International Journal of Multiphysics
Volume 18, No. 4, 2024
ISSN: 1750-9548

The Importance of Oral Biopsy in a Thalassemia Patient Affected with Pemphigus- A Rare Case Report

Maryam Jalili Sadrabad[1], Elahe Jandaghi MD[2], Sahar Maleki[3], Minoudokht Ghamari Gilvaei[4] ,Abdollah Ebrahimi[5*]

1- Associate Professor, Oral and Maxillofacial Medicine Department, Dental School, Semnan University of Medical Sciences, Semnan, Iran. Email: dr.njalili@gmail.com
2- Assistant Professor, Internal medicine Dept,Semnan university of medical sciences,Semnan ,Iran . Email: dr.ejandaghi@gmail.com
3- Student Research Committee, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran. Email: saharmlki2001@gmail.com
4- Doctor of Medicine in Dentistry, Member of Royal Australian College of Dental Surgery , Melbourne, Victoria,Australia. Email: m.ghamari89@gmail.com
5- Student Research Committee, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran. Email: ebrahimi56666@gmail.com

***Corresponding Author**:* Abdollah Ebrahimi, Student Research Committee, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran. Email: ebrahimi56666@gmail.com

Abstract:

Introduction and purpose: Pemphigus is a severe and potentially fatal autoimmune blistering disease. Given the risks associated with misdiagnosis or delayed diagnosis and the possibility of overlapping clinical features and treatments, suspected pemphigus often requires a thorough clinical evaluation and laboratory testing. Studies have also reported the simultaneous presence of pemphigus with neurological, genetic, and metabolic diseases. Few reports of thalassemia have been complicated with pemphigus vulgaris or vice versa. Here we introduce a patient with β -thalassemia inrermedia who suddenly got pemphigus vulgaris.

Case report: A 31-year-old woman with a painful mouth ulcer was referred to the Oral Diseases Clinic of Semnan University. Oral ulcers started six months ago, and the blisters spread to the whole body after some time. Several skin biopsies were performed, but each time non-specific inflammation was observed. Oral biopsy revealed the answer to this mystery, and the diagnosis of pemphigus vulgaris was reported. The patient's treatment was started with topical steroids and oral nystatin, and then she was referred to a dermatologist.

Conclusion: Therefore, it is recommended that doctors and dentists, when faced with patients with chronic and multiple oral lesions, consult and cooperate to make the best diagnosis for the patients and benefit from the advantages of early treatment and prevent the use of wrong drugs.

Keywords: pemphigus vulgaris, mouth Ulcer, corticosteroids, nystatin

1. Introduction

Pemphigus is a family of rare autoimmune acantholytic dermatoses of the mucous membrane, characterized histologically by suprabasal fissures and acantholysis [1]. In it, acantholysis, or loss of cell-to-cell adhesion, causes potentially fatal blisters and erogenous formation. Several subtypes of pemphigus disease have been identified based on their distinct clinical features and pathophysiology, including pemphigus vulgaris (PV), pemphigus foliaceous (PF), pemphigus IgA, and pemphigus paraneoplastic (PNP)[2].

Serologically, the center of pemphigus pathogenesis is the presence of immunoglobulin (Ig) antibodies against proteins on the cell surface of keratinocytes. Antigenic targets in PV and PF are desmogleins, transmembrane glycoproteins associated with desmosomes that mediate cell adhesion in the epidermis [3-5].

Pemphigus occurs worldwide, with a prevalence of 0.1–0.5 per 100,000 persons per year [6], affecting all racial and ethnic groups[7].

The age of onset is usually between 40 and 60 years old [8].Although pemphigus is generally very rare in children, it has been observed in the pediatric population, even in 6-year-old patients[9].Recent studies have found pemphigus to be increasingly diagnosed in younger patient populations, with the global male-to-female ratio of pemphigus patients being nearly equal. However, adolescent girls are more susceptible than teenage boys [10, 11].

Pemphigus vulgaris is the most common form of pemphigus, accounting for more than 80% of cases [12]. In most patients, it affects the oral mucosa and is sometimes difficult to diagnose when there is only mucosal involvement [13].

