Case Report

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Intraepithelial Vesiculobullous Lesions: Review and A Case Report

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ABSTRACT

Background: The oral cavity presents with a variety of pathological lesions ranging from benign to malignant. Many of the lesions may become potentially fatal if they are undiagnosed or misdiagnosed in their early stages. Pemphigus vulgaris is an autoimmune vesiculobullous lesion which is misdiagnosed upon several times in its initial stages leading to failure in providing proper treatment. Hence, it is necessary to be familiar with clinical & radiographic features, histopathological findings, immunofluorescence techniques for ruling out differential diagnosis. Here we present a case report of pemphigus vulgaris with emphasis on various intraepithelial vesiculobullous lesions.

Keywords: Intraepithelial Vesiculobullous Lesions, oral pathology, dentistry.

INTRODUCTION

Autoimmune bullous diseases are those that have autoimmunity to the components of a cell junction. These cell junctions help in maintaining cell-cell and cell-matrix adhesion in the skin and mucous membranes. Among these autoimmune bullous diseases, pemphigus vulgaris involves both the skin and mucosal areas, that is characterized by the presence of intraepithelial flaccid blisters and erosions. These autoantibodies are directed against the anchoring complex proteins of the hemidesmosomes (desmoglein1 & desmoglein3)[1].

Due to mechanical injury or may be due to infectious, drug-induced, immunologically mediated, and hereditary diseases, vesicles may exhibit in the oral cavity. These vesicles or bullae may develop within the epithelium or below the epithelium and are fragile. Among these, intraepithelial vesicles/bullae being the most fragile rupture quickly and get ulcerated.

Most of the patients presented with the pemphigus vulgaris are misdiagnosed in the early stages and being treated improperly up to many months or years[2]. Hence, as a general practitioner or dentist, it is essential to consider various lesions which mimic the pemphigus vulgaris in differential diagnosis and to carry out necessary investigations such as histopathological & immunofluorescence techniques. In the present article, we present a case report on pemphigus vulgaris along with a brief discussion on different intraepithelial vesiculobullous lesions.

CASE REPORT

A 38-year-old female patient came to G. Pulla Reddy Dental College and Hospital, with a chief complaint of burning sensation along the right and left inner cheek region for two months. She stated that the burning sensation started suddenly two months back while having food and too hot beverages. She also had difficulty in swallowing. After a few days,

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she noticed severe bleeding from the gums while brushing. On consultation with a physician, medicaments, including both topical and systemic, were advised. No relief was noticed after the usage, and patient discontinued the medication 15 days as there was no relief. The patient also noticed itching on the skin surface with a water bubble like overgrowths on the upper abdomen, which peeled on scraping. A review of medical and family history was non-contributory.

Intra-oral examination revealed erythematous lesions present on bilateral buccal mucosa. On the left buccal mucosa (Fig.1), diffuse erythematous lesions along with hyperkeratinisation were found along the line of occlusion which extended from the commissure area to retromolar trigone. On the right side (Fig.2), ulcerative lesions were found in the lower buccal vestibule in the molar region. Linear erythematous lesions were also noticed on the upper (Fig.3) and lower labial marginal gingiva (Fig.4). Erythematous areas along with hyperkeratinisation were also noticed in the left palatal mucosa and along soft palate region. Gingiva is erythematous with generalized bleeding on probing. Peeling off of mucosa is noticed on scraping. Nikolsky's sign was also noticed.

Based on history and clinical presentation of multiple erythematous lesions along with bullae on the upper abdomen, a provisional diagnosis of pemphigus vulgaris was made. Differential diagnosis included benign mucous membrane pemphigoid, bullous lichen planus, cat-scratch disease, epidermolysis bullosa, herpangina, primary herpetic gingivostomatitis, herpes zoster, pemphigus, and its variants, foot-and-mouth disease, Hand-foot and mouth disease.

Along with perilesional site of the right buccal mucosa, an incisional biopsy was performed in the region of right buccal mucosa under local anesthesia and sutures were placed after the biopsy. Two tissue specimens with dimensions of 0.7× 0.5 ×0.1 cm and 0.5×0.2×0.1 cm (Fig. 5) were obtained from biopsy for histopathological examination.

