Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

CASE REPORT -Diagnostic Challenges of a Rare Case of Pemphigus in the Oral Cavity

1. Dr.A.Hari Priya (Corresponding author), 2.Dr.Ilangani.I, 3.Dr.Anbu Meena.S, 4.Dr. Sahanaz Praveen Ahmed, 5. Dr. Kannan.A,

1Department of Oral Medicine and Radiology
SRM Dental College,
Bharathi Salai,
Ramapuram,
Chennai,
Tamil nadu – 600089.

2Department of Oral Medicine and Radiology
SRM Dental College,
Bharathi Salai,
Ramapuram,
Chennai,
Tamil nadu – 600089.

3Department of Oral Medicine and Radiology
SRM Dental College,
Bharathi Salai,
Ramapuram,
Chennai,
Tamil nadu – 600089.

4Department of Oral Pathology
SRM Dental College,
Bharathi Salai,
Ramapuram,
Chennai,
Tamil nadu – 600089.

5Department of Oral Medicine and Radiology
SRM Dental College,
Bharathi Salai,
Ramapuram,
Chennai,
Tamil nadu – 600089.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

ACKNOWLEDGMENTS

We are indebted to our patient and his family who cooperated with us for this case report.

INTRODUCTION

Vesiculobullous diseases are an idiosyncratic group of oral maladies characterized by the development of vesicles or bullae of which pemphigus group of disease is more common. Pemphigus belongs to a group of possibly life-threatening organ-specific autoimmune blistering diseases. It affects the skin, oral mucosa and may also affect the mucosa of the nose, conjunctiva, genitals, esophagus, pharynx and larynx. (1) Pemphigus is usually divided into 2 major forms depending on blister location: Pemphigus Vulgaris (PV) and Pemphigus Foliaceus (PF). The incidence of pemphigus ranges from 0.76 to 5 new cases per million per year. In a recent analysis of pemphigus, the PV to PF ratio was found to be 12 : 1. However, this ratio varies widely in different parts of the world. PF is an autoimmune blistering disease of unknown etiology with antibodies produced against desmoglein 1(Dsg1). Binding of the antibody results in the loss of cell adhesion or acantholysis and formation of the clinical picture of PF(4). Cumulative evidence is evolving for a steady upsurge of autoimmune diseases in the last decades. Undeniably, the growth in autoimmune diseases equals the surge in allergic and cancer pathology. Oral manifestations are frequently the primary sign of autoimmune diseases (5). The dentists therefore play a pivotal role in the recognition, detection and in multidisciplinary treatment. Precise and timely diagnosis escalates the efficiency and efficacy of treatment strategy.

Hereby, we present a rare case report of both Pemphigus Foliaceus and Oral Pemphigus Vulgaris coexisting together with its advanced diagnostic investigations and treatment with a follow up period of 6 months.

CASE REPORT

A 43-year-old male (Fig 1) was referred to the Oral Medicine Department in July 2017, with a chief complaint of multiple painful sores in his mouth for past 1 month (Fig 2,3 & 4) . Patient was apparently normal until1 month back following which blisters developed which later turned into painful sores with gradual increase in number and spread throughout the mouth. The lesion aggravated in the past 15 days with increase in size over a period of 1 month attaining the present size. The patient had been under the care of Dermatology since September 2016 for an itchy rash on the legs, scalp and chest. A biopsy on the scalp was done in 2016 which revealed acantholysis of the keratinocytes in the upper part of the prickle cell layer and direct immunofluorescence studies showed IgG

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

positivity around the upper epidermal cells. These features were consistent with a diagnosis of Pemphigus Foliaceus. He was prescribed medicine by Dermatology in 2016, which had resulted in excellent control of his cutaneous lesions. Oral involvement began in June 2017 which required hospital admission for a short period.

Extraorally, on inspection multiple blisters were evident on the left side chest region (Fig 2) and left commissure of lip (Fig 3(a) &(b)). The ulcer presented with distinct and erythematous margins, sloping edges with whitish slough covering the floor, with the largest ulcer measuring approximately 1.5×1cm in size and smallest ulcer measuring approximately 0.5×0.5cm in size. The ulcer was tender, non - scrapable with no induration of the base and bleeding on palpation.

Intraorally, on inspection, multiple well defined irregularly shaped ulcers were evident involving the buccal mucosa, tongue, and soft palate (Fig 4(a),(b),(c) &(d)). The ulcers presented with distinct and erythematous margin, sloping edge with whitish slough covering the floor, present in the buccal mucosa, tongue and palate, the largest measuring approximately 3×2.5cm in size and smallest measuring approximately 0.5×0.5cm in size. The ulcer is tender, non-scrapable with no induration of the base, and bleeding on palpation.

