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AN OVERVIEW OF PEMPHIGUS VULGARIS – A CASE STUDY AND IT'S TREATMENT STRATEGIES

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ABSTRACT
Pemphigus vulgaris is a common autoimmune blistering disease affecting the oral mucosa and skin, in which oral mucosa is the initial site of presentation. Assessment of etiological factors, oral lesions along with cutaneous manifestations is hence vital for early diagnosis and treatment. In this article, a case of pemphigus vulgaris affecting both the oral cavity and skin is reported. A detailed review of the treatment modalities of pemphigus vulgaris and management of recalcitrant lesions is described in this article.

KEYWORDS: Pemphigus, Pemphigus vulgaris, Blistering disease, Auto-immune disorders.

INTRODUCTION

Pemphigus refers to a group of autoimmune, mucocutaneous blistering diseases, in which keratinocyte antigens are the target of the autoantibodies, leading to acantholysis and blister formation.[1,2] There are about 0.5 to 3.2 cases per 100,000 population reported each year, with the highest incidence between the 5th and 6th decade of life with a clear female prediliction.[3]

The major variants of pemphigus are pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, paraneoplastic pemphigus (PNP) and drug related pemphigus.[4] Among these, pemphigus vulgaris is the most common form, accounting for more than 80% of cases.[6] In majority of patients, painful mucous membrane erosions are the presenting sign and may be the only sign for an average of 5 months before skin lesions develop.[5]

A case report of pemphigus vulgaris affecting both oral cavity and skin along with a brief review of literature is reported here.

CASE REPORT

A 44-year-old female patient reported with the chief complaint of ulcers in the mouth and difficulty in chewing and swallowing since the past 5 months.

She started experiencing pain in the oral cavity 5 months ago after which she noticed the ulcers. The ulcers bled on brushing, with increased salivation in the morning. She also noticed a few skin lesions at this time. On having some ayurvedic medicine one month back, her condition worsened with appearance of genital lesions.

The patient reported to be under extreme stress since past 6 months due to her husband passing away and son being terminally ill. She was taking counselling sessions for stress and depression.

There was presence of a single blister on the left hand, one ulcerative lesion on chest and left shoulder, **(Figure 1)** five ulcerative lesions on areola of right breast and on areola of left breast. Ulcers on the breast and the left shoulder had well defined borders with erythematous base. The cutaneous lesions were tender on palpation and the blister was flaccid. Nikolsky's sign was negative.

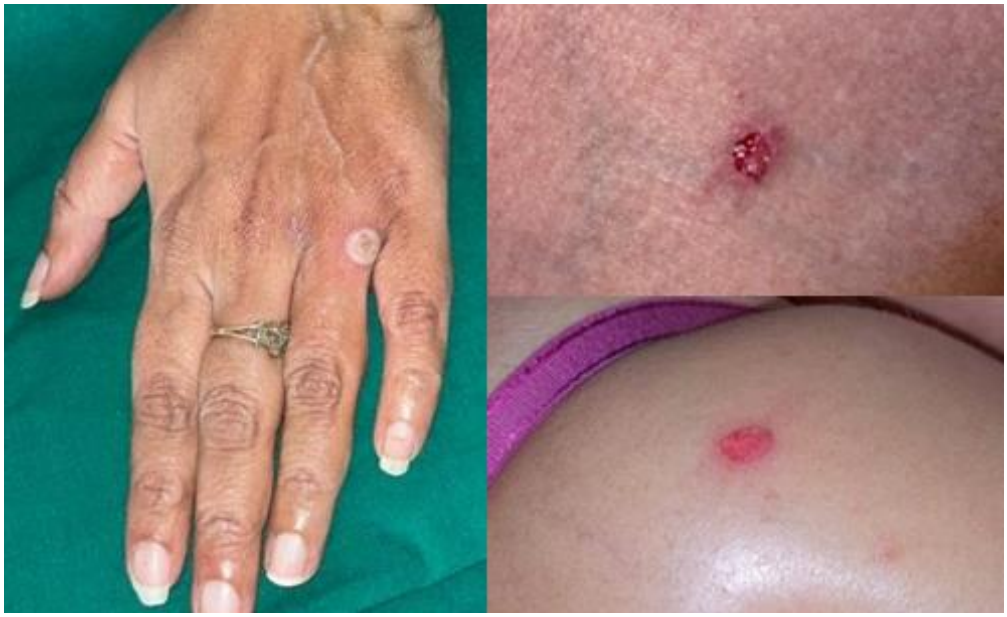

Figure 1: Picture showing flaccid blister on left hand and ulcer on the chest and shoulder.