Histopathological examination revealed parakeratinized stratified squamous epithelium exhibiting spongiosis, and cellular edema of superficial layers of cells was noticed. Intraepithelial split above the basal layer (Fig.6 & 7), and Tzanck cells were observed. Chronic inflammatory cell infiltrates evident in the subepithelial and perivascular region.

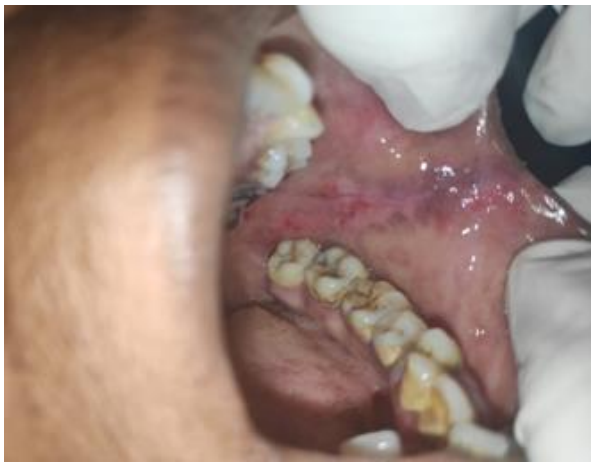

Fig 1: Ulcerative lesions seen along the line of occlusion of left buccal mucosa.

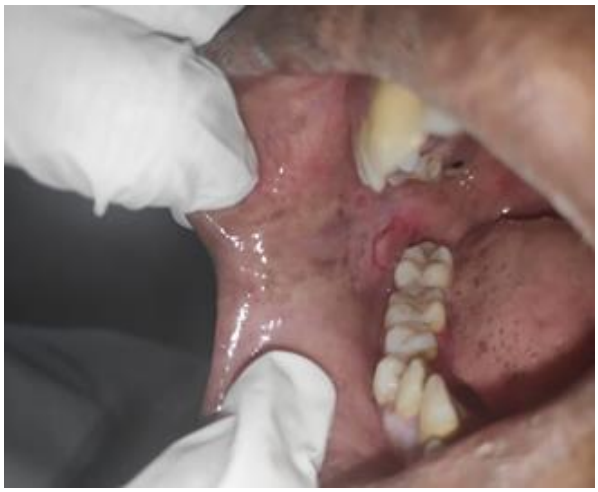

Fig 2: Ulcerative lesion on the right side seen along the lower buccal vestibule.

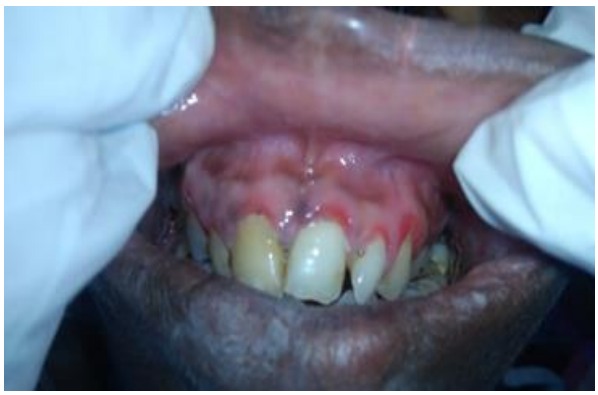

Fig 3: Linear erythematous lesions along the marginal gingiva of upper anterior teeth.

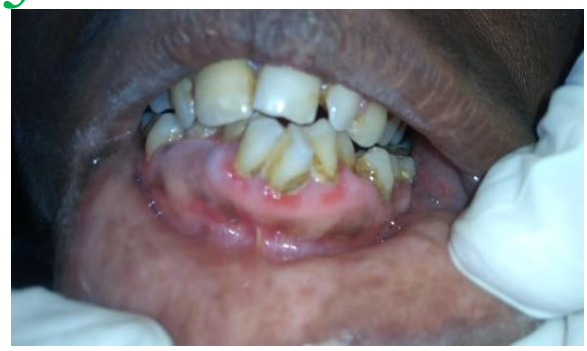

Fig 4: Linear erythematous lesions along the marginal gingiva of lower anterior teeth.

Fig 5: Biopsied tissue specimens.

