Pemphigus Vulgaris Triggered by Herpes Simplex Virus Infection: A Case Report

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ABSTRACT

Pemphigus vulgaris is a life-threatening and rare autoimmune disease characterized by the development of mucocutaneous blisters resulting from autoantibody-induced disruption of keratinocyte adhesion. The following case report presents a very rare manifestation of vesiculoulcerative rash in the oral cavity, diagnosed as pemphigus vulgaris triggered by herpes simplex virus infection. It underlines the challenge of diagnosis and points out the importance of histological examination to confirm the diagnosis of pemphigus vulgaris. Therapeutic options include systemic steroids and steroid-sparing medications; current guidelines on the use of corticosteroids and rituximab as the first line of treatment and related adverse effects are discussed herein. This case report delineates diagnosis and comprehensive care for fast improvement in patient outcomes.

Keywords: Herpes simplex virus; Pemphigus vulgaris

INTRODUCTION

Vesiculobullous diseases (VB) such as mucous membrane pemphigoid, epidermolysis bullosa acquisita, pemphigus vulgaris (PV), and paraneoplastic pemphigus, are a group of diseases usually characterized by the development of blisters and erosions, which are often initially present in the oral cavity [1]. Antipsychotics, nonsteroidal anti-inflammatory drugs (NSAIDs), potassium-sparing diuretics, and sulfonamides have been shown to cause or exacerbate VB lesions [1].

Pemphigus vulgaris is a multifactorial autoimmune disease resulting from combination of environmental, genetic, and lifestyle factors. Genetic susceptibility such as HLA-DR4 and HLA-DR6, associated with an increased risk of PV. Environmental factors that have been associated are ultraviolet light exposure and human herpes viruses (HHV), such as cytomegalovirus, HHV-6, Epstein-Barr virus, and HHV-8. Human Immunodeficiency Virus (HIV) has been associated to BP. BP was also reported to be associated with Toxoplasma gondii, Helicobacter pylori, and Hepatitis B and C viruses [2,3]. Moreover, bacterial infections could also be possible trigger BP disease, which was demonstrated in a 63-year-old man who developed localized BP on the left calf after two episodes of erysipelas [4]. Lifestyle variables such as dietary habits, play a crucial role in the onset of the disease [5]. Moreover, there is an association between psychological stress and immune responses that might initiate or worsen autoimmune diseases like PV. Furthermore, patients with other autoimmune diseases, such as thyroid disorders, may be more susceptible to PV, reflecting a shared immunopathological mechanism. These factors demonstrate the complex character of PV, stressing the connection between genetic and preceding\exposure to infections [6].

Patients with VB diseases often have sores and short-lived blistering lesions that turn into ulcers. Common sites of lesions are intraoral, although lesions might spread into the throat, oropharynx, larynx, nasopharynx, conjunctiva, and skin. These lesions can cause secondary infection, eating difficulties, and pain, significantly affecting the patient's quality of life. Untreated severe cases may cause extensive erosions, system-wide complications, and even fatal conditions [7,8].

Pemphigus vulgaris is a mucocutaneous autoimmune disease targeting surface antigens on keratinocyte cells and comes under the three main types of pemphigus. This results in blistering and erosions on the skin and mucous membranes due to the autoantibodies disrupting the attachment between keratinocytes. Oral lesions frequently serve as the initial and most enduring sign, positioning dentists as crucial in early identification and treatment [9-11].

Diagnosis includes clinical analysis, biopsy, and histopathological evaluation, including direct immunofluorescence techniques to confirm the presence of antibodies. Untreated PV has a mortality rate of 60% to 90%, emphasizing the severity of this condition [12]. This is a case report of a female patient who presented in a hospital with a progressive vesicular rash and has been diagnosed with pemphigus vulgaris triggered by herpes simplex virus infection.

CASE PRESENTATION

A 15-year-old female patient live with her father presented to emergency department on 4th Aug 2024 complaining of two months history of a recurrent on/off vesicular rash on the lip, with no other significant medical history.

The patient presented with a painful vesicular rash on her lip, which increased in the size gradually, with yellow fluid discharge and swelling in the face for around 2 weeks of duration, Figure 1.

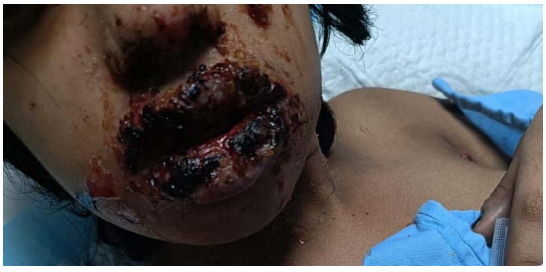

Figure 1. Severe erosions and hemorrhagic crusts over lipsFurthermore,

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the rash spread from the lips to the face, neck, hands, arms, chest, lower limb, genitalia and the back, Figure 2.