Conventional exfoliative cytology showed exfoliated epithelial cells, in the midst of which few round cells with hyperchromaticpyknotic nucleus suggestive of Tzanck cells were seen. Incisional biopsy was done intraorally and the specimen was given for immunofluorescence and histopathological investigation separately.

Direct immunofluorescence,(Fig 6(a) &(b)) showed linear C3 and fibrinogen in the subcoronal region with prominent fishnet pattern suggestive of Pemphigus Vulgaris. Enzyme-linked immunosorbent assay (ELISA) showed positive for both desmoglein 1 & 3.

Histopathologically, (Fig 7(a),(b) &(c))the given specimen showed hyperplastic stratified squamous epithelium and minimal connective tissue component. Most of the areas show acanthosis and prominent intercellular bridges. In some areas the spinous cells appear enlarged showing intracellular edema and vesiculated nuclei. An intraepithelial split is seen in an area, showing loss of cohesion between the cells and acantholysis. The basal cells are seen attached to the connective tissue showing a tombstone pattern. Free floating acantholytic cells are seen within the split. The underlying connective tissue is loose to densely

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

packed with collagen fibres, fibroblasts, blood vessels, and numerous chronic inflammatory cells. Thus histopathology is suggestive of Intra-epithelial blistering disorder.

Patient was given topical and systemic steroids, 20mg per day, and was kept in follow-up, for a period of 3 months. Patient showed satisfactory healing of both oral and cutaneous lesion (Fig 5 (a),(b),(c) & (d)) and showed no recurrence over a follow-up period of 2 years. The drug dosage was tapered down with corresponding cessation of the drug.

Thus our case showed presence of both Pemphigus Foliaceus and Oral Pemphigus Vulgaris coexisting together.

DISCUSSION

A literature search was done using Pubmed, and Web of Science using the search terms ‘Pemphigus Vulgaris’ and ‘Pemphigus Foliaceus’ and ‘coexisting’ or ‘transtition’. A total of 10 papers were identified, however only 3 of these papers showed patients with both cutaneous and oral mucosal involvement. The remaining papers involved patients with cutaneous lesions only, with one describing a case of concurrent PV and PF of the nose. Of the three papers describing both cutaneous and oral mucosal involvement, only Komai et al. demonstrated a histological diagnosis of both PV and PF in three patients. The other two papers only had a histological diagnosis of PV, with the diagnosis of PF being made clinically.

Our case showed rare characteristics of PF in the cutaneous region and PV in the oral mucosa. Transitions between the two pemphigus subtypes are a known phenomenon and therefore, it could be possible that a transition from PV to PF has occurred in our patient. The process of transition may be explained by qualitative changes in desmoglein autoantibody profile. Exactly how this occurs is not fully known, however one proposed mechanism is epitope spreading.

In the epitope spreading, primary autoimmune response leads to tissue damage which causes a new epitope to be revealed, hence provoking a secondary autoimmune response. Epitope spreading can occur both within the same protein (intramolecular) and between distinct proteins within the same tissue (intermolecular).

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

Epitope spreading occurs in several other autoimmune skin diseases, including epidermolysis bullosa acquisita, bullous pemphigoid, lichen planus, pemphigoides and Systemic Lupus Erythematosus.

Usually either immunoblotting or enzyme-linked immunosorbent assay (ELISA) or both is used to detect autoantibodies and confirm shifts between Dsg1 and Dsg3. Both techniques are used to identify target proteins, however, studies have shown ELISA to be more highly specific and sensitive for detecting autoantibodies in the sera of patients with PF and PV. PF sera only react with Dsg1 whereas PV sera can react with both Dsg1 and Dsg3. In our case ELISA was done and it showed high titres for both Dsg1 and Dsg3. However immunoblotting could not be done. Thus we can say that both the subtypes of this Pemphigus existed together. The transition or transformation phenomenon remains uncertain.

However treatment is very crucial and follows a multidisciplinary system. Owing to the friable nature of the involved skin/mucosa, it is preferable to biopsy tissue a short distance from clinically evident disease (perilesional tissue). Separate tissue specimens should be sent for histopathology to show suprabasal acantholysis and direct immunofluorescence to demonstrate IgG antibody and activated complement (C-3) in the intercellular space.

The oral mucosa is the optimum site for biopsy to show suprabasal acantholysis.