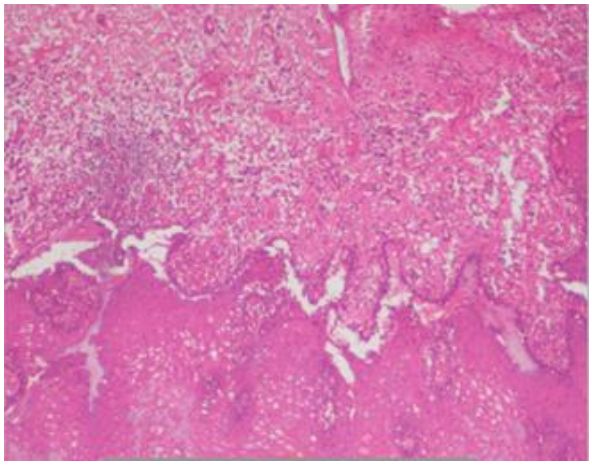

Fig 6: H & E stain (4X).

Based on the above histopathological findings, a differential diagnosis of pemphigus vulgaris, bullous pemphigoid, familial benign chronic pemphigus, epidermolysis bullosa, mucosal erythema multiforme & recurrent herpes lesions were made. Direct immunofluorescence exhibited prominent intercellular deposition of antibodies directed against IgG and C3 for the confirmatory diagnosis of pemphigus vulgaris.

The treatment comprised of prednisolone 20 mg for five days. The patient was reviewed after one month. History of remission of burning sensation of mouth on medication was given by the patient. Diffuse erythematous areas with hyperkeratinisation were noticed along left buccal mucosa, and right buccal mucosa. Mild pinpoint erythematous areas along soft palate were noticed. Healing with post inflammatory pigmentation noticed along face, neck, and trunk.

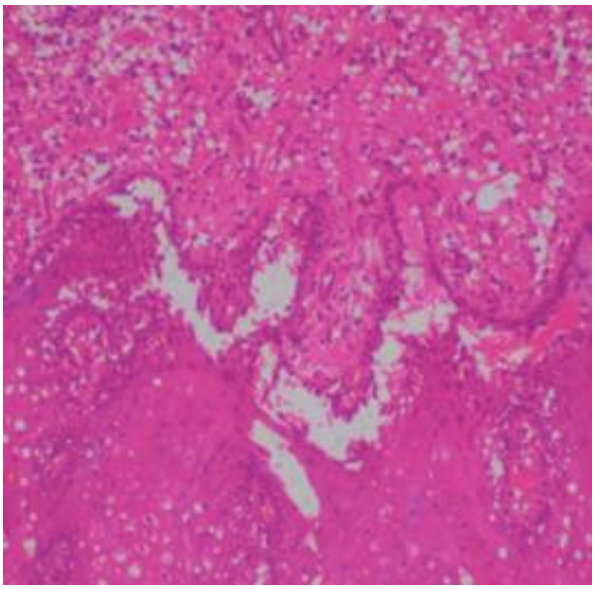

Fig 7: H & E stain (10X).

DISCUSSION

Vesiculobullous lesions, a type of mucocutaneous disorders characterized by vesicles, bullae, or blisters. These are fluid-filled lesions and are differentiated by their size. Vesicles are elevated blisters containing clear fluid that are less than 1 cm in diameter. Bulla is greater than 1cm in diameter. The diagnosis of vesiculobullous diseases should be made on the basis of clinical, histopathological, and immunological characteristics. These vesiculobullous lesions may be intraepithelial and subepithelial.[2]

Intraepithelial vesiculobullous lesions: Lesion is formed within the epithelium.

- HSV infection
- Varicella infection
- Herpangina

- Hand, foot and mouth disease
- Pemphigus
- Familial benign chronic pemphigus
- Mucosal erythema multiforme

Subepithelial vesiculobullous lesions: Lesions formed between the epithelium and lamina propria.

- Bullous pemphigoid
- Cicatricial pemphigoid
- Epidermolysis bullosa
- Dermal erythema multiforme
- Dermatitis herpetiformis
- Linear IgA disease

In the Indian population, pemphigus occurs at a younger age when compared with the western countries[3]. Initiation of therapy with early diagnosis is considered to be essential. Due to its potentially fatal outcome and with features that mimic various other lesions, it is necessary to diagnose precisely for proper treatment. A good understanding of the features of vesiculobullous intraepithelial lesions will help in reaching an accurate diagnosis.

