A Rare Clinical Manifestation of Pemphigus Vulgaris in Elderly Patient: A Case Report and Brief Review

Fika Faradillah Drakel[1], Irna Sufiawati[2]*

1. Oral Medicine Residency Program, Faculty of Dentistry Universitas Padjadjaran, Indonesia.
2. Oral Medicine department, Faculty of Dentistry, Universitas Padjadjaran, Indonesia.

Abstract

Pemphigus Vulgaris (PV) is a serious autoimmune disorder in the form of acute or chronic blisters on the mucocutaneous surface. The oral mucosa is the initial site of involvement in 50-60% of patients. Many known *triggers* have been associated with *PV*. This case report aims to describe a case of PV with an unusual clinical manifestation with multiple risk factors in elderly patient. A 78-year-old woman came with a chief complaint of swelling on the lower lip for 3 months proceeded by oral ulcers on the lip vermillion. Extraoral examination showed diffuse swelling on the lower lip and a a cutaneous lesion on the right side of lower chin. Intraoral examination revealed ulcers and erosive lesion on the buccal mucosa. The medical history was rheumatoid arthritis treated with D-penicillamine for 6 months. Working diagnosis of pemphigus vulgaris, acute pseudomembranous candidiasis, and angioedema were made. Several laboratory tests were performed. The anti-HSV-1 IgG test showed reactive. A tongue smear showed Gram-positive and -negative, and yeast. CBCT 3D examination showed inflammatory lesions, with the differential diagnosis includes malignant lesions, chronic osteomyelitis. Histopathological examination showed suprabasal acantholysis. A definitive diagnosis of PV was established. The patient was treated with acyclovir, corticosteroid, nystatin, chlorhexidine gluconate and multivitamin. Unusual clinical presentations challenging the early clinical diagnosis of PV in elderly patient with multiple risk factors. Hence, the appropriate laboratory test related to the risk factors is mandatory to provide the patient the adequate treatment.

Case report (J Int Dent Med Res 2021; 14(3): 1144-1148)

Keywords: Pemphigus Vulgaris, Elderly Patient, Rheumatoid Arthritis And HSV-1 Infection.

Received date: 11 April 2021 **Accept date:** 16 June 2021

Introduction

Pemphigus vulgaris (PV) is an autoimmune disease in which IgG antibodies target desmosomal proteins to produce blisters on the skin and mucosa. Desmoglein (Dsg) 3 is the main antigen but 50-60% of patients have additional antibodies to Dsg1, which is the antigen that plays a role in pemphigus foliaceus.[1] There are 6 main types of pemphigus vulgaris and their classification is based on the anatomical features of the lesion and the target antigen that is involved. recognized by autoantibodies. Specifically, the antigen that plays a role in the oral mucosa is desmoglein (Dsg) 3 and is associated with IgG antibodies.[1,2]. The antigens that play a role are BP180, BP230, laminin 332, α6β4 integrin and IgG and IgA antigens.[3]

The incidence of PV is 0.076 for five cases per 100,000 population per year, and adults between 40 and 60 years are more frequently affected, but with other classifications associated with paraneoplastics over 70 years of age.[4] The prognostic factor is age, time between symptom onset. and initiation of treatment, extent of lesion and dose of corticosteroid needed to control disease. [4,5]

Different etiological factors are considered for the pathogenesis of PV, namely genetic and environmental factors including virus infection. Some HLA facilitates this pathogenesis and is associated with secretion of inflammatory molecules towards keratinocytes after exposure to antibodies supported by the ST18 promoter tumor necrosis factor (TNF), IL-1α and IL-6.[6 7] Comorbidities that trigger PV are thyroid disease, type 1 diabetes mellitus, *cardiovascular disease*

Corresponding author:
Irna Sufiawati
Department of Oral Medicine
Faculty of Dentistry, Universitas Padjadjaran
Jl. Sekeloa Selatan No.1, Bandung 40132, West Java, Indonesia
E-mail: irna.sufiawati@fkg.unpad.ac.id

and Rheumatoid arthritis (RA).[8,9]

