Herpes Simplex Virus-1 in Oral Pemphigus Vulgaris: A Causal Versus Casual Relationship (Case Report)

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Abstract

Pemphigus vulgaris (PV) is a group of autoimmune bullous diseases that results in multiple chronic mucocutaneous bullae, erosions, and/or ulcers presenting orally first. Several previous studies reported that viral infections, especially herpes simplex virus (HSV), may trigger activation of pemphigus. The relationship between PV and viral infection can be classified into 3 groups which are casual, such as viral infection due to a complication of immunosuppressive therapy, causal, HSV is a trigger before the pemphigus is present, and studies that were examined for HSV infection in PV patients but could not find any evidence. A 37-year-old male had a 4-week history of oral ulceration. Aphthous stomatitis was initially diagnosed, and was treated with chlorhexidine gluconate. Intraoral examination revealed multiple painful erosion with sloughing on the buccal mucosa, labial mucosa and dorsum of the tongue. Anti-HSV-1 IgG was reactive, while ANA test was not. Histopathology examination revealed suprabasal acantholysis. The patient was diagnosed with oral PV concurrent HSV. We used acyclovir, systemic and topical corticosteroids, chlorhexidine gluconate and multivitamin, as well aspharmacological therapy. Some lesion healed without any further clinical sequel within 6 months. The patient is still under observation without any sign of relapse. In this case, HSV was a trigger before the oral PV presented. It is important to know the relationship between oral PV and HSV in order to provide appropriate therapy to the patient and whether or not to use antiviral in oral PV therapy.

Keywords: Herpes simplex virus, Oral ulcerations, Pemphigus vulgaris.

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Introduction

The word pemphigus originates from the Greek word “pemphix” meaning blister or bubble.¹ PV is one of the most frequent representatives of the pemphigus diseases group with an incidence of 0.1-0.5/100000 people per year. The incidence of PV varies in various populations and differs among ethnic groups. There is a higher incidence of PV at lower latitudes than higher latitudes. PV affects individuals of all ages, but usually occurs in adults and predominantly female with the prevalent onset of disease between the fourth and sixth decade of life.²,³

The aetiology of PV is multifactorial, with complex interactions between individual predisposing genetic background and environmental precipitating factors contributing to the onset and course of the disease.²,⁴,⁵ The inducing or triggering factors are various, but it is considered that the disease results from an infection between endogenous (genetic predisposition) and exogenous factors. Ultraviolet radiation, X-rays, drugs (principally those containing thiol and/or phenol groups), neoplasms, pregnancy, emotional stress, vaccinations, nutritional issues, and viruses are exogenous factors linked to the aetiopathogenesis of PV.⁶ Several previous studies reported that viral infections, especially HSV, also may trigger activation or exacerbation of pemphigus.⁷

Herpes viruses have often been related to the onset or reactivations of pemphigus. Krain is the first person who reported the association between HSV and PV.⁸ Since then, there have
been few such studies, prompting us to examine this relationship. The relationship can be classified into 3 groups: (i) viral infection caused by a complication of immunosuppressive therapy, (ii) HSV as a trigger before the pemphigus is present, also with an etiologic function in its pathogenesis or (iii) studies that were examined HSV infection in PV patients but could not find any evidence.9,10

The aim of this case report is to describe the relationship between HSV in an oral PV patient who was treated with acyclovir combined with corticosteroids. By knowing the presence of oral HSV 1 infection in oral PV, we can give antiviral therapy as soon as possible. Antiviral therapy, such as acyclovir, can help prevent viral replication and speed up the healing process of oral PV lesions.

**Case Report**

A 37-year-old man was referred from a dentist to the Oral Medicine Department at Dr Hasan Sadikin Hospital with a 4-week history oral ulceration. Aphthous stomatitis was initially diagnosed, and the patient was treated with chlorhexidine gluconate. Several days later his oral ulcers worsened, and he was referred to the hospital. An intraoral examination revealed multiple painful erythematous erosion with sloughing on both buccal mucosa, both labial mucosa, and both lateral of the tongue (Figure 1). This led to difficulties in chewing and swallowing. At extraoral examination revealed multiple seropurulent crusts on thumb and palms (Figure 2). The patient was afebrile and had tender submandibular adenopathy. Suspected oral PV and oral candidiasis diagnoses were made. The patient was treated with a topical corticosteroid (mouthwash compounding of 5 mg prednisone pulvis in 15 mL distillation water 3 times/day), 2 mL nystatin oral suspension 4 times/day (swish and swallow), and a multivitamin. The patient was suggested to perform some laboratory tests including blood tests on 8 parameters: anti-HSV-1 IgG, IgE, CD4, anti-HIV, and casual plasma glucose.