Prior to the advent of corticosteroid therapy in the 1950s, the disease was in most cases fatal within 5 years. Systemic corticosteroids (prednisolone) rapidly brought the disease under control and up until recently have been the mainstay of treatment. However when used as a single agent patients often relapse when the corticosteroid is tapered. Complications associated with the long-term use of corticosteroids lead to a move towards immunosuppressants with a steroid-sparing effect. Plasmapheresis in combination with steroid-sparing immunosuppressants (azathioprine, cyclophosphamide) has been successful in controlling the disease. However, the unfavourable side effect profile of these drugs (pancytopenia, hepatotoxicity) has lead to the development of newer immunosuppressants such as mycophenolatemofetil (MMF) that are better tolerated by patients. This drug has been shown to significantly reduce relapse of the disease when corticosteroids are tapered.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

CONCLUSION

Oral lesions are often the first manifestations of the disease and can predate cutaneous lesions by up to a year. Early referral by the physician/dentist to the dermatology/ oral and maxillofacial surgery department is necessary to ensure a prompt diagnosis before the onset of the more severe form of the disease. Patients presenting with severe Pemphigus Vulgaris will have multiple life-threatening issues. It is important to recognise these early and involve the appropriate medical/surgicalspecialty to ensure a rapid and comfortable path to recovery for the patient.

