Case Report

International Journal of Dental and Health Sciences
Volume 03, Issue 02

PEMPHIGUS VULGARIS AND MUCOUS MEMBRANE PEMPHIGOID: DISSIMILARLY SIMILAR LESIONS

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ABSTRACT:

Pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) are two frequently encountered vesiculobullous diseases affecting the skin and mucous membrane. Though both these lesions have characteristic clinical presentations, many a times it may not be possible to differentiate them based on the clinical examination alone. PV lesions usually present as widespread areas of erosions and ulcerations. When present with intact vesicle and desquamative gingivitis, they would resemble MMP. In the present article, we report a case of pemphigus vulgaris which resembled mucous membrane pemphigoid on its initial presentation. Detailed review of literature regarding the investigations and management protocols has also been discussed.

Key Words: Pemphigus vulgaris, Mucous membrane pemphigoid, Vesiculobullous lesions

INTRODUCTION

Pemphigus is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membrane that is mediated by circulating autoantibodies directed against keratinocyte cell surfaces.[1] It most commonly occurs in middle aged adults and affects both sexes equally.[2]

Variants of pemphigus have been described based on their distinct clinical and immunopathologic features. These include pemphigus vulgaris (PV), pemphigus vegetans, pemphigus foliaceous, paraneoplastic pemphigus.[3] Among them, pemphigus vulgaris is the most common type. In 90% of the patients with pemphigus vulgaris, oral lesions are the indicators of the disease. These lesions are insidious in onset and manifest as painful erosive and ulcerative lesions commonly involving the buccal mucosa. Though pemphigus is a vesiculobullous lesion, its clinical presentation as an intact vesicle is rare. Thin mucosal layer overlying the vesicle causes it to rupture easily resulting in mucosal erosions and ulcers.[3] Rarely, gingiva may also be affected in the form of desquamative gingivitis.

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In contrast, presence of intact vesicle and involvement of gingiva are the common features of mucous membrane pemphigoid which is also a mucocutaneous autoimmune disease but usually occurring in the elderly. It is characterized by autoantibodies against the basal keratinocyte hemidesmosomes in the dermoepidermal junction causing its split which clinically results in the formation of tense blisters.[4]

Among the vesiculobullous lesions, pemphigus vulgaris and mucous membrane pemphigoid are often the two most frequently encountered ones. Though they have characteristic clinical presentations, many a times it may not be possible to differentiate them based on clinical examination alone. With an aim of providing an insight to the similarities and differences among these two vesiculobullous lesions, we report a case of pemphigus vulgaris which resembled mucous membrane pemphigoid on its initial presentation. Detailed review of literature regarding the investigations and management protocols have also been discussed.

CASE DETAIL

58 year old female patient reported to the Department of Oral Medicine and Radiology with the chief complaint of pain in the lower front teeth region since 15 days. Pain was gradual in onset, dull, moderate in intensity, intermittent which aggravated on chewing and got relieved without any intervention. She also complained of peeling away of a layer in the same region occasionally since 15 days which lead to mild bleeding. She gave a history of extraction of her lower front teeth 6 months back due to looseness which was replaced by removable teeth set. However she had discontinued using it over the last 15 days as it was uncomfortable. Trimming of the dentures by a local dentist had not relieved her from pain. There was no history of pain in any other part of the body. Her medical history and family history were non contributory.

On general physical examination, patient was moderately built and nourished with normal gait and erect posture. There was no abnormality detected on extraoral examination.

On intraoral examination, maxillary complete denture and removable partial denture i.r.t 31,32,41,37,46 was noticed. On examination of the mandibular anterior region after removal of the denture, a solitary white lesion was seen on the lingual gingiva i.r.t 33,34,35. The lesion measured about 1.5 X 2 cm and extended mesiodistally from 32 to the mesial surface of 35 and superoinferiorly from marginal gingiva to the lingual vestibule (Fig 1). Surface of the lesion was smooth. The surrounding area was erythematous. On palpation, the lesion was scrapable and the underlying mucosa was tender and erythematous. An intact vesicle was seen on the alveolar ridge mucosa in the 41 region (Fig 2). On application of pressure on the unaffected mucosa, a vesicle was formed suggestive of positive Niklosky's sign.

The gingiva i.r.t to the mandibular posteriors appeared erythematous. Surface was peeling on gentle air blow indicating desquamative gingivitis.(Fig 3)
Examination of the edentulous maxillary arch showed erythematous mucosa on the anterior two thirds of the hard palate measuring about 0.6 X 0.8 cm and on the alveolar ridge mucosa i.r.t 13,14 measuring about 0.4 X 0.6 cm. These lesions were non tender on palpation. (Fig 4)

Skin and other mucosal surfaces appeared normal.