Rheumatoid arthritis (RA) is a long-term disorder that causes inflammation of the joints and can affect other organs. RA is an autoimmune disease whose cause is still unknown. The oral mucosal lesions and periodontal diseases are frequent in patients with RA.[10,11] Treatment of RA is known to cause pemphigus in the oral cavity.[10,12] There are several associations besides RA drug induction that can also be attributed to the role of HLA in the initiation of PV as well as a role in osteoclastogenesis related to RA.[13] Because they are both autoimmune categories, a multi-autoimmune syndrome (MAS) condition can occur which increases susceptibility to autoimmune diseases. The susceptibility of women is higher than men and in the age range of 15 - 50 years.[9,14] The emergence of pemphigus vulgaris in patients with systemic rheumatoid arthritis disorders, arises as a result of therapy for rheumatoid arthritis disorders such as *D-penicillamine*.[10] PV in patients with rheumatoid arthritis due to drugs can induce acantholysis.[8]

It is well known that viral infection can also trigger a recurrence of PV. Herpes simplex virus-1 (HSV-1) infection is often associated with the PV condition. Theoretically, the causative factor is believed that infection can cause autoimmunity through several pathways such as activation of *antigen-presenting cells* (APC) and *activations of toll-like receptors* (TLR).[15]

Case Report

A 78-year-old woman was referred from the private hospital with a chief complaint of painful swelling on the lower lip for 3 months proceeded by oral ulcers on the lip vermillion causing difficulty in eating, speaking and swallowing. She had a medical history of rheumatoid arthritis for five years and routinely taking RA-related drugs. Extraoral examination revealed a diffuse swelling on the lower lip, desquamation surrounded by erythematous lesions with a yellowish crust, and saliva was drooling out. In addition, there were a cutaneous lesion on the right side of lower chin. (Figure 1-A, -H). The nasogastric tube (NGT) was inserted due to a limited mouth opening. On the intra oral examination, we found a white plaque on the dorsal surface of the tongue that can be scraped off leaving behind erythematous area, and erosive lesions on the lateral border of the tongue (Figures 1-B, -C, -D). There were also erosive lesions on the right and left buccal mucosa (Figure 1-E and -F). On the hard palate, white plaque can be scraped off by leaving an erythematous area was also found (Figure 1-G).

Based on history taking and clinical examination, a working diagnosis of pemphigus vulgaris, acute pseudomembranous candidiasis and suspect angioedema. Differential diagnosis includes herpes labialis and osteomyelitis. We performed several laboratory examinations related to the risk factors to support the definitive diagnosis, including the mucosa smear, anti HSV-1 IgG, cone beam computed tomography (CBCT), and histopathological examination. The patient was referred to the Dermatologist for the treatment of the skin lesions. Treatment consisted of the administering of NaCl 0.9 % compressed to the lesions on the lip, chlorhexidine digluconate mouthwash 0.12%, nystatin oral suspension, oral acyclovir 400 mg 3 times daily, vitamin B12 and folic acid for a week. The patient was also instructed to clean his teeth with a gauze moistened with NaCl 0.9% at least three times a day.

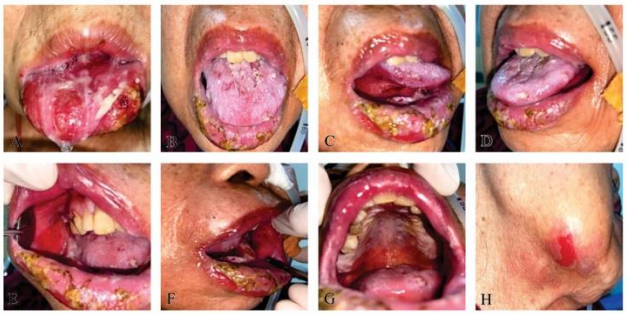

Figure 1. The clinical features of the first visit. A. *Oedema*, desquamation surrounded by erythematous lesions with a yellowish crust, and drooling; B, C, & D. A white plaque on the dorsal surface of the tongue that can be scraped off leaving behind the erythematous area, and erosive lesions on the lateral border of the tongue; E & F. Erosive lesions on the right and left buccal mucosa; G. A white plaque can be scraped off by leaving an erythematous area on the hard palate; H. A diffuse swelling on the lower lip, desquamation surrounded by erythematous lesions with a yellowish crust; H. A cutaneous lesion on the right side of the lower chin.