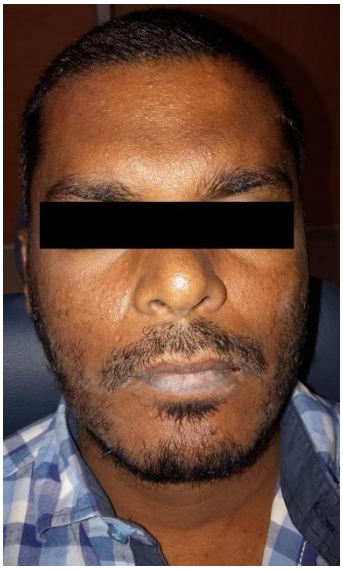

Fig 1: Extraoral picture

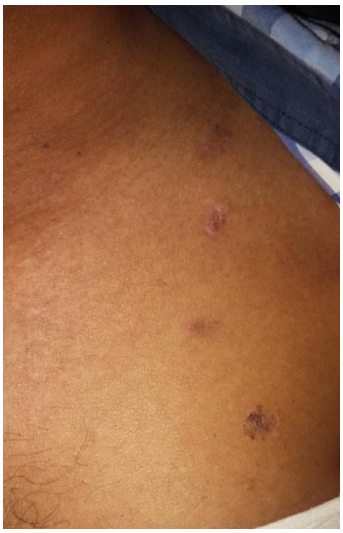

Fig 2: Ruptured blisters on the chest

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

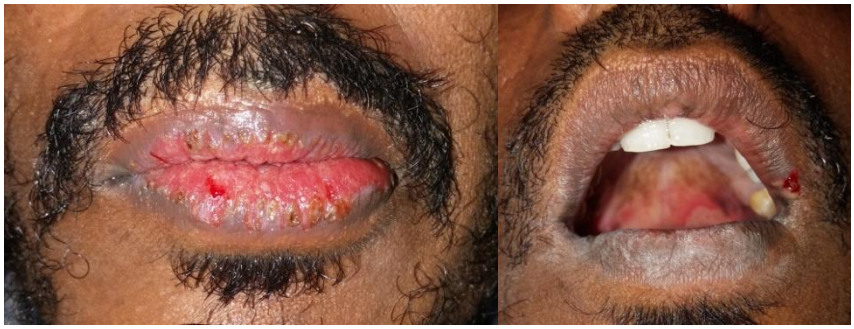

Fig 3:Pre-operative Extraoral Ruptured ulcerative blisters on the lips

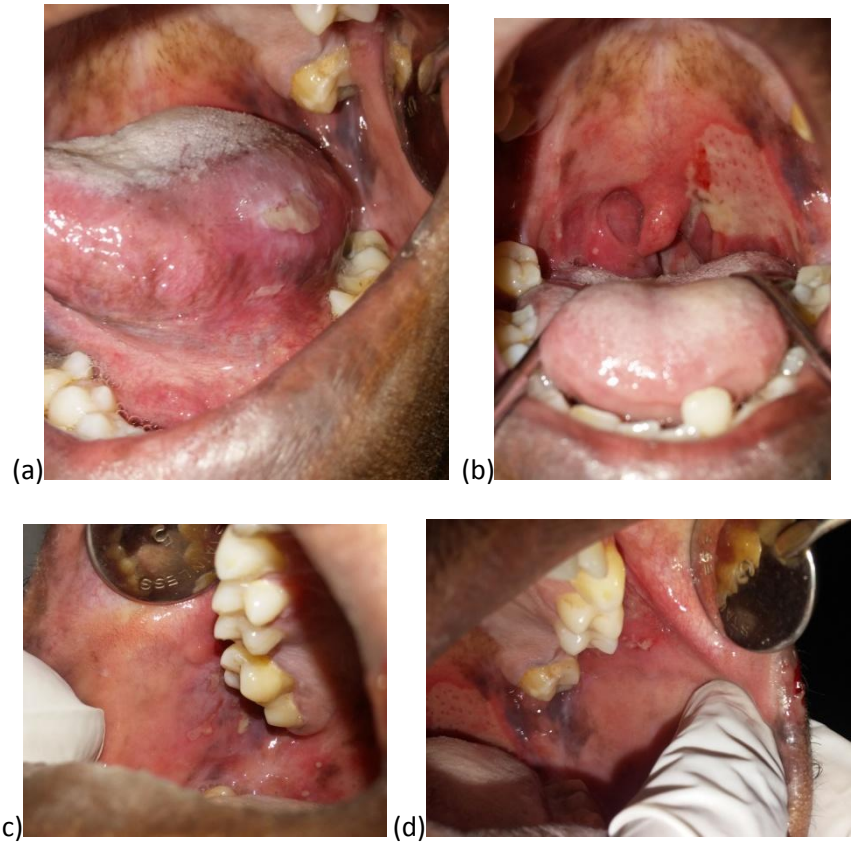

Fig 4: Pre-operative Introral ruptured ulcerative blisters on the (a)Lateral surface on the tongue (b) palatal surface and tonsils (c)&(d) right & left buccal mucosa

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

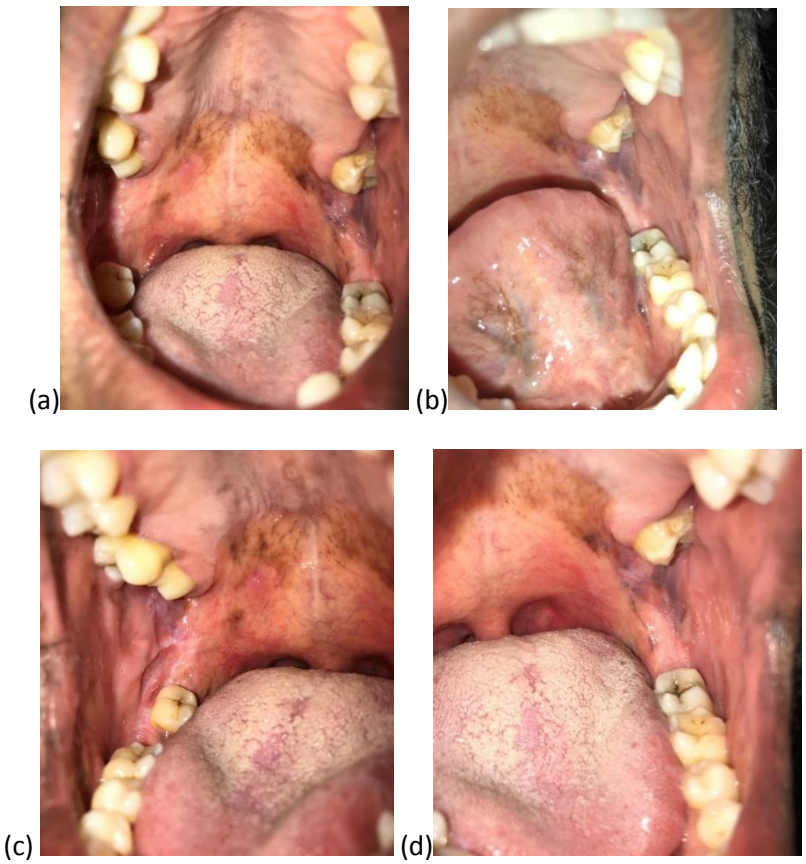

Fig 5: Post-operative Introral healed ulcers(a)Palatal surface and tonsils (b) Tongue surface (c)&(d) right & left buccal mucosa