On intraoral examination, there was presence of ulcerations and erosions on both buccal mucosae, extending from the commissural area to retromolar trigone including the posterior palatal area. **(Figure 2 and 3)** The tongue was coated and had presence of discrete ulcerations covered with pseudomembranous slough on the left and right lateral borders. **(Figure 3)** Lower labial mucosa had an erosive lesion with slight blood tinge. On the upper left labial mucosa, there was presence of a healing ulcer with an erythematous periphery. **(Figure 2).**

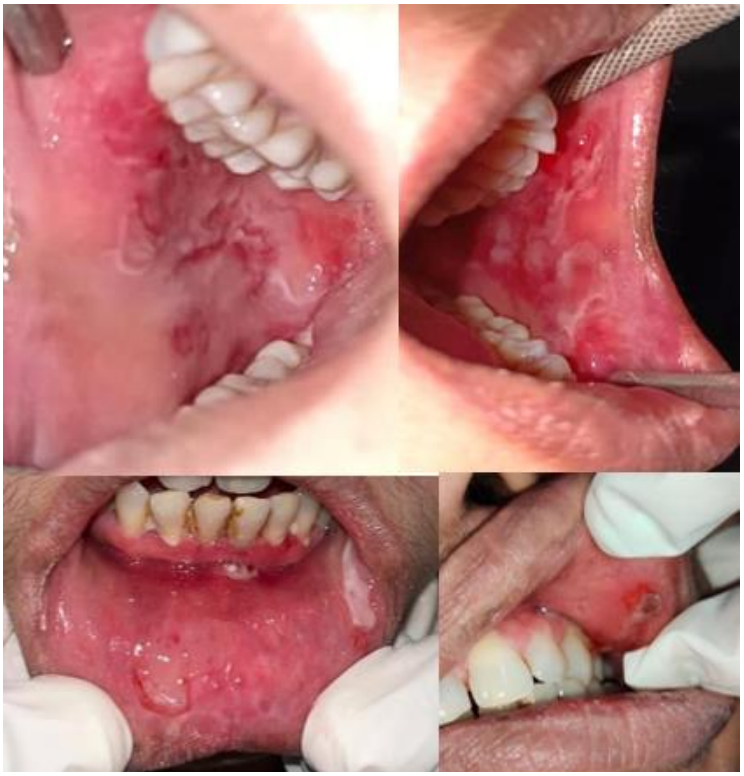

Figure 2: Ulcerative lesions with overlying pseudo membrane and tissue tags on the right and left buccal mucosae and lower labial mucosa and presence a healing ulcer with encrustation on upper labial mucosa.