The patient was closely *followed up* every *week*. On the *second visit*, we found that IgG HSV-1 test was reactive (> 200 U/ml). A tongue smear showed Gram-positive and -negative, and yeast. The CBCT 3D showed a soft tissue mass on the anterior labial mucosa of the mandible, accompanied by an appearance resembling multiple radiolucent osteolytic lesions with partially ill-defined margins anteriorly and extending to the left & right mandibular bodies (past the symphysis). This interpretation of CBCT concluded inflammatory lesions. Differential diagnosis includes malignant lesions, chronic osteomyelitis (Figures 2). Histopathological examination showed suprabasal acantholysis (Figures 3). A definitive diagnosis of PV was established. The treatment given from the Dermatologist include methylprednisolone 16 mg at a dose of 2x2 per day, betamethasone dipropionate 0.05% and gentamicin sulphate 0,1% cream, and cetirizine 2x1 per day.

After 8 weeks followed up, the lesions showed a significant improvement. The NGT was removed and patient could consume soft foods orally. The treatment was continued. Systemic corticosteroid has been tapering-off, combined with topical corticosteroid for the lesions on the buccal mucosa, chlorhexidine digluconate and hyaluronic acid mouthwash were used alternately every 2 weeks to have anti-inflammatory action, bacteriostatic effect and antioxidant properties. Six weeks later, the PV *lesions* were *almost completely healed (Figure 4).* The patient has no complaint of difficult to swallow and eating again. She is still under observation without any sign of relapse.

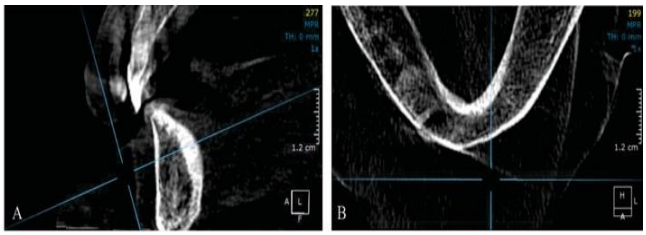

Figure 2. Cone beam computed tomography (CBCT) interpretation. A. Sagittal view showed resembling multiple radiolucent osteolytic lesions, partly well-defined and partly ill-defined on the left and right mandibular bodies; B. The anterior alveolar bone of the mandible appears asymmetrical (left side of the anterior mandible is thinner than the right) but cortical remains intact, possibly due to a mass on the labial side.

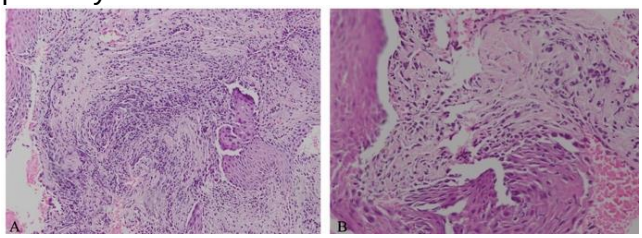

Figure 3. Histopathological features of the specimen show the suprabasal acantholysis. (A) 20x magnification, (B) 200x magnification.

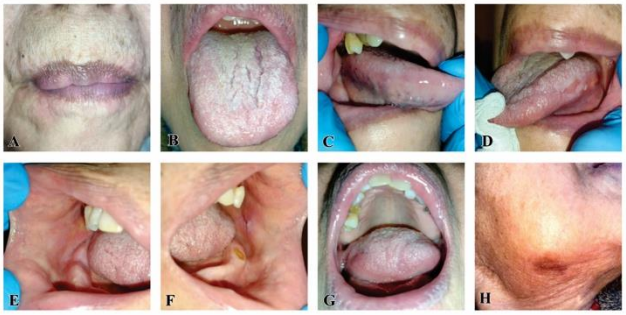

Figure 4. The improvement of the oral mucosa and skin lesions at the last visit.