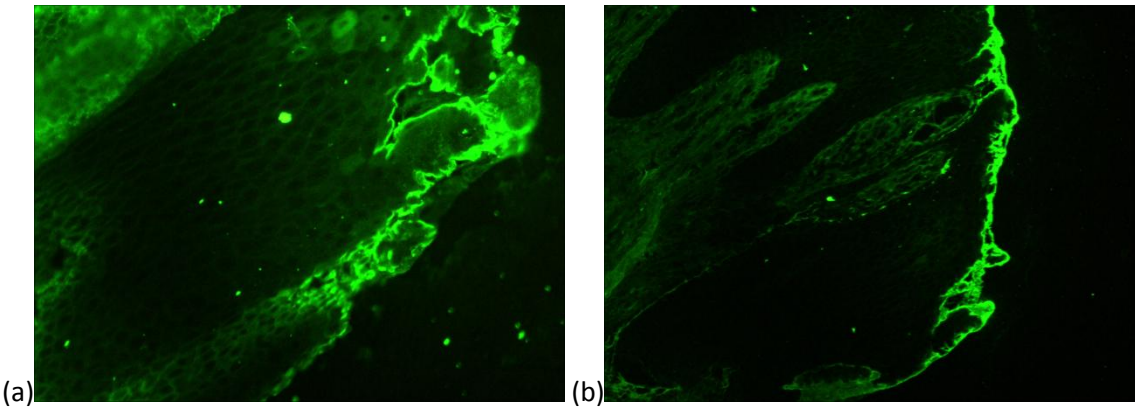

Fig 6: Immunoflorescence(a)& (b) Linear C3 and fibrinogen shows positivity in subcorneal region with prominent fishnet pattern.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 5366 - 5374
Received 05 March 2021; Accepted 01 April 2021.

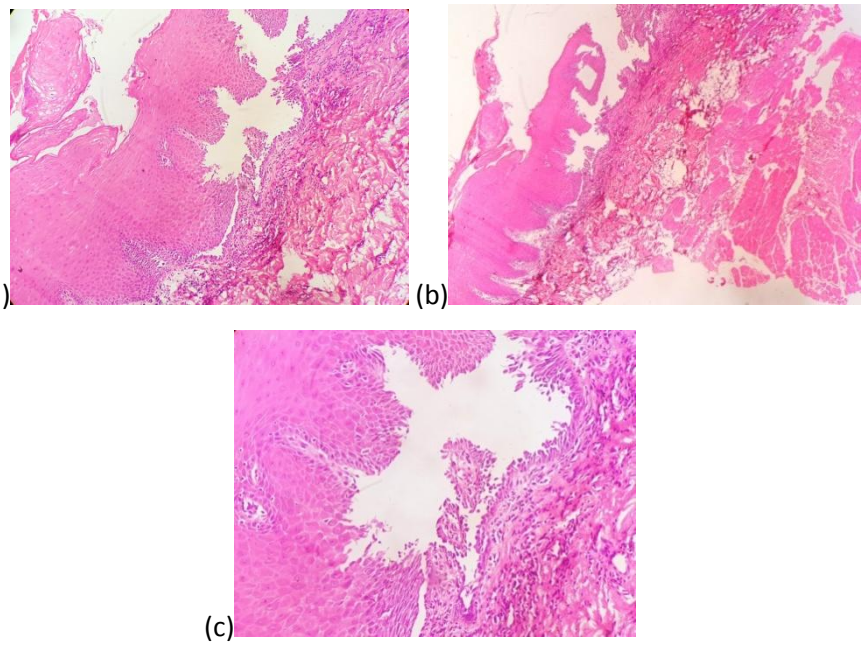

Fig 7: Histopathology(a)20× ,(b) 10× & (c)40× shows areas of acanthosis and prominent intercellular bridges, the spinous cells appear enlarged showing intracellular edema and vesiculated nuclei, Epithelium is highly proliferative and shows severe dysplastic feature.

REFERENCES

1. Padma R, Kalaivani A, Sundaresan S, Sathish P. The relationship between histological differentiation and disease recurrence of primary oral squamous cell carcinoma. J Oral Maxillofac Pathol. 2017;21(3):461.
2. Robinson ND, Hashimoto T, Amagai M, Chan LS. The new pemphigus variants. J Am Acad Dermatol. 1999;40(5):649–71.
3. Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Esmaili N, Balighi K, Hallaji Z, et al. Pemphigus: analysis of 1209 cases. Int J Dermatol. 2005;44(6):470–6.
4. ADAMS JM, REICHEL BM, KING AI, MARSDEN DM, GREENWOOD DM, THIRLWELL H, et al. Characterization of the regulatory regions in the human desmoglein genes encoding the pemphigus foliaceous and pemphigus vulgaris antigens. Biochem J. 1998;329(1):165–74.
5. Mays JW, Sarmadi M, Moutsopoulos NM. Oral manifestations of systemic autoimmune and inflammatory diseases: diagnosis and clinical management. J Evid Based Dent Pract. 2012;12(3):265–82.