Clinical evidence of an intact vesicle channelized the diagnosis towards the possibility of the lesion to be of vesiculobullous nature. Provisional diagnosis of mucous membrane pemphigoid (MMP) was given based on the presence of desquamative gingivitis in association with vesicular lesions.

Bullous pemphigoid (BP), pemphigus vulgaris, bullous lichen planus, pseudomembranous candidiasis and erythema multiforme were considered in differential diagnosis.

Oral lesions of BP are characterised by small, slowly forming slightly painful bullae associated with erosive and ulcerative areas. Oral lesions commonly involve the buccal mucosa followed by soft palate and are often preceded by skin lesions.

Observing an intact vesicle/bulla in PV is rare and it most commonly involve the buccal mucosa. Painful vesicles rupture rapidly to leave ill defined erosive areas. Desquamative gingivitis is reported only in 2.3% of cases.

Bullous lichen planus generally involves buccal mucosa, tongue, gingiva, palate, lips, and floor of the mouth. The painful lesions generally show symmetrical distribution. One has to look for associated Wickham's striae.

Pseudomembranous candidiasis manifest as areas of erythema or even shallow ulceration on removal of the plaques. It is common in children and older adults. The lesions are generally painless and the plaques are easily scrapable. It can involve any mucosal surface, however tongue and palate are the most common sites of involvement.

Erythema Multiforme is an acute inflammatory disease. Patients may have only oral mucosal lesions; which may range from mild erythema to large, irregular, extremely painful areas of erosion which have reddened margins and are overlaid with slough covering the entire oral cavity. It predominantly affects men in the age group of 20 – 40 years. The lips are the most common site of involvement (36%).

Lesions listed under differential diagnosis were autoimmune diseases with an exception of candidiasis. The investigations were furthered based on this aspect. As a routine baseline work up, haematological investigations were done. Her haematological reports showed all parameters within normal limits. RBS was

also performed report of which ruled out diabetes. Cytological smear and examination to detect candidiasis was reported negative. Following these preliminary investigations, excisional biopsy of the lesion from the anterior mandibular alveolar ridge mucosa that included an intact vesicle was performed. The tissue specimen was subjected to histopathological examination (HPE) and immunofluorescence. Histopathologically, presence of hyperplastic stratified squamous epithelium exhibiting acantholysis and minimal inflammation was noted (Fig 5). Direct Immunofluorescence (DIF) showed intercellular positivity for IgG and negativity for IgA, IgM, C3c, C1g (Fig 6). Based on the HPE and DIF report, the lesions were confirmed to be PV.

Because of the acute symptoms and extensive involvement, patient was prescribed systemic corticosteroids (Tab Prednisolone 20mg twice daily). Follow up after 2 weeks showed remarkable improvements. Her symptoms subsided and the lesions began to resolve. Because of severe periodontitis, she underwent total extraction followed by replacement with complete denture prosthesis(Fig7). Following administration of systemic steroids, patient was followed up every fortnightly. During her visit, detailed history regarding alleviation of symptoms was recorded; clinical examination of the mucosa was done to appreciate for resolution of the lesion. Her blood pressure was recorded. She was subjected to haematological and blood sugar level investigations. After two months of complete resolution of the lesions (Fig. 8), the dosage of the corticosteroid was gradually tapered to 10mg/day and then to 5 mg daily for the next 4 months. During the follow-up, there were no exacerbations noted. Post 6 month follow up, the medications were discontinued. Patient is still under periodic review. She has not developed new lesions over the last 1 year.

DISCUSSION

Vesiculobullous diseases are a group of disorders in which primary lesion is a vesicle or a bulla, on the skin or mucous membrane or both. Among the various chronic vesiculobullous lesions, pemphigus and mucous membrane pemphigoid are the most frequently encountered.