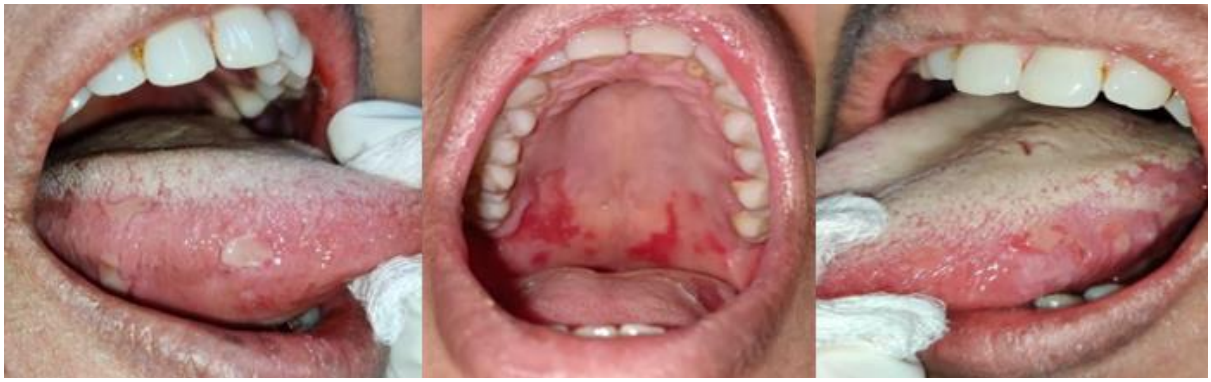

Figure 3: Ulcerative lesions with tissue tags and pseudomembranous slough on right and left lateral borders of tongue and erythema with posterior palate.

The lesions on buccal mucosae, labial mucosa and tongue were covered by whitish pseudo membrane with tissue tags and surrounded by erythematous periphery. There was bleeding from these lesions on even the slightest manipulation. Considering the oral and dermal manifestations, the condition was provisionally diagnosed as a muco-cutaneous blistering disease.

Due to the chronicity of the lesion, the gender of the patient, presence of thin flaccid easily rupturing blisters with tissue tags a differential diagnosis of Pemphigus Vulgaris was given. Since Nikolsky's sign was negative for cutaneous lesions and the patient being of middle age, bullous pemphigoid was considered as the second differential diagnosis.

The patient was adviced complete blood count, a desmoglin 3 autoantibody test to confirm pemphigus vulgaris and a thiopurine methyl transferase enzyme activity test (TPMT) for formulation of treatment protocol. Desmoglin 3 autoantibody test gave positive result with observed value above 200 which confirmed pemphigus vulgaris. TPMT levels and CBC values were within the normal range, except WBC count which was raised to 15,500 cells per cubic mm.

She was prescribed 10 mg tablet of Wyosolone to be taken four times a day for one week, and the dosage was tapered by reducing one tablet in each of the successive weeks for a total of 4 weeks. The patient was also prescribed an ointment formulation, which was a combination of Clotrimazole (antifungal), Neomycin (antibiotic) and Beclomethasone (steroid) 5mg for oral lesions three times daily along with supplementation of Vitamin D3 60,000 IU once a week. She was followed up every week for 4 weeks. The patient was adviced meditation and exercises to reduce stress.

At the end of 4 weeks, 80% of her lesions had resolved. **(Figure 4)** As the TPMT levels were within normal range. Tablet Azathioprine (immunosuppressant) was prescribed, with a dose of 50 mg for a day to start with to assess for idiosyncratic reactions or any side effects. The dosage was increased to 100 mg once a day per week for four weeks, as no adverse reactions were reported. At the end of 3 months there was complete resolution of the lesions and her quality of life improved significantly.

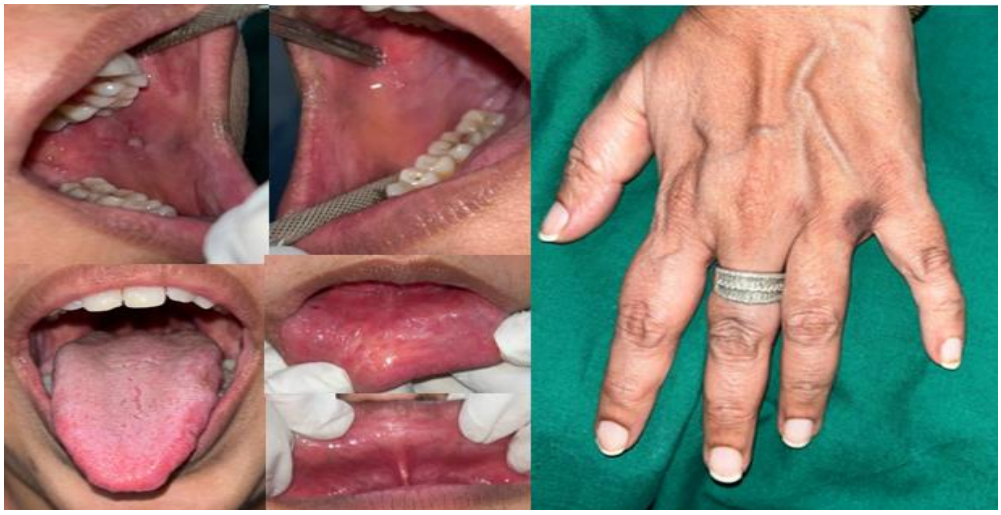

Figure 4: Healed lesions can be appreciated with right, left buccal mucosa, tongue, upper, lower labial mucosa and hand with presence of scar on hand.