In a 2-month follow-up, his oral symptoms appeared as new painful erosion dorsal tongue lesions that led to eating difficulty. Laboratory investigation revealed 190 cell/UL nonreactive ANA test. Histopathology examination revealed a suprabasal epithelial cleavage with acantholysis associated with an inflammatory infiltrate (contained 1-2 PMN and eosinophil, erythrocytes and, lymphocyte cells). No visible signs of malignancy (Figure 4) were found. Oral PV and concurrent HSV was diagnosed. The patient was treated with 200 mg acyclovir 5 times/day for a week, 30 mg prednisone 2 times/day, 50 mg potassium diclofenac 2 times/day, and 0.1% chlorhexidine gluconate 3 times/day. The patient was confirmed to have routine control once a week, complaints of the oral cavity were reduced significantly, that patient could eat well, and finally a loss of swallowing pain complaints and difficulty opening his mouth.

**Figure 1.** Oral Mucosa lesions at the first visit. Multiple painful erosion and/or ulcer with sloughing on: (A)(B) both labial mucosa, (C)(D) both buccal mucosa, (E)(F) both lateral of the tongue, and (G) diffuse erythema on the dorsum of the tongue.

**Figure 2.** Cutaneous lesions with seropurulent crusts on: (A) palm and (B) thumb.
Figure 3. After 2-month-follow-up, appeared new painful erosion on the dorsum of the tongue, leading to eating difficulty. Multiple painful erosion with sloughing on: (A)(B) both labial mucosa, (C)(D) both buccal mucosa, (E)(F) both lateral of the tongue, and (G) the dorsum of the tongue with difficulty to open the mouth.

Figure 4. Histopathology examination of specimen from buccal mucosa patient shows acantholysis (black arrow) (A) 20x, (B) 100x, in the lower spinous cell layer. Basal layer cells are attached to the connective tissue and suprabasal cleft are seen at the tips of the epithelial rate ridges.

At the 3-month-follow-up, the lesions flared-up again. This was attributed to not taking the drug for two days (Figure 5). Systemic corticosteroid 40 mg prednisone 2 times/day was combined with a topical corticosteroids (mouthwash compounding of 5 mg prednisone powder diluted in 10 mL distillation water 3 times/day), 2 mL nystatin oral suspension 4 times/day for fungal side effects caused by the use of corticosteroids, lansoprazole tablets once a day, and 1 mg folic acid tablet once a day.

At the 4-month-follow-up, the lesions on the dorsum of the tongue, left and right lateral of the tongue, and left and right buccal mucosa gradually showed significant improvement. Doses of systemic corticosteroid therapy were tapered-off, while continuing the administration of 1 mg folic acid 1 times/day and lansoprazole 2 times/day.

The lesions on the upper and lower labial mucosa, left and right buccal mucosa, dorsal tongue, and left and right lateral tongues gradually resolved in 6-months-follow-up (Figure 6). The patient had no complaint of difficulty swallowing and/or eating again. The systemic corticosteroid was tapered-off, while the combined topical corticosteroid 0.05% clobetasol propionate 3 times/day and 0.2% chlorhexidine gluconate 3 times/day were still used. The patient is still under observation without any signs of relapse.

At the 4-month-follow-up, the lesions on the dorsum of the tongue, left and right lateral of the tongue, and left and right buccal mucosa gradually resolved in 6-months-follow-up (Figure 6). The patient had no complaint of difficulty swallowing and/or eating again. The systemic corticosteroid was tapered-off, while the combined topical corticosteroid 0.05% clobetasol propionate 3 times/day and 0.2% chlorhexidine gluconate 3 times/day were still used. The patient is still under observation without any signs of relapse.

Figure 5. At 3-month-follow-up, the lesions were flare-up again. Multiple painful erosion and/or ulcer with sloughing on: (A)(B) both labial mucosa, (C)(D) both buccal mucosa, (E)(F) both lateral of the tongue, and (G) the dorsum of the tongue.