Pemphigus is a group of autoimmune blistering diseases of skin and mucous membranes which are characterized histologically by intraepidermal blisters due to acantholysis.[1] Pemphigus vulgaris (PV) accounts for 81% of cases of pemphigus. The disease is mediated by circulating autoantibodies which are directed against both desmoglein 1 and desmoglein 3 present in the desmosomes in keratinized epithelium resulting in loss of cell to cell adhesion which clinically results in formation of vesicles and bullae of varying diameter. On skin, these vesicles and bullae can arise on normal skin or on an erythematous base. These vesicles rupture easily as they are fragile and results in painful erythematous denuded areas which are painful. Scaling, crusting, ulcerations and sloughing of the

areas are seen in later stages. The incidence of PV is varied widely, 0.09 to 1.8%. The middle aged adults are most commonly affected.[2]

Mucous membrane pemphigoid (MMP) is an autoimmune blistering disease associated with autoantibodies directed against basement membrane zone target antigens. Autoantibodies of the IgG subclass, particularly IgG_4, are associated with MMP; however, IgA antibodies have also been detected. The two major antigens associated with MMP are bullous pemphigoid antigen2 (BPAG2) and epiligrin (laminin-5), that predominately affects the mucous membranes, including the mouth and the oropharynx, the conjunctiva, the nares, and the genitalia. The disease occurs nearly twice as frequently in females as it does in males with the peak age of involvement being between 40 and 50 years. Patients with cutaneous involvement present with tense blisters and erosions, often on the head and the neck or at sites of trauma. Blisters heal with scarring and pigmentation. Sequelae of mucosal involvement include decreased vision, blindness, and supraglottic stenosis with hoarseness or airway obstruction. Typically, the vesiculobullous lesions occur on the oral mucous membranes and conjunctiva.

Oral manifestations in PV are seen in 80-90% of cases and they present for many months before skin lesions develop.[1] The oral lesions are insidious in onset and painful. Lesions may be anywhere but the most common sites are the buccal mucosa. Patients usually exhibit widespread areas of ill-defined, irregular erosions as the vesicles or bullae are fragile and rupture easily. Intact vesicle or bulla in the oral cavity is rare. The erosions extend peripherally with shedding of the epithelium. Gingival involvement may produce desquamative gingivitis rarely.

The most consistent oral lesions to occur in MMP are those involving the gingiva, although ultimately other sites in the oral cavity become involved. The lesions in their onset and symptoms are similar to PV but are generally smaller. The vesicles or bullae appear to be relatively thick-walled, and for this reason, may persist intact for 24–48 hours before rupturing and desquamating. Eventually their rupture does occur leaving a raw, eroded, bleeding surface. The gingiva frequently demonstrates an erythema persistent for weeks or even months after the original erosions have healed. These oral lesions rarely scar. In the past, this disease has often been diagnosed as ‘chronic desquamative gingivitis,’ a term now used only in the descriptive sense and not as a specific disease entity.[5]

Desquamative gingivitis (DG) is the clinical term used to describe manifestation of the gingiva that is characterized by intense redness and desquamation of the surface epithelium. DG is a feature in many vesiculobullous diseases such as mucous membrane pemphigoid, lichen planus and pemphigus. However DG is least common in PV accounting for 2.3% of cases and most frequently seen in

mucous membrane pemphigoid, accounting for 48.9%.[6] Diagnosis of the vesiculo bullous diseases is established by histopathological and immunofluorescent studies.[6]

Histopathological findings in pemphigus includes presence of intraepithelial vesicle or bullae above the basal layer producing suprabasilar split, prevesicular edema, inflammatory infiltrate, acantholysis and arrangement of keratinocytes in a tombstone pattern.[7,8]Tzanck cells can also be demonstrated. These features do not establish a definitive diagnosis. This is best done by direct immunofluorescence which demonstrates IgG, IgA, and IgM immune complexes in the intraepithelial layer confirms the diagnosis and differentiates pemphigus vulgaris from other bullous disorders.[9] Indirect immunofluorescence can used during the active stage, the serum is positive for immune complexes in 95% of cases. In remission, the titre is lower or even normal. Consequently, indirect immunofluorescence may be used to monitor the effectiveness of drug therapy. The histopathologic picture of MMP shows subepithelial clefting of the mucosa without acantholysis and with intense inflammatory infiltrate and the direct immunofluorescence demonstrates the deposition of immune complexes binding IgG and C3 in the basement membrane.

Management of PV is aimed to control the disease progression and increase the remission period.[10] Systemic corticosteroids are the mainstay of treatment for pemphigus. Methyl prednisolone is the agent most commonly used and first employed in lower doses and then increased if no clinical improvement is found. The efficacy of steroid-sparing agents such as azathioprine, rituximab, methotrexate and cyclophosphamide and their administration by pulse therapy have also been evaluated in the treatment of pemphigus vulgaris.[11]