Figure 2. Neck blisters due to Pemphigus vulgaris

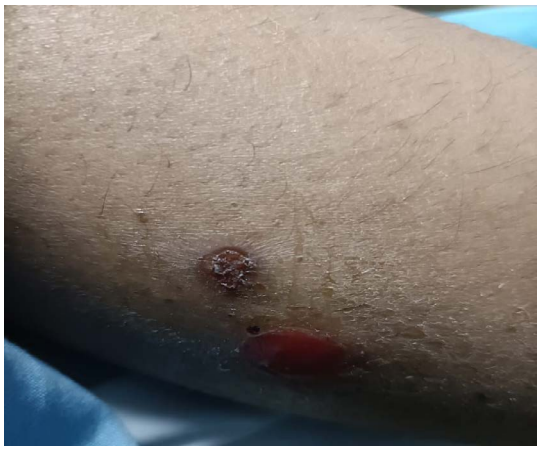

Figure 3. Hand blisters due to Pemphigus vulgaris

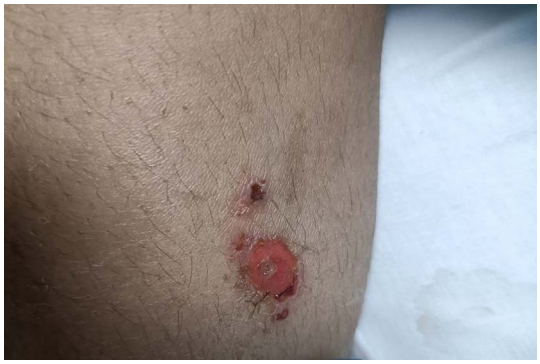

Figure 4. Leg blisters due to Pemphigus vulgaris

The patient didn't report any recent travel history or used new medications, and no similar symptoms in her family.

Upon the admission, the Glasgow Coma scale score was 15/15, the patient was conscious, alert, and oriented. The patient face had diffused vesiculoulcerative rash involving face, neck, chest, abdomen, back and extremities. Hemorrhagic crusts are seen around the right eye. Examining the oral cavity revealed a significant stomatitis, erosion and ulceration observed in the tongue and all surface of the gum and esophagus, but full examination was not obtained due to pain. However, the patient refused the internal examination of the gentitalia, but diffuse vesiculobullous was observed.

Herpes Simplex Virus (HSV) PCR was performed during the clinical examination, and HSV serology was positive. Methicillin Resistance Staphylococcus Aurius (MRSA), was positive in the urine culture, Umbilical and wound swab. While HIV, ANA and Chlamydia trachomatis/Neisseria gonorrhoeae tests were all negative. highlighting the need to consider herpes simplex virus infection in the differential diagnosis. Several laboratory tests were performed for more investigations. Immunology tests for antibodies such as Iga, IgG and IgM levels were normal, and CRP =3.2 mg/L. Skin punch biopsy was performed and the result revealed suprabasal clefting bullous disease, which suggests pemphigus vulgaris with differential diagnosis including Halley Hailey disease, HSV infection and other immunobullus diseases.

HOSPITAL MANAGEMENT

The patient was admitted for further evaluation and treatment. Initial differential diagnosis tests were performed, included: herpes simplex virus, HIV, or bacterial, autoimmune disease such as pemphigus vulgaris, and malignant etiologies. The hospital treatment includes different drugs to manage viral and bacterial infections, such as: acyclovir 5mg / kg every 8 hours for viral infection. Vancomycin and cefepime due to MRSA presents. Additionally, corticosteroids such as prednisolone 20 mg daily, and betamethasone topically was given to patient due to pemphigus vulgaris. Furthermore, Moxifloxacin eye drops, nystatin as mouth wash and paracetamol and morphine as painkiller were given to patient as needed. Patient's images upon discharge are demonstrated in Figures 5,6, 7, and 8.