In terms of clinical features, a universal feature of the PV subtype of pemphigus disease is mucosal involvement in the form of painful and erogenous blisters, which predominate in the mucous membranes of the oropharynx. More than 90% of patients with PV present with mucosal membrane involvement, and the oral cavity is the most common site of mucosal lesions in PV patients, and the initial manifestations of the disease appear there more [14].

Lesions can occur anywhere in the oral mucosa, but the buccal mucosa is the most commonly affected site, followed by the palate, tongue, and lip mucosa. The gums are the least damaged, and desquamative gingivitis is the most common manifestation of the disease when the gums are involved [12].

Recurrent oral ulcers can only be clinical manifestations before progressing to skin lesions [15].

Mucous membrane involvement can spread to other mucosal sites, such as the eyes, nose, esophagus, vagina, cervix, and anus, causing eye irritation, dysphagia, hoarseness, vaginal irritation, and dyspareunia[3, 14].

Mucosal ulcers can be very painful for some patients and can make daily tasks such as chewing and eating more difficult as the disease progresses. PV includes two main subgroups: the mucosal-predominant type, which causes mucosal Lesions but minimal skin involvement, and the mucocutaneous type, which causes diffuse mucosal participation in addition to blisters and cutaneous ulcers. PV skin lesions typically reflect loose, crusted erogenous blisters on an erythematous base [14, 16]

The loose nature of blisters seen in PV is secondary to intraepidermal acantholysis caused by anti-desmoglein antibodies. PV lesions are often Nikolsky-positive, meaning mechanical pressure applied to the blister with little force results in an incision of the adjacent skin [2].

Skin lesions can be localized or diffuse and can affect any surface. Lesions are usually very painful. Notably, the palms and soles are usually spared in patients with PV. The absence of palmoplantar involvement can be helpful in the differential diagnosis of PV from other vesicolobular dermatoses such as PNP or erythema multiforme [2].

The diagnosis of pemphigus begins with a thorough history and physical examination. In the past, clinicians should look for mucosal involvement, as mucosal lesions can differentiate subtypes of pemphigus [17].

If a proper history is taken, the doctor should be able to distinguish pemphigus lesions from lesions caused by acute viral infections such as herpes and erythema multiforme. Immunocompromised patients with recurrent herpes simplex infections present with atypical sores that may last for several weeks or months if not diagnosed and treated [17].

After a thorough history and physical examination, the laboratory workup for pemphigus disease includes at least two biopsies with or without serum collection for indirect immunofluorescence (IIF), enzyme-linked immunosorbent assay (ELISA), or immunoblotting [16, 18].

The diagnosis is confirmed by the characteristic deposition of IgG and other C3 antibodies that bind to the cell surface of the skin or distal mucosa [19, 20].

The therapeutic approach to pemphigus is primarily based on immunosuppression to prevent new lesion formation and heal existing bullous skin and mucosal lesions while minimizing the severe side effects of treatment. For all forms of pemphigus, corticosteroids are recommended as first-line therapy, with or without adjuvant therapies [2].

High doses of systemic corticosteroids, such as oral prednisolone, control painful and spreading lesions in the acute phase. When the acute phase is controlled, immunosuppressive agents (ISAs) maintain the steroid effect and reduce pathogenic autoantibody production [1, 21].

Most treatments are considered successful if they significantly improve the disease within the first two months, characterized by healed lesions without the appearance of new lesions. If successful, treatment should be tapered, starting with corticosteroids and then adjunctive nonsteroidal therapy [16, 22].

PV mortality is related to the degree of mucocutaneous involvement, the dose of corticosteroid therapy, high-risk diseases, immunodeficiency, and age over 65 [23].

Physicians and dentists should consider the differential diagnosis of pemphigus vulgaris in patients with chronic oral ulcers [1].

2. Case presentation

A 31-year-old woman was referred with a complaint of widespread oral ulcers for the last six months.

β-thalassemia intermedia has been reported in the medical history, and she has also had a splenectomy.The patient's grandfather had pemphigus in his family history. All the body and face skin had blisters, wounds, and crusts in the extraoral examination. In the intra-oral examination, the whole mouth (tongue, cheek, lips, gums, palate, and floor of the mouth) had a map-like ulcer with a diffuse tissue tag. According to the patient's report, oral and skin ulcers were observed. The skin was biopsied twice over six months, and the results of non-specific inflammation were reported each time.