One of the main steroid-sparing agents used in PV is azathioprine. A randomized controlled trial comparing a combination of prednisolone plus azathioprine to prednisolone plus placebo in the treatment of 56 patients with newly diagnosed PV found no statistically significant difference between the 2 groups after a year of treatment. But it shows that Azathioprine, however, has a significant steroid-sparing effect equivalent to steroids. Rituximab, an anti-CD20 monoclonal antibody, is found to be effective in recalcitrant pemphigus and is typically prescribed for patients who are unable to taper steroids without flare of their disease or in patients who are still flaring despite combination therapy (steroids + steroid sparing agent). 375 mg once a week can be administered for 4 consecutive weeks. The clinical benefits are believed to be noticed within 2 to 3 months of infusion which can last for years.[12]

Strong evidences in the form of randomized control trials are lacking for some of the newer treatment modalities such as cyclophosphamide despite case

reports suggesting its role beneficial role.[11,13,14]

CONCLUSION

Pemphigus vulgaris may clinically manifest with striking resemblance to MMP such as presentation of intact vesicles and desquamative gingivitis. A definitive diagnosis in such cases mandates histopathological and immunological examinations. In patients with PV who have lesions confined to the oral cavity, proper management and close follow up is essential to control the disease and prevent progression.

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FIGURES:

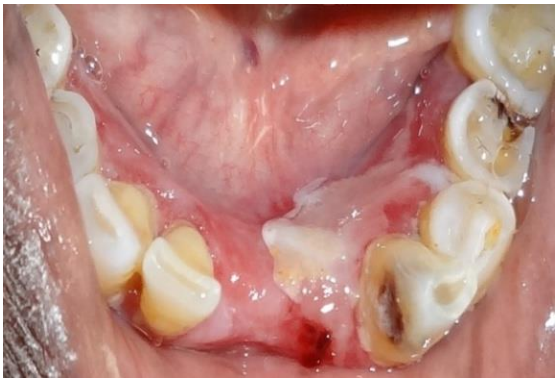

Fig 1 shows presence of a white lesion on the lingual gingiva i.r.t 33

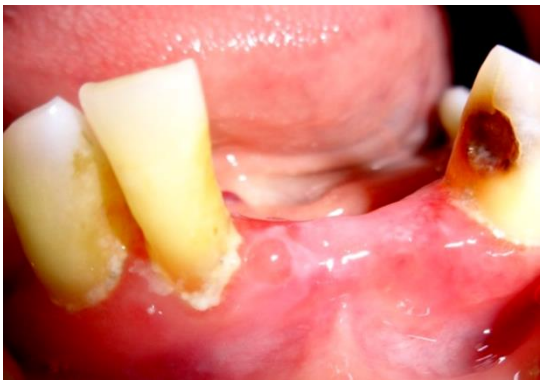

Fig 2 shows presence of an intact vesicle on the alveolar ridge mucosa i.r.t 41 region

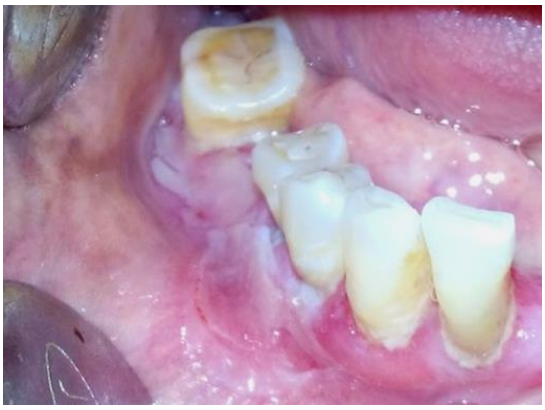

Fig 3 shows desquamation of the gingiva in the 44 – 47 region

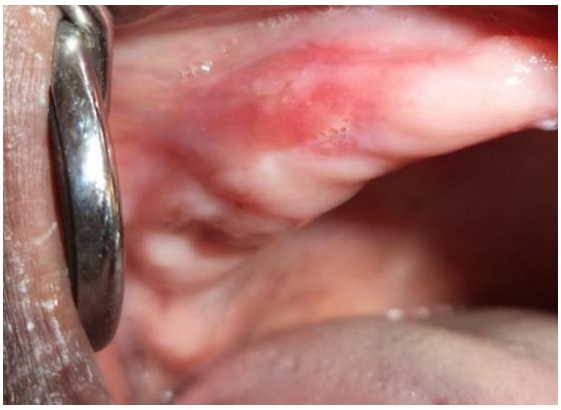

Fig 4 shows an erythematous area on the mandibular alveolar mucosa i.r.t 13,14 region