Figure 6. Some lesion healed in 6 month-follow-up. (A)(B) both labial mucosa, (C)(D) both buccal mucosa, (E)(F) both lateral of the tongue, and (G) dorsum of the tongue.

Discussion

Pemphigus is generally considered to stem from a genetic predisposition to the disease triggered and/or aggravated by one or more external factors. An acronym has been suggested from the name of the disease, PEMPHIGUS, to encompass those factors including pesticides, malignancy, pharmaceuticals, hormones, infectious agents, gastronomy, ultraviolet, radiation, and stress. There are several factors that can be a trigger or exacerbate PV, such physical agents, drugs,
neoplasm, hormones, and viruses, notably HSV. HSV is a common human pathogen classically causing orofacial (mostly HSV-1) or genital (mostly HSV-2) infections.\textsuperscript{12} Brandao et al. (2011) have detected the infectious pathogens including HSV-1 in PV patient with recalcitrant lesions using the PCR method.\textsuperscript{6} Oliveira-Batista et al. (2013) have also identified mixed viral infection in reactivated, persistent, and exacerbated lesions of PV patients. HHV-6 and/or HHV-7 were present in all co-infections in association with HSV-1.\textsuperscript{14}

The association between PV and HSV was reported by Krain in 1974.\textsuperscript{6,9,13,14} Since then, several studies have classified this association into three parts: First, there are studies in which introduced HSV as trigger factor prior to the occurrence of pemphigus and have considered the probable etiologic role for HSV in the pathogenesis of PV (causal factor).\textsuperscript{10} Theoretically, a causal factor was believed that infections can induce autoimmunity by some pathways such as activation of antigen presenting cells (APC) and activations of toll-like receptors (TLR). In some pemphigus patients, the cross-reaction between viral antigen and host antigen as well as a change in immune system due to viral infection can induce the recurrence.\textsuperscript{9} Pathogenically, it can also be supposed that herpetic infection may induce up-regulation of humoral and cellular pro-inflammatory factors, thus facilitating the outbreak of PV. Genetically, HSV infection has been shown to induce high levels of IFN-γ, IL-4, and IL-10 that may trigger or increase autoantibody production.\textsuperscript{5} There are 5 mechanisms taken into consideration to explain the association of virus infection and autoimmunity\textsuperscript{10} which are molecular mimicry, bystander activation, viral super-antigen, polyclonal activation, and epitope spreading. Molecular mimicry describes viral fragment, processed by antigen presenting cells, closely resembling a self-protein, that an immune response is initiated toward self-healthy cells. Bystander activation describes viral infection unmask an autoimmune potential, inflammation, and cytokines lead to the proliferation of pre-existing auto-reactive T cells, which were held under control and set off the self-directed immune response. Viral super-antigens are encoded by some viruses that are able to break self-tolerance by bridging major histocompatibility and toll cell receptor molecules resulting in a polyclonal T cell activation. Polyclonal activation describes lymph cytotropic viruses that can directly affect B lymphocytes, leading to their proliferation and enhanced antibody production. While epitope spreading describes a viral infection, inflammation, and cell destruction unmask previous 'sequestered' self-antigen which are recognized as foreign and processed by antigen-presenting cells.\textsuperscript{10}

Second, some studies show that HSV-1 is one of the complications of PV with resistant lesion or immunosuppressive therapies (a casual factor).\textsuperscript{15} These studies have suggested that herpes virus infections represented a complication of pemphigus resulting from immunosuppressive therapies, such as corticosteroids.\textsuperscript{16} Theoretically, when mucosa is infected, the keratinocytes can pass through structural changes leading to exposure of the antigen, this favours viral opportunistic infections such as immunosuppressive therapy.\textsuperscript{5} Finally, a third investigation was designed for detecting the evidence of viral infections in a patient with PV but they could not find any evidence of viruses in their patient.\textsuperscript{13}