After short-term use of nystatin and oral and dental hygiene education through dental gas, an oral biopsy was done for the patients. The biopsy result was pemphigus vulgaris. After taking topical corticosteroid and nystatin mouthwash, oral improvement was achieved within 14 days .The patient was referred to a dermatologist for the treatment of skin lesions.

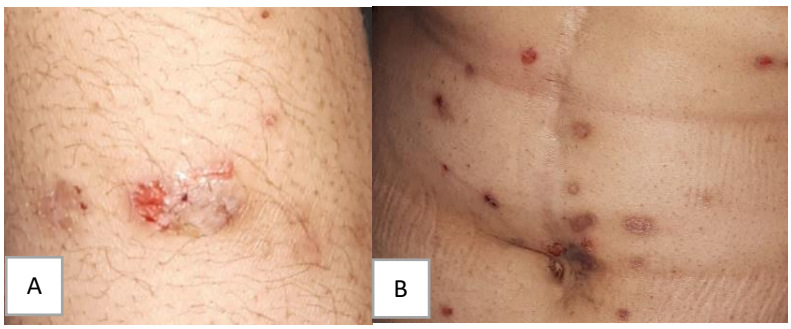

Figure 1. A) Hand ulcers B) Trunk ulcers

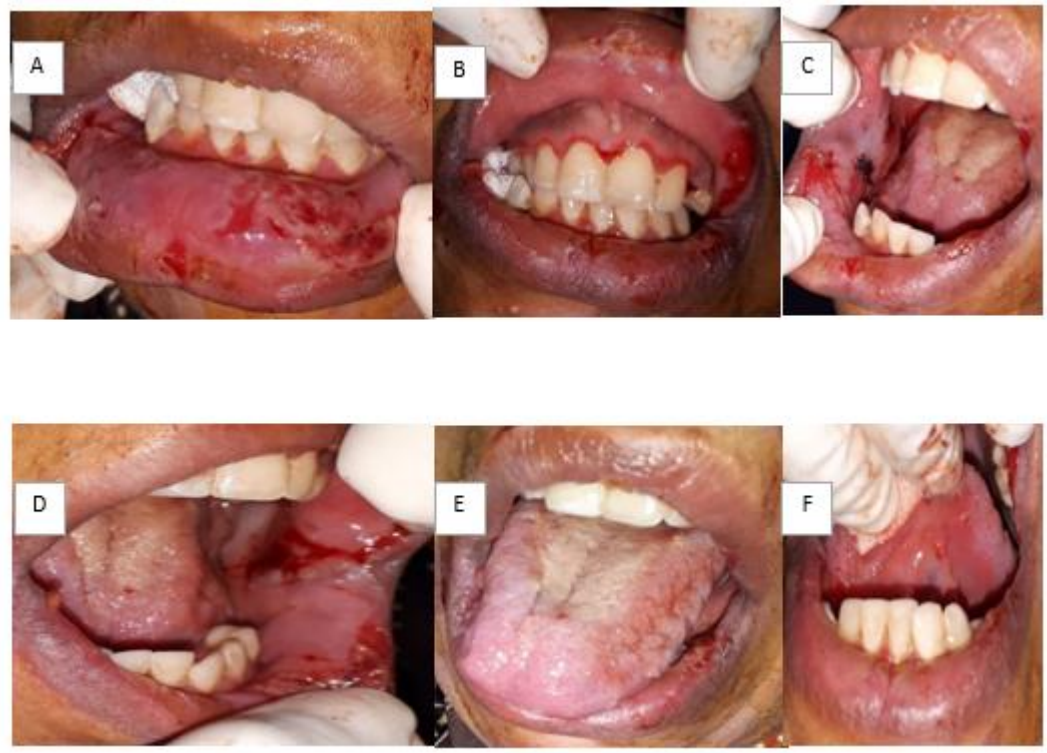

Figure 2. Oral cavity ulcers. A) Lower labial, B) Upper labial C, D) Cheeks E) Dorsal side of the tongue F) Ventral side of the tongue