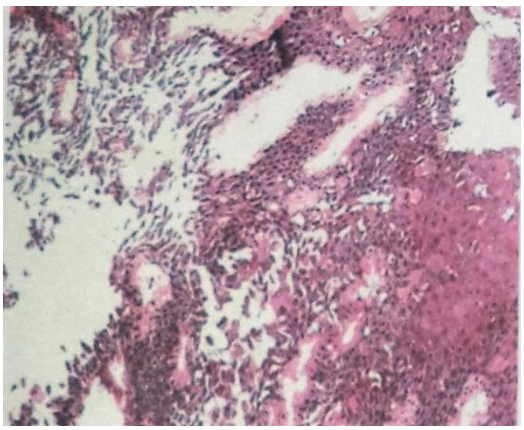

Fig 5: Photomicrograph of the tissue speciemen with H&E stain under10X magnification shows hyperplastic epithelium and acantholysis

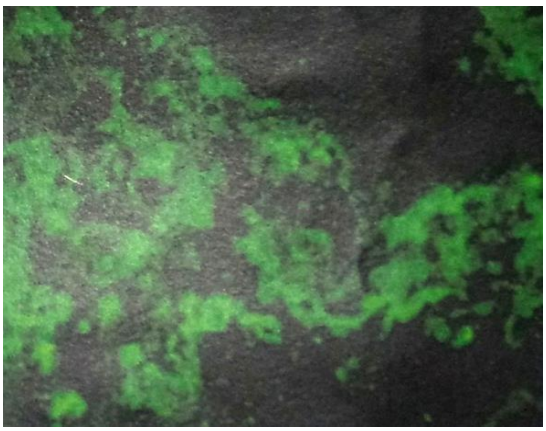

Fig 6: Photomicrograph of image of tissue direct Immunofluorescence staining shows intercellular positivity for IgG

Fig 7: shows complete denture prosthesis

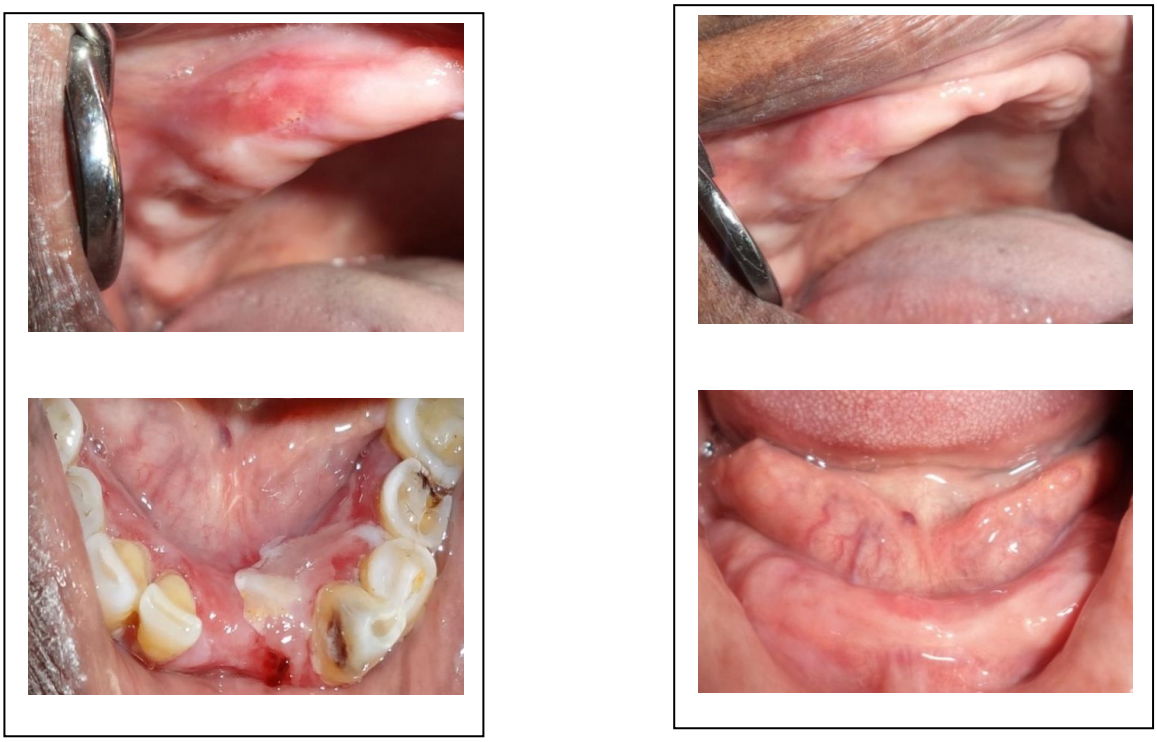

Fig 8 : 2 months post-operative intra oral pictures showing complete resolution of the lesion