In this case, we conclude that HSV might act as a trigger or exacerbate for development of oral PV, because of the laboratory examination revealed a reactive anti-HSV-1 IgG. The measurement of IgG can be a diagnostic tool. An individual’s immune response to particular pathogens can be measured with IgG antibody levels. Specific IgG against viruses is produced one to two weeks after initial infection and increases to maximum titer in four to eight weeks and then decreases.\textsuperscript{17} In most cases, HSV diagnosis was delayed for several weeks, because the viral lesion mimicked PV lesion. The lesions did not respond to tripling the dose of corticosteroids but did respond dramatically to acyclovir therapy. Clinically, it might be difficult to identify HSV-1 in oral PV patients. Persistent concomitant herpetic co-infections should be considered in the context of PV lesions that need to be confirmed by the laboratory test.\textsuperscript{14} Due to that reason, the patient was treated with 200 mg oral acyclovir five times/day after 2-month-follow-up when the oral symptoms appeared to be getting worse followed multiple vesicles that had dried up. Previous reports showed that oral PV lesions were significantly improved after acyclovir therapy. It is recommended to give the combination of antiviral agent and
immunosuppressive therapy when the infectious agent is isolated and PV lesions are refractory to corticosteroid therapy.6

The hallmark of PV is the eruption of mucocutaneous vesiculobullous lesions and development of chronic, hemorrhagic erosion caused by rupture of the preceding bullae.18 The first sign of disease frequently appears on the oral mucosa, and usually starts on non-keratinized epithelial, such as buccal mucosa, labial mucosa, and lateral tongue. The oral vesiculobullous lesion contains a thin, watery fluid, that quickly and easily ruptures within hours to days, leaving easily removable white-grey patches and multiple chronic painful bleeding non-healing ulcers and/or erosions with irregular borders. Ulcers are initially red surrounded by whitish patches, develop a yellow slough, and heal slowly with scarring.19 The cutaneous lesion is usually asymptomatic and less frequently pruritic. The lesion may be localized or generalized and predominate in seborrhea areas, and mechanically stressed regions as well as on the extremities.4 Extraoral examination revealed multiple seropurulent crusts on thumb and palm, whereas the intraoral examination revealed multiple painful chronic ulcers and/or erosion with sloughing on buccal mucosa, labial mucosa, lateral and ventral tongue. Many patients with PV could be initially misdiagnosed, usually with aphthous stomatitis, and may be treated improperly for months or even years.19 It is probably because of the nature of early-onset oral PV lesions that include ‘aphthous-like’ or ‘transient’ or ‘abortive’ lesions that heal in a few days.20

PV diagnosis is based on four criteria include clinical presentation, histopathology, direct immunofluorescence of perilesional lesions, and serological detection of serum antibodies against epithelial cell surface by indirect immunofluorescence microscopy (IIF) and/or enzyme-linked immunosorbent assay (ELISA). Based anamnesis and clinical examination, our patient had a history of persistent non-healing painful erosion and/or ulcers with sloughing in the oral mucosa, with cutaneous involvement. The presence of persistent multiple mucosa erosion and blisters must be suspected for PV.

A histopathology investigation from the perilesional biopsy of his buccal mucosa revealed a suprabasal cleavage with acantholysis associated with a sparse inflammatory infiltrate (eosinophil, neutrophil, lymphocyte cells) as well as retention of a single layer of basal keratinocytes along the basement membrane (tombstone appearance). Histopathologically, PV is characterized by an intra-epidermal cleft between the basal and spinous layer (suprabasal acantholysis),21,22 as the result of deleterious action of autoantibodies directed against the desmosomal cadherins, desmoglein 1 (Dsg-1) and Dsg-33, which manifest clinically as painful mucosa lesions and skin blister formation.22 Based on the Dsg compensation hypothesis, oral mucosa lesions appear early and are associated with the presence of anti-Dsg-3 autoantibody in dominant mucosa type of PV. Based on histopathology examination and clinical examination, the patient's lesions showed only in oral mucosa without cutaneous involvement, the definitive diagnosis of oral PV was established.

PV management is complex, and a wide variety of interventions have been established with the optimal treatment strategy remaining unclear. Treatment choice is often based not only on efficacy, but also safety, cost, and availability. Furthermore, the diversity of PV makes every patient become a unique challenge, because treating the patient during the onset of disease is quite different with recalcitrant disease or patients after multiple remissions. The PV treatment goals are to control and heal the mucocutaneous bullous eruption and/or lesion, relief of symptoms, prevent or strictly limit relapse or recurrences which also associated with functional impairment, and avoid or limit adverse events.3,21,23,24