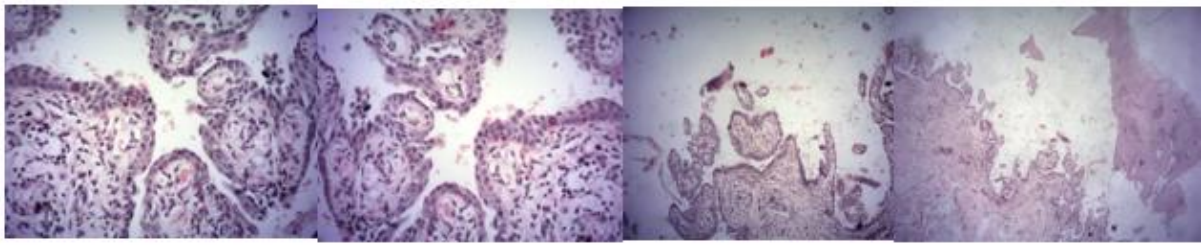

Figure 3. Histopathological features which showed the suprabasal intraepidermal layer accompanied by acantholysis

3. Discussion

Pemphigus vulgaris is a Vesiculobulos mucocutaneus disease. A loss of cohesion between epidermal cells is characterized by the formation of loose blisters in the epidermis caused by acantholysis. PV often begins in the oropharynx, and the nasal mucosa, larynx, and esophagus may also be involved, then spreads to areas including the trunk, eyes, and intertriginous regions [25 ,24]. In most cases, mouth ulcers are associated with skin lesions[26].

In more than 50% of cases, stomatitis is symptomatic. Epistaxis and hoarseness are also seen due to nose, pharynx, and larynx involvement. Most patients present with painful oral lesions; this is the only clinical presentation for some. It occurs six months before the development of skin lesions. Most patients show a sore erogenous mouth [27]. Skin involvement causes a loose blister with clear fluid that eventually ruptures, resulting in a painful erogenation covered by a crust that does not tend to heal [28]. The presence of a cerebral or "scrotal" tongue, along with lesions and plaques, among other manifestations, is very helpful in diagnosing PV [29].

Pemphigus vulgaris usually affects people between 40 and 60 years of age. Our patient was only 31 years old at the time of the diagnosis. This suggests we consider diagnosis early, even in childhood [30 ,21].

In a study, Kridin et al. investigated the relationship between pemphigus and neurological diseases and showed that Parkinson's, epilepsy, MS, and dementia are associated with pemphigus [31].

In another study, Kridin et al. observed a significant relationship between pemphigus and chronic leukemia, multiple myeloma, and non-Hodgkin's lymphoma [32].

In a case study, Le Peillet et al. reported the simultaneous presence of Gaucher type I genetic disorder with bullous pemphigoid and Parkinson's disease [33].

Robert et al., in another case study, reported the simultaneous presence of diabetes metabolic disease and pemphigus [34].

In the present study, we introduced a patient with β-thalassemia intermedia who suddenly developed pemphigus vulgaris.

The primary treatment is corticosteroids; these drugs reduce the synthesis of antibodies [35]. Rituximab and mycophenolate mofetil or azathioprine are adjuvant treatments used in resistant cases [36 ,21]. Some studies used prednisolone alone for treatment [1]. In our study, treatment with nystatin and topical corticosteroids was started, and the patient was referred to a dermatologist.

Despite these advances in treatment, death still occurs in selected patients with pemphigus, mainly due to secondary infections. If left untreated, PV is usually fatal due to bacterial and viral infections and fluid and electrolyte imbalances [23]. Without adequate treatment, the reported mortality from PV is greater than 75% [37].

This disease can be diagnosed early; however, diagnostic delays are expected in oral pemphigus vulgaris, which causes the oral and skin lesions to progress [26].

The significant morbidity and mortality associated with pemphigus disorders warrant a review of their pathogenesis, clinical manifestations, and diagnostic workup. Evaluation of standard and new treatments will provide more confidence in evaluating and managing these rare blistering dermatoses. This family of diseases is characterized by severe complications for patients, and before the advent of corticosteroid therapy, mortality was high [2].