DISCUSSION

The worldwide prevalence of pemphigus vulgaris is about 0.1 to 0.5% per million population per year.[8] The incidence of pemphigus, however, varies as per the geographic area and ethnic population. Literature reports suggest that the incidence of pemphigus vulgaris ranges from 0.76 to 16 per million population per year in Europe.[9] In India, the prevalence of pemphigus vulgaris is lesser than the rest of the world and is in the range of 0.09% to 1.8%.[10]

The classical lesion of pemphigus is a thin-walled bulla arising on otherwise normal skin or mucosa, which rapidly breaks and continues to extend peripherally, eventually leaving large denuded areas. This disease also exhibits positive "Nikolsky's sign" – the ability to induce peripheral extension of a blister and/or removal of epidermis as a consequence of applying tangential pressure with a finger or thumb to the affected skin, peri-lesional skin, or normal skin in patients affected with pemphigus.[11] In this case, inspite of Nikolsky's sign being negative for the skin lesions, desmoglin 3 test was positive. This suggests that the condition was not bullous pemphigoid wherein Nikolsky's sign is commonly negative. Hence there is a possibility for presence of hybrid lesions within pemphigus vulgaris cases which needs to be further investigated.

A detailed history is essential in distinguishing the lesions of pemphigus from those caused by acute viral infections such as herpes and EM (Erythema Multiforme). This is because a similar clinical picture can be seen in undiagnosed and/or untreated immunocomprised patients, suffering from RHS (Recurrent Herpes Simplex) infections in the form of atypical ulcers which lasts several weeks or months. Moreover, cytological presence of Tzanck cells may complicate the diagnosis.[12] Our patient did not give any positive history of compromised immunity like acquired immune deficiency syndrome or chemotherapy, organ transplant. Hence, RHS infection and EM were ruled out.

An early diagnosis is vital to patient management, when lower doses rendered for shorter periods can effectively control the disease. The treatment is administered in two phases: a loading phase, to induce disease remission, and a maintenance phase, which is further divided into consolidation and treatment tapering to improve quality of life.[13]

In cases of extensive oral lesions or involvement of other mucosa and skin, systemic corticosteroid therapy is initiated immediately. An initial dose of prednisone 0.5–2 mg/kg is recommended.[14] Our patient was prescribed a dosage of 10 mg tablet Prednisolone, four times a day for one week, which was tapered by reducing 1 tablet in each successive week for a total of 4 weeks.

The patient was also prescribed an ointment formulation of Clotrimazole (antifungal), Neomycin (antibiotic) with Beclomethasone (steroid) 5mg for local application on the oral lesions 3 times daily along with Vitamin D3 supplementation of 60,000 IU (international units) once a week.

Depending on the response to medication, the dosage was gradually decreased to the minimum therapeutic dose, once daily in the morning to minimize side effects. Adjuvants such as Azathioprine or Cyclophosphamide are added to the regimen to reduce the complications of long-term corticosteroid therapy.[15]

Azathioprine which was prescribed to our patient, is one of the main adjuvants used in PV (Pemphigus Vulgaris).[15,16] It is considered as a first-line adjuvant immunosuppressant according to the (European Dermatology Forum) EDF guidelines. The dosage varies between 1 and 3 mg/kg/day, based on the activity of the thiopurine methyltransferase (TPMT) enzyme, involved in the metabolism of the drug. When TPMT levels are high, normal doses of azathioprine (up to 2.5 mg/kg/d) are administered, while adults with PV and intermediate or low TPMT levels should receive a maintenance dose (up to 0.5–1.5 mg/kg/d). Azathioprine should not be used in patients with no TPMT activity. A dose of 50 mg/d could initially be administered, and if no idiosyncratic reactions occur, it can be increased after a week. In case of any idiosyncratic reactions, it should be discontinued.[17,18] The primary benefit of adjuvant azathioprine is its steroid-sparing effect.[15,19]