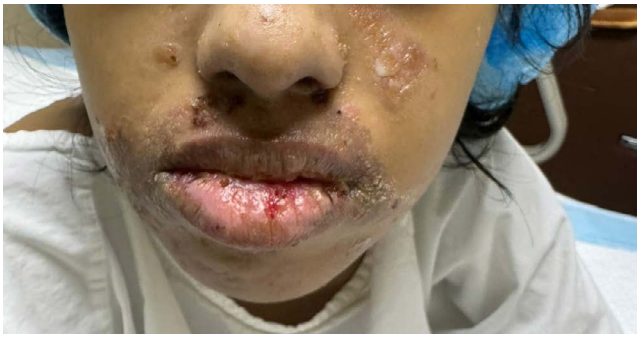

Figure 5. Lips state improvement upon discharge

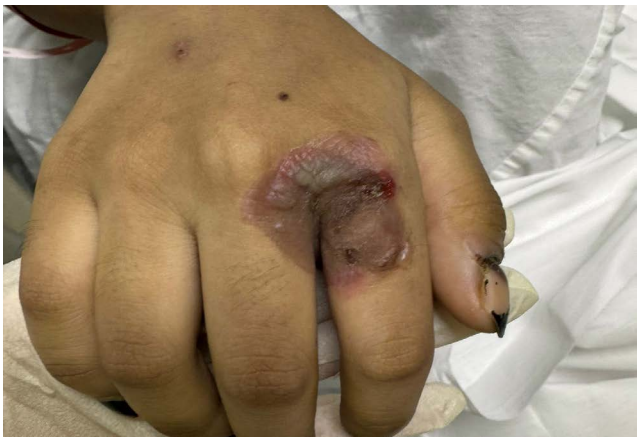

Figure 6. Hand state improvement upon discharge

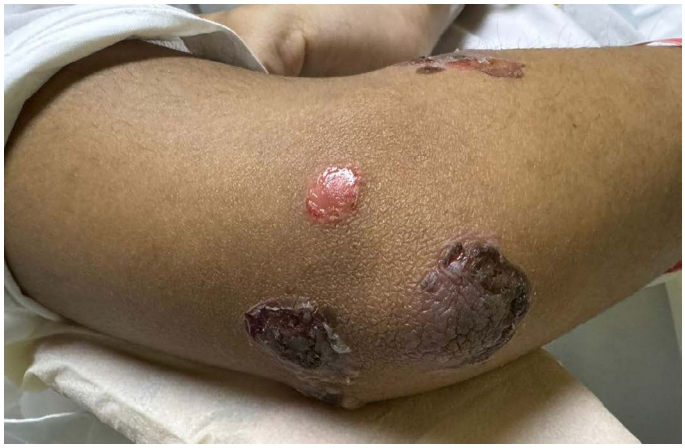

Figure 7. Elbow state improvement upon discharge

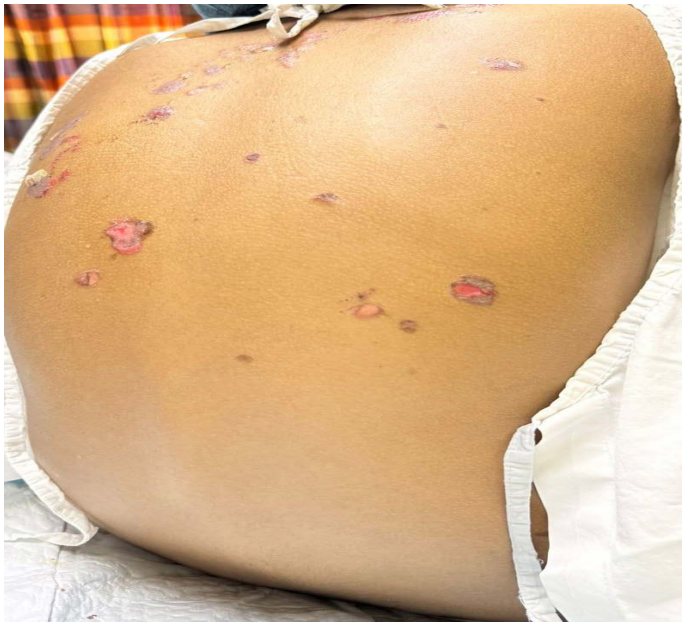

Figure 8. Back state improvement upon discharge

DISCUSSION

Pemphigus vulgaris is an autoimmune blistering disease that affect the skin and mucous membrane, primarily due to the disruption of proteins by autoantibodies. Early detection of PV and its clinical manifestations is crucial for effective management.

PV is a potentially fatal autoimmune skin disease characterized by the presence of IgG autoantibodies against the desmoglein-3 (Dsg3), a 130-kDa glycoprotein found in the spinous and basal layers of both epidermis and oral mucosa [13,14]. This mechanism explains the blistering of the skin and erosion of mucous membranes, as PV leads to a loss of cell-to-cell adhesion in the suprabasal layer (acantholysis) [13-15].

The onset of autoimmunity has been connected to viral infections, presumably through molecular mimicry, viral infections that reveal autoimmune potential, viral superantigens encoded by some viruses, polyclonal activation, and epitope diffusion [16].

Previous literature that examined the relationship between pemphigus and HSV either emphasized that viral infection is a complication of immunosuppressive therapy; claimed that HSV is a trigger before the pemphigus is present, with an etiologic function in its pathogenesis; or found no evidence on the association between them [17].