Therefore, a timely diagnosis of this disease is essential. As it was said in previous studies, this disease manifested in people suffering from neurological, genetic, and metabolic disorders, and in our case, it occurred in the field of thalassemia. Therefore, the importance of special attention for people with other underlying problems is twofold: timely diagnosis and appropriate treatment.

Conclusion: Therefore, the occurrence of pemphigus vulgaris in patients with thalassemia is probable, so doctors and dentists should investigate the differential diagnosis of pemphigus vulgaris in patients with chronic and multiple oral lesions, regardless of age, especially in patients with underlying problems. Dental professionals should be familiar enough with the clinical manifestations of pemphigus vulgaris to ensure timely diagnosis and treatment, determining the disease's prognosis and course.

Acknowledgments

The authors would like to acknowledge the patient herself and his relatives who gave consent for this clinical case report.

Consent:

The patient signed the consent Form.

Conflict of Interest:

The authors declared that there is no conflict of interest.

References:

1. Lamichhane, R. and S. Chaudhary, *Delayed Diagnosis of Pemphigus Vulgaris Initially Presenting as an Oral Ulcer: A Case Report.* JNMA: Journal of the Nepal Medical Association, 2022. **60**(251): p. 641.
2. Malik, A.M., et al., *An updated review of pemphigus diseases.* Medicine, 2021. **57**(10): p. 1080.
3. Kridin, K., S. Zelber-Sagi, and R. Bergman, *Pemphigus vulgaris and pemphigus foliaceus: differences in epidemiology and mortality.* Acta dermato-venereologica, 2017. **97**(9): p. 1095-1099.
4. Amagai, M. et al., *Autoantibodies against the amino-terminal cadherin-like binding domain of pemphigus vulgaris antigen are pathogenic.* The Journal of clinical investigation, 1992. **90**(3): p. 919-926.
5. Sardana, K., V. Garg, and P. Agarwal, *Is there an emergent need to modify the desmoglein compensation theory in pemphigus based on Dsg ELISA data and alternative pathogenic mechanisms?* British Journal of Dermatology, 2013. **168**(3): p. 669-674.
6. Kneisel, A. and M. Hertl, *Autoimmune bullous skin diseases. Part 1: Clinical manifestations.* JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 2011. **9**(10): p. 844-857.
7. Simon, D.G., et al., *Pemphigus in Hartford County, Connecticut, from 1972 to 1977.* Archives of Dermatology, 1980. **116**(9): p. 1035-1037.
8. Laskaris, G., A. Sklavounou, and O. Bovopoulou, *Juvenile pemphigus vulgaris.* Oral Surgery, Oral Medicine, Oral Pathology, 1981. **51**(4): p. 415-420.
9. Laskaris, G. and E. Stoufi, *Oral pemphigus vulgaris in a 6-year-old girl.* Oral surgery, oral medicine, oral pathology, 1990. **69**(5): p. 609-613.
10. Hietanen, J. and O. Salo, *Pemphigus: an epidemiological study of patients treated in Finnish hospitals between 1969 and 1978.* Acta dermato-venereologica, 1982. **62**(6): p. 491-496.
11. Hübner, F., et al., *Prevalence and age distribution of pemphigus and pemphigoid diseases among pediatric patients in Germany.* Journal of the European Academy of Dermatology and Venereology, 2020. **34**(11): p. 2600-2605.
12. Scully, C., et al., *Pemphigus vulgaris: the manifestations and long-term management of 55 patients with oral lesions.* British Journal of Dermatology, 1999. **140**(1): p. 84-89.
13. Rai, A., et al., *Oral pemphigus vulgaris: case report.* Ethiopian journal of health sciences, 2015. **25**(4): p. 637-372.
14. Mustafa, M.B., et al., *Oral mucosal manifestations of autoimmune skin diseases.* Autoimmunity reviews, 2015. **14**(10): p. 930-951.
15. Raju, R., *Comparison of direct immunofluorescence of oral mucosa and plucked hair in pemphigus*. 2018, PSG Institute of Medical Sciences and Research, Coimbatore.
16. Popescu, I.A., et al., *Pemphigus vulgaris-approach and management.* Experimental and Therapeutic Medicine, 2019. **18**(6): p. 5056-5060.
17. Alhajj, M. and S.B. Chandra, *Pemphigus Vulgaris: A Comprehensive Presentation of the Desmosomal Adhesion Disrupting and Oral Blister Causing Multifactorial Autoimmune Disease.* Journal of Experimental & Integrative Medicine, 2016. **6**(4).
18. Lotti, R. et al., *In vitro, ex vivo, and in vivo models for studying pemphigus.* International Journal of Molecular Sciences, 2022. **23**(13): p. 7044.
19. Kanwar, A.J. and D. De, *Pemphigus in India.* Indian Journal of Dermatology, Venereology, and Leprology, 2011. **77**: p. 439.
20. Harman, K., S. Albert, and M. Black, *Guidelines for the management of pemphigus vulgaris.* British Journal of Dermatology, 2003. **149**(5): p. 926-937.
21. Chen, I.-H., et al., *Oral ulcers as an initial presentation of juvenile pemphigus: a case report.* Pediatrics & Neonatology, 2016. **57**(4): p. 338-342.
22. Joly, P., et al., *Updated S2K guidelines on managing pemphigus vulgaris and foliaceous initiated by the European Academy of Dermatology and Venereology (EADV).* Journal of the European Academy of Dermatology and Venereology, 2020. **34**(9): p. 1900-1913.
23. Baican, A., et al., *Prediction of survival for patients with pemphigus vulgaris and pemphigus foliaceous: a retrospective cohort study.* Orphanet Journal of Rare Diseases, 2015. **10**(1): p. 1-14.
24. Bjarnason, B. and E. Flosadóttir, *Childhood, neonatal, and stillborn pemphigus vulgaris.* International journal of dermatology, 1999. **38**(9): p. 680-688.
25. Merchant, S. and M. Weinstein, *Pemphigus vulgaris: the eyes have it.* Pediatrics, 2003. **112**(1 Pt 1): p. 183-185.
26. Daltaban, Ö., et al., *Clinical presentation and diagnostic delay in pemphigus vulgaris: A prospective study from Turkey.* Journal of Oral Pathology & Medicine, 2020. **49**(7): p. 681-686.