Intraepithelial vesiculobullous lesions

• Intraepithelial vesiculobullous lesions

1. HSV infection
2. Varicella infection
3. Herpangina & Hand, foot and mouth disease
4. Pemphigus
5. Familial benign chronic pemphigus
6. Epidermolysis bullosa
7. Mucosal erythema multiforme
8. Keratosis follicularis

1. HSV infection:

Two types of DNA viruses cause Herpes simplex virus infection. They are respectively HSV 1 and HSV 2 [1]. Characteristically, HSV 1 is responsible for infections above the waist, including the Gingivostomatitis, keratoconjunctivitis, genital, and skin lesions.[4] Infections below the waist more commonly anogenital infections are due to HSV 2. The most common pattern of symptomatic primary HSV infection is Acute herpetic gingivostomatitis. Epithelial cells are mostly infected cells by the virus. These infected cells in the epithelium exhibit acantholysis and ballooning degeneration and referred to as Tzanck cells.[5] Lipschutz bodies are seen as intranuclear inclusions in the infected epithelial cells. Multinucleated giant cells are seen which are formed due to the fusion of adjacent cells. Nucleolar fragmentation is seen around the nuclear periphery. Intraepithelial vesicle is formed following the development of intercellular edema. Vesicles on the mucosal surfaces rapidly rupture giving rise to the formation of the fibrinopurulent membrane.

2. Varicella infection:

Cytological smears derived from the vesicles reveal multinucleated giant cells along with intranuclear inclusion bodies. These changes are similar to those seen in the HSV.[2] For the confirmation of Varicella Zoster infection, PCR and direct immunofluorescence assay are more effective. Viral isolation in cell culture or fluorescein-conjugated VZV monoclonal antibodies for rapid diagnosis is performed for the confirmation of VZV.

3. Herpangina & Hand, Foot, and Mouth Disease:

Intracellular and intercellular edema is seen in the infected epithelium, leading to extensive spongiosis with an intraepithelial vesicle formation.[5] The vesicle enlarges and forming a subepithelial vesicle by rupturing through the basal epithelial layer. Epithelial necrosis and ulceration are seen. Inclusion bodies and multinucleated epithelial cells are absent.

4. Pemphigus:

It is an autoimmune condition representing four disease entities – Pemphigus vulgaris, Pemphigus vegetans, Pemphigus erythematosus, and Pemphigus foliaceus.

- Pemphigus vulgaris: Microscopically the vesicle or bullae formation is intraepithelial. There is distinctive suprabasilar split formed by the intraepithelial vesicle or bullae just above the basal layer.[6] The appearance of perivascular edema and loss of intracellular bridges is seen. It will ultimately lead to loss of cohesiveness between the cells resulting in acantholysis and appearance of Tzanck cells. Tzanck cells are

characterized by degenerative changes such as the hyperchromatic nuclei and nuclear swelling, especially in the freshly taken smears. Attached to the dermal-epidermal basement membrane is a single layer of basal keratinocytes referred to as a row of tombstones. The relative scarcity of inflammatory cell infiltration in both the vesicular fluid and in the connective tissue at the base of the vesicle or bulla is suggestive of pemphigus. Immunofluorescence testing is proven as most conclusive in establishing a diagnosis. IgG autoantibodies are shown to react with autoantigens such as desmoglein 3 and desmoglein 1. Various autoantigens, like 9-acetylcholine receptor and pemphaxin, were demonstrated in patients of pemphigus vulgaris with less prevalence.

- Pemphigus vegetans: The histopathology in pemphigus vegetans exhibits epidermal hyperplasia, intraepidermal eosinophilic abscesses, and papillomatosis. Suprabasal acantholysis is subtle, masked by the exuberant proliferation of squamous epithelium which may show pseudoepitheliomatous hyperplasia Histopathology of Pemphigus vegetans seem to differ from pemphigus vulgaris by the formation of eosinophilic microabscesses and extent of vesiculation.

- Pemphigus foliaceous: It is an autoimmune skin disorder and a benign variant of pemphigus vulgaris. Histologically acantholysis of the upper epidermis is seen. Granular cell layer is the only layer affected showing discrete acantholytic bullae. These bullae contain rounded, acantholytic keratinocytes with few inflammatory cells. Hyperkeratosis and parakeratosis may be evident.

- Pemphigus erythematosus: It is also referred to as Senear-Usher syndrome. It contains features of lupus erythematosus (LE) and pemphigus foliaceus. Pemphigus is demonstrated by acantholysis and immunoglobulin deposits in the interkeratinocyte substance.