HSV-1 causes primary and recurrent vesicular outbreaks in the orolabial and vaginal mucosa. HSV-1 infection can manifest as orolabial herpes, herpetic sycosis (HSV folliculitis), herpetic whitlow, ocular HSV infection, herpes gladiatorum, herpes encephalitis, Kaposi varicelliform eruption, and severe or chronic HSV infection [18,19].

At admission, the patient face presented with a diffuse vesiculoulcerative rash affecting the face, neck, chest, abdomen, back and extremities. Although a full examination was not conducted, vesiculobullous was observed in the genital area. Oral lesions are often the first sign of this disease, frequently resembling other ulcerative disorders, which can lead to significant delays in the diagnosis. Diagnostic methods include histopathological examination, which reveals suprabasal acantholysis, and direct immunofluorescence, which demonstrates the deposition of IgG and C3 in a characteristic ‘fishnet’ pattern. Enzyme-linked immunosorbent assay (ELISA) testing for anti-Dsg antibodies has enhanced the accuracy of the diagnosis and allows for the quantification of disease activity, aiding in the monitoring of treatment response and differential diagnosis. The clinical spectrum of PV ranges from involvement often presents as non-healing erosions on the buccal mucosa, palate, or gingiva [20-22].

Pemphigus vulgaris is a chronic autoimmune blistering disorder that predominantly affects adults of both sexes; however, some studies suggest a higher prevalence in women [23]. Prior literature indicates that patients with bullous autoimmune disorders and individuals with skin and mucosal lesions are predisposed to viral infections [24], while other studies suggest that in cases of recalcitrant lesions lasting a minimum of 3 months, the identification of HSV is imperative [25]. A prior investigation by Brandão et al. documented a case in which the nasal lesion tested negative for several viruses, while the upper eyelid lesion tested positive for HSV-1, managed by acyclovir treatment. This study's findings corroborate the association between pemphigus and HSV [26]. Additionally, a study conducted by Oliveira et al. analyzed 23 patients with PV, from whom 105 samples were obtained. HSV was identified using 36 samples from 17 patients, while 6 patients tested negative for the virus. This research found HSV infections in recurrent or chronic PV lesions [27]. Conversely, other literature showed contradictory findings and found no association between PV and HSV [28].

Early detection of the infection such as HSV, can aid patients in disease management and reduce the risk of transmission and complications. Early testing and prior knowledge of patient history are critical in determining the right course of treatment and offering counseling to patients and their significant others, according to disease management research [29].

In PV, clinical symptoms are used to make the diagnosis, which is then confirmed by biopsy. Direct immunofluorescence is used to make a definitive diagnosis of PV. In bullous autoimmune diseases such as PV, and mucous membrane pemphigoid (MMP), which have a similar clinical presentation to PV, oral lesions begin early in the disease before other lesions appear elsewhere, and oral lesions may be the only symptom during disease progression. However, early diagnosis is critical to initiate the treatment and reduce complications since PV is a lethal disease with a 75% mortality rate if untreated early [30].

Although corticosteroids, such as prednisolone, remain the cornerstone in the treatment for PV, the reported remission rates with corticosteroid monotherapy are relatively low, averaging approximately 25% of patients [31]. Systematic corticosteroids are associated with a significant

safety concern due to adverse effects, including increased risk of diabetes, hypertension, osteoporosis and infection, which limit their long-term use [32-34].

To address these issues, corticosteroids are often combined with other immunosuppressants such as azathioprine or rituximab, to enhance efficacy and reduce steroid- related side effects. A study evaluating the combination of rituximab and systematic prednisolone demonstrated that patients receiving this regimen achieved higher rates of complete remission compared to those on prednisolone monotherapy. Additionally, rituximab exhibited a steroid – sparing effect, reducing the cumulative prednisolone dose, and was associated with fewer serious adverse events [35].

Current research aims to enhance diagnostic biomarkers, investigate genetic predispositions more precisely, and develop novel medication treatments targeting specific immune pathways. Applying precision medicine approaches and patient-reported outcomes to PV studies is anticipated to shift disease management and enhance long-term outcomes.

CONCLUSION

In conclusion, PV remains a challenging disorder because of its potential severity and impact on patients' quality of life. Several triggering factors, such as concurrent infection with HSV, may provoke, worsen, and complicate the treatment of PV. Early and precise diagnosis through clinical evaluation and biopsy is crucial. Prednisolone improved the condition of the patient by reducing discomfort and bleeding in the lesion. Further research and specialized care are needed to optimize outcomes and reduce risks associated with long-term immunosuppressive therapy. This case emphasizes the significance of early detection and intervention in the efficacious management of PV.

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