27. Murphy, P.J. and E.R. Harrell, *Pemphigus vulgaris in childhood.* American Journal of Diseases of Children, 1972. **123**(1): p. 70-71.
28. Nguyen, V.T., et al., *Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of the paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus.* Archives of Dermatology, 2001. **137**(2): p. 193-206.
29. Hadlaq, E. et al., *Pemphigus vegetans presenting as serpiginous oral, esophageal, and genital mucosal ulcers undiagnosed for three y.* Nigerian Journal of Clinical Practice, 2018. **21**(9): p. 1238-1241.
30. Farzam, K. and V. Tivakaran, *StatPearls [Internet]*. 2020, StatPearls Publishing.
31. Kridin, K., et al., *Association between pemphigus and neurologic diseases.* JAMA dermatology, 2018. **154**(3): p. 281-285.
32. Kridin, K., et al., *Pemphigus and hematologic malignancies: a population-based study of 11,859 patients.* Journal of the American Academy of Dermatology, 2018. **78**(6): p. 1084-1089. e1.
33. Le Peillet, D., et al., *Type I Gaucher disease with bullous pemphigoid and Parkinson disease: a case report.* Medicine, 2018. **97**(13).
34. HARRIS, R.H. and F. TAYLOR, *Pemphigus vulgaris, and diabetes mellitus: A case report.* AMA Archives of Dermatology, 1959. **80**(4): p. 442-443.
35. Asarch, A. and A. Razzaque Ahmed, *Treatment of juvenile pemphigus vulgaris with intravenous immunoglobulin therapy.* Pediatric dermatology, 2009. **26**(2): p. 197-202.
36. Joly, P. and N. Litrowski, *Pemphigus group (vulgaris, vegetans, foliaceus, herpetiformis, brasiliensis).* Clinics in Dermatology, 2011. **29**(4): p. 432-436.
37. Bystryn, J.-C. and N.M. Steinman, *The adjuvant therapy of pemphigus: an update.* Archives of dermatology, 1996. **132**(2): p. 203-212.