Azathioprine has been reported to require a lower cumulative corticosteroid (CS) dose for remission, with some investigators reporting superior steroid-sparing effect when compared to MMF (Mycophenolate mofetil) and cyclophosphamide.[15,20] When compared to steroid monotherapy, adverse events are significantly reduced with adjuvant azathioprine treatment without any compromise in the rate of clinical remission.[15,20]

As the TPMT levels were within normal range in the case reported here, Tablet Azathioprine (immunosuppressant) was prescribed to our patient, with an initial dose of 50mg once a week, as precautionary dose to assess for any idiosyncratic reaction. The dosage was increased to 100mg once a week for 4 weeks as no adverse reactions were reported. At the end of 3 months, there was complete resolution of lesions giving a much better quality of life for the patient.

A relapse is said to occur when there is appearance of ≥3 new lesions/month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved control of disease activity.[15] In an event of relapse, a Rituximab therapy was planned for the patient.

Rituximab is an anti-CD20 monoclonal humanized antibody, with the potential to reduce desmoglein autoantibodies and selectively deplete B cells.[21] [22]

Rituximab is indicated in patients who remain dependent on more than 10 mg prednisolone combined with an immunosuppressive adjuvant according to the EDF. Administration schedule in literature is either 1,000 mg IV every 2 weeks or 375 mg/m^2 every week.[23,24] The same dosage can be administered again in case of clinical relapses. A meta-analysis on treatment with rituximab in severe pemphigus showed remission in approximately 95% of the total patients.[21] Prophylactic infusion after complete remission does not seem to provide any additional benefit.[25] Rituximab does not eliminate the need for steroids or immunosuppressive agents, and most patients in published studies did use such therapy along with rituximab.[21]

Before the advent of corticosteroid therapy, pemphigus was fatal, with a mortality rate of up to 75% in the first year. It is still a serious disorder, but the existing 5% to 10% mortality rate is primarily due to the side effects of therapy.[26] Morbidity and mortality due to the chronic and fatal course of this condition can be reduced with early diagnosis and prompt treatment leading to complete resolution as reported in the present case.