Results and Discussion

The swelling of the lips is a rare clinical feature of pemphigus vulgaris. Therefore, we performed several laboratory examinations to identify the risk factors and to establish the definitive diagnosis. We have identified some risk factors that related to PV in this case. The previous studies and reports have been suggested that rheumatoid arthritis (RA) and HSV-1 infection are the common risk factors of PV as seen in this case. The RA patient had a history of RA for 5 years but did not routinely take penicillamine. She started taking RA drugs routinely 6 months ago before the lesions appeared in her oral cavity. Hence, it was suggested that the effect of drugs associated with the PV incidence in this case.

Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic joint inflammation and pain. The cause of RA is still unclear, but RA is thought to be triggered by a combination of genetic and environmental factors that cause mucosal surface damage. Even though the pathogenesis of RA remains unclear, the previous study hypothesized that T cells and B cells produce antibodies to protect from infection or diseases that abnormally attack

healthy cells which later causing swelling, tenderness, and restricted joint movements.[16,17] RA has known a very close relationship with the condition of the oral mucosa and the periodontium tissue.[17,18] Three factors are that are related to the negligence of PV in the oral cavity, they are the effect of long-term RA drug consumption, HLA gene equations and Autoimmune Multi Syndrome condition.[13,18,19] HLA and Autoimmune Multi Syndrome conditions, HLA DRB1 in PV patients has been shown to also be present in RA, this is related to the role of T cells that carry the HLA DRB1 antibody.[17,20]

The association of HSV-1 and PV is related to infectious or environmental factors, and latent conditions that already exist in the mucosa and are supported by antigens and antibodies.[21] HSV antibodies can be detected, although many cases describe the relationship between HSV infection and PV, this has not been studied in more depth.[21,22] The association of HLA DRB1 in patients with PV has a genetic link to HSV infection and has no association with systemic disease.[22] A good immune condition will suppress the activation of HSV in PV patients. The role of immunosuppressive agents causes susceptibility to HSV reactivation.[15,22] HSV may act as a trigger or exacerbate the development of oral PV since laboratory studies have shown anti-HSV-1 IgG is reactive. IgG measurement can be a diagnostic tool. Clinically, it may be difficult to identify HSV-1 in oral PV patients. Concomitant HSV infection in PV lesions needs to be confirmed by laboratory tests. For this reason, the patient was treated with oral acyclovir 400 mg 3x1 daily after anti HSV-1 IgG test revealed reactive. The diagnosis of HSV-1 infection usually is based on the patient's medical history. However, laboratory confirmation may be required when the clinical features are atypical or when patients are immunocompromised.[23]

Conclusions

Unusual clinical presentations of swelling on the lips challenging the early clinical diagnosis of PV in elderly patient with multiple risk factors. Identification of risk factors of PV play an important role in establishing the definitive diagnosis and a strategy for the treatment. Hence, the appropriate laboratory test related to the risk factors is mandatory to provide the patient the adequate treatment.

Declaration of Interest

The authors report no conflict of interest.