5. Familial Benign Chronic Pemphigus:

Also known as Hailey – Hailey disease. The histologic appearance of the epithelial lesions in familial benign chronic pemphigus have resemblance with those seen in pemphigus vulgaris and keratosis follicularis or Darier's disease. More extensive acantholysis and usually lower damage to acantholytic cells are seen in familial benign chronic pemphigus when compared with pemphigus vulgaris. The distinctive feature of the disease is the presence of intercellular bridges with some cells and making the cells to adhere to each other rather than entirely acantholytic.

6. Epidermolysis bullosa:

It comprises of a wide variety of inherited mucocutaneous disorders. It has been identified into 21 different forms and broadly divided into three categories, i.e., simple, junctional, and dystrophic. Accordingly, the histopathological findings of each variant differ from others. Formation of the intraepithelial cleft is seen in case of simple epidermolysis bullosa while the junctional and dystrophic forms of epidermolysis show subepithelial cleft. The cleft formation in the junctional form of epidermolysis bullosa is seen at the level of lamina lucida whereas in the case of dystrophic form the cleft is seen at the level of lamina densa and basement membrane. The autoantigen of epidermolysis bullosa is type VII collagen, whereas the pemphigus vulgaris has autoantigens such as desmoglein 3 and desmoglein 1. A confirmative diagnosis of direct immunoelectron microscopy revealed the presence of IgG and/or C3 deposits in the sub-lamina densa region of the dermal-epidermal junction.

7. Mucosal erythema multiforme:

A rare, acute inflammatory disorder affecting the skin, or mucous membranes, or both. It is sometimes recurrent exhibiting papular, bullous and necrotic lesions. Erythema multiforme occurs due to the allergic host response to antigenic challenge.[7] Multiple factors are considered for the development of Erythema multiforme (EM). A viral infection is the most commonly considered etiological factor with the dominance of HSV1 & HSV2. Other viral and bacterial infections are also considered (Mycoplasma pneumoniae). Diagnosis of these lesions is dependent mostly on the clinical history and findings (Target lesions / Bull's eye lesions). On histopathology, epithelial intercellular edema and necrosis in the keratinocytes are noticed. An intra- or sub-epidermal blister is seen

present with a necrotic epidermis.[7] A peri-vascular lymphocytic infiltration without necrotic vascular lesion is seen in the superficial dermis. At the basement membrane zone, intense lymphocytic infiltration with nonspecific immune deposits of IgM, C3, and fibrin perivascularly is seen.

8. Keratosis follicularis:

It is also known as Darier's disease, an autosomal dominant disorder. Darier's disease is characterized by keratotic papules and longitudinal eyrthronychia. It is rare and distributed worldwide. A papular rash of discoloration which typically commences on the forehead, neck, and back, from where spreading of the rash to other parts of the body, is noticed. Longitudinally ridged and fissured nails may be seen.

Some authors assumed that familial benign chronic pemphigus is a bullous or exudative form of keratosis follicularis. Others have argued that the two diseases are unrelated. Since both conditions are relatively rare, their simultaneous occurrence in the same patient, occasionally described (Finnerud and Szymanski, 1950; Degos and Civatte.1060), might help elucidate their possible relationship. [8] Involvement of the mucous membrane has received little attention, although it was first reported by Reensfierna (1917). Gorlin & Chaudhry (1959), sharer et al. (1963), Spouge et al. (1966), and Witkop (1966) have drawn attention to the condition in the dental literature.

Keratosis follicularis is caused by the mutations within the ATP2A2 gene. [9] A calcium pump endoplasmic reticulum is encoded by the ATP2A2 gene. Persons inheriting this condition will have one or more manifestations of the disease, but its severity and features will differ in all the affected persons. Due to this reason, recalling family history by the patient is somewhat tricky. Hence, it may not be the right thing to exclude the presence of Dariers disease with negative family history.

On histopathology, keratosis follicularis is characterized by the presence of dyskeratosis and acantholysis. Dyskeratosis is related to apoptosis and is premature keratinization of keratinocytes. It is seen as corps ronds (round keratinocytes with basophilic nuclei in the granular layer). [9] Acantholysis may be seen as lacunae in the keratinocytes above the basal layer. The epidermis may also show hyperkeratosis sometimes.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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