REFERENCES

1. Kumar SJ, Nehru Anand SP, Gunasekaran N, Krishnan R. Oral pemphigus vulgaris: A case report with direct immunofluorescence study. J Oral Maxillofac Pathol, 2016 Sep-Dec; 20(3): 549. doi: 10.4103/0973-029X.190979. PMID: 27721634; PMCID: PMC5051317.
2. Grando SA. Pemphigus autoimmunity: Hypotheses and realities. *Autoimmunity,* 2012; 45: 7–35.
3. Shamim T, Varghese VZ, Shameena PM, Suddha S. Pemphigus Vulgaris in oral cavity. Clinical analyses of 71 cases. Med Oral Pathol Buccal, 2008; 13: 2622-6.
4. Arpita R, Monica A, Venkatesh N, Atul S, Varun M. Oral Pemphigus Vulgaris: Case Report. Ethiop J Health Sci., 2015 Oct; 25(4): 367-72. PMID: 26949302; PMCID: PMC4762976.
5. Fassmann, A., Dvořákován, N., Holla, L.I., Vaněk, J., & Wotke, J. Manifestation of pemphigus vulgaris in the orofacial region. Case report, 2003.
6. Lester William Burket, Greenberg MS, Glick M. Burket's Oral Medicine. B.C. Decker; 11th edition, 2003.
7. Robinson NA, Yeo JF, Lee YS, Aw DCW. Oral pemphigus vulgaris: A case report and literature update. Ann Acad Med Singapore, 2004; 33(Suppl): 63S-68S.
8. Karisetty B, Reddy KN, Lahkar M. Prevalence of Pemphigus vulgaris and Pemphigus Foliaceus in tertiary care hospital in India: an update. The Pharma Innovation Journal, 2013; 2: 68-72.
9. Huang YH, Kuo CF, Chen YH, Yang YW. Incidence, mortality, and causes of death of patients with pemphigus in Taiwan: a nationwide population-based study. Journal of Investigative Dermatology. 2012; 132: 92–97.
10. Kanwar AJ, De D. Pemphigus in India. Indian J DermatolVenereolLeprol, 2011; 77: 439-49.
11. Seshadri D, Kumaran MS, Kanwar AJ. Acantholysis revisited: Back to basics. *Indian J Dermatol Venereol Leprol.* 2013; 79: 120–6.
12. Banerjee I, Bhowmik B, Maji A, Sinha R. Pemphigus vulgaris - A report of three cases and review of literature. J Family Med Prim Care, 2018 Sep-Oct; 7(5): 1109-1112. doi: 10.4103/jfmpc.jfmpc_133_18. PMID: 30598970; PMCID: PMC6259552.
13. Rai A, Arora M, Naikmasur VG, Sattur A, Malhotra V. Oral pemphigus vulgaris: Case report. *Ethiop J Health Sci.*, 2015; 25: 367–72.
14. Toth GG, Jonkman MF. Therapy of pemphigus. *Clin Dermatol*, 2001; 19(6): 761–767.
15. Gregoriou S, Efthymiou O, Stefanaki C, Rigopoulos D. Management of pemphigus vulgaris: challenges and solutions. Clin Cosmet Investig Dermatol, 2015 Oct 21; 8: 521-7. doi: 10.2147/CCID.S75908. PMID: 26543381; PMCID: PMC4622091.
16. Schiavo AL, Puca RV, Ruocco V, et al. Adjuvant drugs in autoimmune bullous diseases, efficacy versus safety: facts and controversies. *Clin Dermatol*, 2010; 28: 337–343.
17. Anstey AV, Wakelin S, Reynolds NJ. British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol*, 2004; 151: 1123–1132.
18. Meggitt SJ, Anstey AV, Mohd Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine *Br J Dermatol*, 2011; 165: 711–734.
19. Chams-Davatchi C, Mortazavizadeh A, Daneshpazhooh M, et al. Randomized double blind trial of prednisolone and azathioprine, vs Prednisolone and placebo, in the treatment of pemphigus vulgaris. *J Eur Acad Dermatol Venereol*, 2013; 27(10): 1285–1292.
20. Chams-Davatchi C, Esmaili N, Daneshpazhooh M, et al. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. *Arch Dermatol*, 2007; 57: 622–628.
21. Schmidt E, Goebeler M, Zillikens D. Rituximab in severe pemphigus. *Ann N Y Acad Sci.*, 2009; 1173: 683–691.
22. Eming R, Nagel A, Wolff-Franke S, et al. Rituximab exerts a dual effect in pemphigus vulgaris. *J Invest Dermatol*, 2008; 128: 2850–2858.
23. Kasperkiewicz M, Shimanovich I, Meier M, et al. Treatment of severe pemphigus with a combination of immunoadsorption, rituximab, pulsed dexamethasone and azathioprine/mycophenolate mofetil: a pilot study of 23 patients. *Br J Dermatol*, 2012; 166: 154–160.
24. Ahmed AR, Spigelman Z, Cavacini LA, et al. Treatment of pemphigus vulgaris with rituximab and

intravenous immune globulin. *N Engl J Med*, 2006; 355: 1772–1779.
25. Gregoriou S, Giatrakou S, Theodoropoulos K, et al. Pilot study of 19 patients with severe pemphigus: prophylactic treatment with rituximab does not appear to be beneficial. *Dermatology,* 2014; 228: 158–165.
26. Lever WF, Schaumburg-Lever G. Treatment of pemphigus vulgaris. Results obtained in 84 patients between 1961 and 1982. *Arch Dermatol*, 1984; 120(1): 44–47.