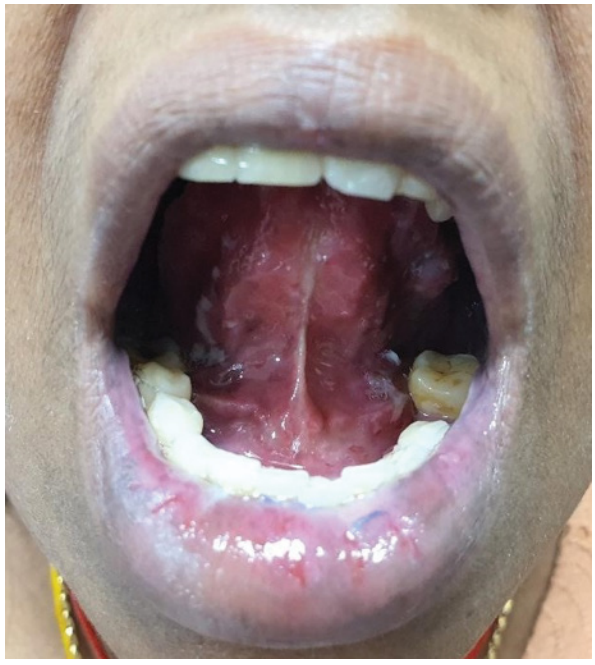

Fig. 4. Improved oral ulceration after treatment

Additionally viruses are considered exogenous factors linked to the etiopathogenesis of PV. It is known that infectious agents, such as HSV, Epstein–Barr virus (EBV), cytomegalovirus (CMV), and herpesvirus 8 (HHV 8), play an important role in initiating and triggering the condition[5]. In our case, only HSV 1 and HSV 2 were the identified factor to trigger PV in our patient.

The exact role of HSV in the pathogenesis of pemphigus is still vague, yet, numerous cases of pemphigus following HSV infection have been reported[1]. Our patient simultaneously developed PV and HSV. Yet, we still feel that as there was no other triggering factor and the patient did not exhibit any other autoimmune disease-related symptoms; HSV triggered PV. It was reported that it often takes more than 5 months from the onset of disease to reach the final diagnosis. PV is often misdiagnosed when coexisting with other infections[8].

Diagnosis can be established following histopathological examination of the respective lesions. Biopsy taken from intact vesicles and bullae less than 24 hours has been advocated to produce a desirable result. The presence of suprabasilar acantholysis, typical for PV is best identified when biopsy is taken from the advancing edge of the lesion[6]. It is important to distinguish PV from sub-epithelial diseases, such as bullous lichen planus, mucous membrane pemphigoid, and chronic ulcerative stomatitis[6]. Additionally, separate tissue specimens should be sent for direct immunofluorescence to demonstrate IgG antibody and activated complement (C-3) in the intercellular space, which is suggestive of PV. In our patient, biopsy from oral mucosa and skin showed negative fish-net pattern for IgG, IgA, IgM, C1 and C3, and immunohistochemistry staining of oral mucosa biopsy revealed positive HSV 1 and HSV 2.

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In early 1950s, prior to the emergence of corticosteroid therapy, mortality due to PV was up to 75%[7]. Systemic prednisolone remains the mainstay of treatment and is commonly administered in 2 phases; a loading phase to control the disease and a maintenance phase for consolidation[7]. However, the drawback of this treatment is that the patient may relapse once the corticosteroid is tapered, while others may face adverse effects from long-term corticosteroid therapy. Thus, some physicians advocate immunosuppressants with steroid-sparing effects, such as azathioprine and cyclophosphamide, to overcome the adverse effects of steroids while controlling the disease. Having said that, the former group of immunosuppressants are known to cause pancytopenia and hepatotoxicity, which led to the use of more recent immunosuppressants, such as mycophenolate mofetil, which are better tolerated by patients and have been shown to significantly reduce relapses once corticosteroids are tapered[7]. Prior to the initiation of steroids, it is vital for patients to be thoroughly informed on the side effects of these agents. The initial prednisone dose of 0.5–2 mg/kg is recommended and, depending on the response, it is gradually reduced to minimum therapeutic dose, taken once a day in the morning to minimize side-effects[5]. In our patient, oral prednisolone 30 mg BD was prescribed for 1 month. The patient experienced weight gain and facial puffiness.

We would like to highlight that early diagnosis and prompt treatment are crucial to hasten the recovery process and ensure better prognosis. Albeit rare, the possibility of the coexistence of PV and HSV infection should be borne in mind, especially when new lesions appear.

CONCLUSION

The coexistence of PV and herpes simplex, albeit rare, is reported here. The coexistence of a viral infection with PV poses a therapeutic challenge. The awareness of the possible coexistence of two different pathologies, as well as early diagnosis and prompt treatment initiation are essential for proper management of this clinical entity.

How does this paper make difference to the public?

- PV is a life-threatening disease, which may overlap with other skin conditions, notably HSV.
- New, secondary skin lesions should always be investigated.
- Multidisciplinary team involvement is crucial in managing a skin condition notably involving different mucosal regions.

Conflict of interest

All authors have no potential conflict of interest.

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