The pharmacologic aim for PV is to reduce the inflammatory response and autoantibody production. Although the optional dose is still unknown, most experts suggest the combination of systemic corticosteroids (prednisolone 0.5-1.5 mg/kg of weight/day) and corticosteroid-sparing immunosuppressive drugs as a standard first-line therapy for PV. Since 1950, corticosteroids have been shown to be effective in treating PV. Corticosteroids have strong anti-inflammatory immunosuppressive, anti-proliferative and vasoconstriction effects, which affect almost every aspect of the immune system.24,25 Corticosteroids can also be used to maintain vascular integrity, promoting synthesis of lipocortins, and to decrease the expression of
leukocyte adhesion molecules. Systemic corticosteroids allow reliable control of acute pemphigus via direct anti-acantholytic effects by acting upon lymphocytes and blocking PV IgG-induced acantholysis. Prednisone and prednisolone were the most commonly used corticosteroid with starting doses ranged from 15 to 180 mg equivalents daily. The duration to start dose tapering from 0.5 to 12 months, while the duration of follow-up ranged from 9 months to 22 years. Previous reports showed clinical improvement of PV after using a corticosteroid for 3 days to 19 weeks. Corticosteroids can be combined with an immunosuppressive agent, particularly when complication due to expected prolonged use (>4 months), such as hypertension, diabetes mellitus, and osteoporosis are expected. In these cases we used 5 mg prednisone 2 times/day, 30 mg/day as the initial dose, 50 mg/day as the maintenance dose and slowly tapered off until 10 mg/day. In 2-month follow-up, the addition of acyclovir to prednisone for HSV-1 infection resulted in a significant reduction of clinical signs and symptoms. Acyclovir was given to the patient to reduce the viral load. Acyclovir is a synthetic guanosine analogue that is initially converted by viral thymidine kinase into acyclovir monophosphate and then converted to acyclovir triphosphate by host-cell kinases. It then competitively inhibits and inactivates HSV-specified DNA polymerases to prevent further viral DNA synthesis without affecting the normal cellular processes. Oral administration of 200 mg acyclovir 2 times/day has shown to be effective for treating HSV-1 infection in oral PV. Beside systemic corticosteroids, topical corticosteroids play a central role in the treatment of vesiculoerosive oral lesions of autoimmune and/or immunologically-mediated diseases, but the evidence for the efficacy of topical corticosteroids in oral medicine is still limited. The major challenges become more problematic as there are few commercial products currently available for the topical treatment of the oral mucosal lesion. As the oral mucosa is constantly bathed in saliva, highly mobile, and highly permeable due to mostly non-keratinized epithelial tissue, adherent vehicles, and aqueous solutions are among the most widely used. Oral solutions (mouthwash) are one appropriate vehicle to treat multiple lesions, because adequate contact time can be achieved with all lesions and the corticosteroid is reported to be released more readily to the oral mucosa. The recommended application of moderate to high potency topical corticosteroid which is applied 2-3 times/day in oral lesions of PV, because we need repeated dosing to prevent the drug from being washed off and lost by saliva. As the last therapy, we asked the patient to continue the topical corticosteroid (0.05% clobetasol propionate three times daily) because the lesion on the lateral right tongue still existed. Preventing oral candidiasis secondary to the use of topical corticosteroids is effectively managed with 0.2% chlorhexidine gluconate three times/day (swish and spit it out). Among the local adverse treatment effects with topical corticosteroids, the appearance of oral candidiasis is directly related to the use of high concentration and stronger topical corticosteroids in treatment for more than 10 days.

In 6-month follow-up, some lesion healed while lead plaque and calculus accumulation was observed resulting in inflammation which increases the risk of long-term periodontal disease. It is a common observation that vesiculoerosive diseases in patients have the self-perpetuating cycle of inflammation getting inflammation. The professional oral hygiene procedures, such scaling, in PV patients could decrease gingivitis.

Conclusions

The role of HSV-1 in the pathogenesis of oral PV is still under debate. The relationship between HSV-1 and oral PV can be classified into a causal (HSV is a trigger before oral PV), a casual (viral infection is a complication of immunosuppressive therapy) and idiopathic one (could not find any evidence). In this case, oral PV was triggered by HSV-1, and the addition of acyclovir to prednisone for HSV-1 infection resulted in a significant reduction of clinical signs and symptoms oral PV. It is important to know to provide appropriate therapy to the patient and whether or not to use an antivirus in oral PV therapy.

Declaration of Interest

The authors report no conflict of interest.
References