References

1. Kilic A. Pemphigus: Subtypes, Clinical Features, Diagnosis, and Treatment. Autoimmune Bullous Dis : IntechOpen; 2018:1–45.
2. Kershenovich R, Hodak E, Mimouni D. Diagnosis and classification of pemphigus and bullous pemphigoid. Autoimmun Rev. 2014;13(4–5):477–81.
3. Di Lernia V, Casanova DM, Goldust M, Ricci C. Pemphigus Vulgaris and Bullous Pemphigoid: Update on Diagnosis and Treatment. Dermatol Pract Concept. 2020;10(3):e2020050.
4. Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, et al. Pemphigus. Nat Rev Dis Primers. 2017;3:17026.
5. DiMarco C. Pemphigus: Pathogenesis to Treatment. R I Med J 2016;99(12):28–31.
6. Karimi A, Esmaili N, Ranjkesh M, Zolfaghari MA. Expression of human endogenous retroviruses in pemphigus vulgaris patients. Mol Biol Rep 2019;46(6):6181–6.
7. Leuci S, Ruoppo E, Adamo D, Calabria E, Mignogna MD. Oral autoimmune vesicobullous diseases: Classification, clinical presentations, molecular mechanisms, diagnostic algorithms, and management. Periodontol 2000. 2019;80(1):77–88.
8. Kridin K, Jones VA, Patel PM, Zelber-Sagi S, Hammers CM, Damiani G, et al. Patients with pemphigus are at an increased risk of developing rheumatoid arthritis: a large-scale cohort study. Immunol Res. 2020;68(6):373–8.
9. Attwood K, Sato R, Sinha AA, Park R, Sinha AA, Rita M, et al. Identification of a new disease cluster of pemphigus vulgaris with autoimmune thyroid disease, rheumatoid arthritis and type I diabetes. bristhis J dermatology 2015;172(3):729–38
10. Narges Gholizadeh, Ali Taghavi Zenouz HE. Pemphigus Vulgaris Associated with Rheumatoid Arthritis in a Patient not Taking Penicillamine. J Dent Res Dent Clin Dent Prospects 2012;6(1):33–5.
11. Suhaimi N, Kamaruzaman N, Taib H, Wan Mohamad WM, Wan Ghazali WS. Assessment of periodontal status in patients with rheumatoid arthritis in Kelantan, Malaysia: A preliminary study. J Int Dent Med Res. 2016;9(2):108–12.
12. Meier FM, Frerix M, Walter Hermann UM-L. Current immunotherapy in rheumatoid arthritis. Immunotherapy. 2013;5(9):955–74.
13. Vincent van Drongelen, Ph.D. and Joseph Holoshitz MD. A reciprocal HLA-Disease Association in Rheumatoid Arthritis and Pemphigus Vulgaris. Front Biosci (Landmark Ed). 2018;909–19.
14. Vodo D, Sarig O, Sprecher E. The Genetics of Pemphigus Vulgaris. Front Med (lausanne) 2018;5:1–7.
15. Nelonda R, Sufiawati I. Herpes simplex Virus-1 in oral Pemphigus vulgaris: A causal versus casual relationship (Case Report). J Int Dent Med Res. 2019;12(2):716–22.
16. Azalan MS, Sains U, Sains U. Functional Status of Rheumatoid Arthritis J Int Dent Med Res. 2021;14(1)::440–5.
17. Gregoriou S, Efthymiou O, Stefanaki C, Rigopoulos D. Management of pemphigus vulgaris: Challenges and solutions. Clin Cosmet Investig Dermatol. 2015;8:521–7.
18. Potempa J, Mydel P, Koziel J. The case for periodontitis in the pathogenesis of rheumatoid arthritis. Nat Rev Rheumatol. 2017;13(10):606–20.
19. Tavakolpour S. Pemphigus trigger factors: special focus on pemphigus vulgaris and pemphigus foliaceus. Arch Dermatol Res. 2018;310(2):95–106.
20. Pollmann R, Schmidt T, Eming R, Hertl M. Pemphigus: a Comprehensive Review on Pathogenesis, Clinical Presentation and Novel Therapeutic Approaches. Clin Rev Allergy Immunol. 2018;54(1).

21. Konda D, Chandrashekar L, Dhodapkar R, Ganesh RN, Thappa DM. Clinical Markers of Herpes Simplex Virus Infection in Patients with Pemphigus Vulgaris. J Am Acad Dermatol. 2019 Jun 10;S0190-9622(19)30905-3.
22. Senger P, Abidi N, Lin DM, Seiffert-Sinha K, Sinha AA. Positive correlation of Anti-Herpes simplex type I virus antibody levels with pemphigus vulgaris disease status and activity in a large patient cohort. Eur J Dermatology. 2017;27(2):132–8.
23. Bohn JC, Teixeira L, Chaiben CL, Kuczynski A. Management of recurrent herpes labialis in immunosuppressed patient – a case report. J Int Dent Med Res. 2011; 4(2);70–3