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Revisiting pemphigus vulgaris: A case report and review of literature

Priya Nimish Deo, Revati Shailesh Deshmukh

ABSTRACT

Introduction: Pemphigus is an autoimmune blistering mucocutaneous disease. Production of auto-antibodies against desmosomal glycoproteins is a characteristic feature of the disease. Oral lesions of pemphigus vulgaris are many a times first sign of the disease and hence it is important for a dentist to be familiar with the clinical appearance, diagnosis, and treatment modalities.

Case Report: This report describes a case of pemphigus vulgaris in a female patient who presented with ulcers on the gingiva. On the basis of clinical examination and histopathology, we arrived at a diagnosis of pemphigus vulgaris, which was confirmed by immunofluorescence.

Conclusion: If left undiagnosed or untreated pemphigus vulgaris may be fatal. Early diagnosis will aid in appropriate treatment and better outcome of the disease.

Keywords: Acantholysis, Autoantibodies, Pemphigus, Tzanck cells

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INTRODUCTION

Pemphigus is a mucocutaneous disease which affects the skin and mucous membrane. It is a life-threatening disorder [1]. The word pemphigus arises from the Greek word Pemphix which means a blister or a bubble. It is an autoimmune disease in which the keratinocyte antigens are the target of the autoantibodies [2].

There are three forms of pemphigus: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Pemphigus vulgaris and pemphigus foliaceus are the first described classic forms of pemphigus [3]. The difference lies in the level of acantholysis. In pemphigus vulgaris it is at the supra-basilar level while in pemphigus foliaceus it is in the upper epidermis [4].

The diagnosis of pemphigus vulgaris is established by biopsy and histopathological examination of the lesional tissue. Pemphigus vulgaris is generally fatal if left untreated and has a mortality rate ranging from 60% to 90%. As it is a life-threatening disease, it is essential that a dentist is able to identify oral manifestations of pemphigus vulgaris and treat and refer accordingly [5].

This case report describes a female patient who complained of ulcers on the gums and the histopathology confirmed the diagnosis of pemphigus vulgaris.

CASE REPORT

A 26-year-old female patient complained of ulcers on the gums in the lower and upper anterior region. The patient was apparently alright three months back when she noticed ulcers on the gums in the upper and lower anterior region. She experienced burning sensation on consumption of spicy food and inability to eat and had stopped eating spicy and hot food since last 1 and ½ months and was on soft and liquid diet. The patient gave history of similar lesions in the genital region. She did

not have any past medical or dental history and any habit history.

Intra-oral examination revealed erythematous lesions on the mandibular anterior gingiva—Marginal gingiva, interdental papilla, and attached gingiva (Figure 1). Erythematous lesions were also seen on the maxillary gingiva—Marginal gingiva and interdental papilla. Lesions were noted in the lower right posterior region—Marginal gingiva, interdental papilla of lower right 45, 46, 47 region (Figure 2). On the basis of clinical examination, a provisional diagnosis of pemphigus vulgaris was made with a differential diagnosis of pemphigus, pemphigoid, and bullous lichen planus. Incisional biopsy was performed.

Histopathological examination showed stratified squamous epithelium and connective tissue. The basal cell layer remained attached to the connective tissue and a separation was seen within the epithelium described as the supra-basilar split (Figure 3). A tomb stone appearance of the basal cell layer was seen. Loss of cell-to-cell adhesion was seen within the epithelium. Acantholytic cells with hyperchromatic nuclei were seen lying free in the split described as the Tzanck cells (Figure 4). Inflammatory cell infiltration in the connective tissue was seen mainly in lymphocytes and plasma cells.

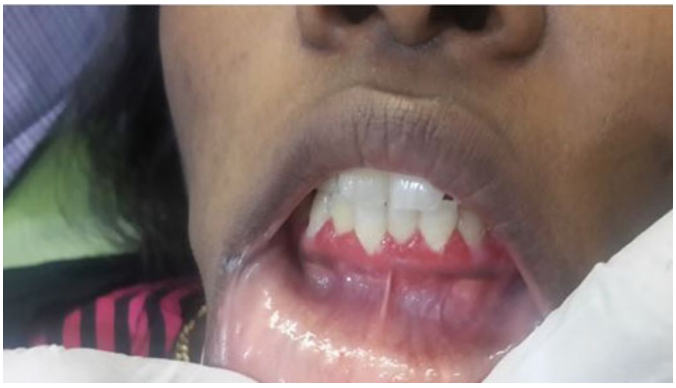

Figure 1: Lesions seen on the marginal gingiva, attached gingiva, and interdental papilla of the mandibular anterior region.

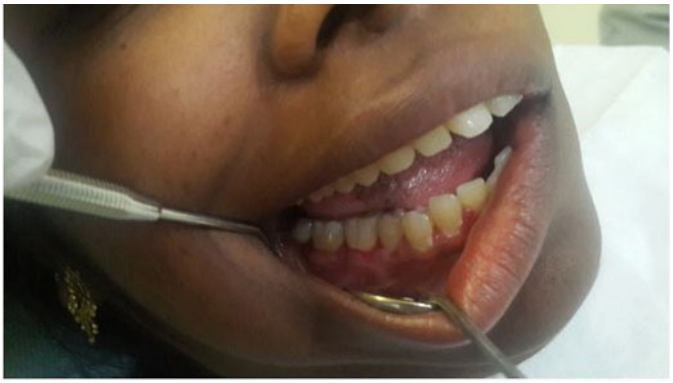

Figure 2: Lesions seen on the marginal gingiva and interdental papilla on mandibular posterior region.

Immunofluorescence findings, intercellular deposition of IgG (Figure 5) and C3 (Figure 6), were found in the squamous epithelium.

On the basis of clinical, histological, and immunofluorescence findings, the diagnosis of pemphigus vulgaris was confirmed.

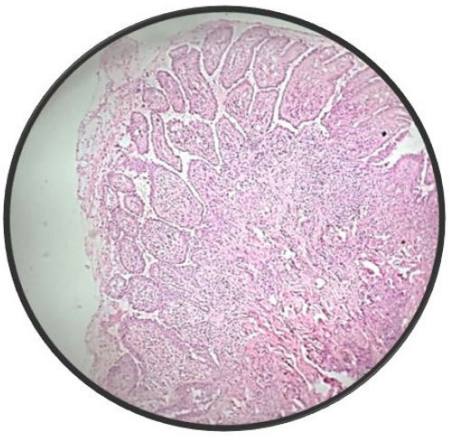

Figure 3: Low power view showing the suprabasilar split within the epithelium and the connective tissue.

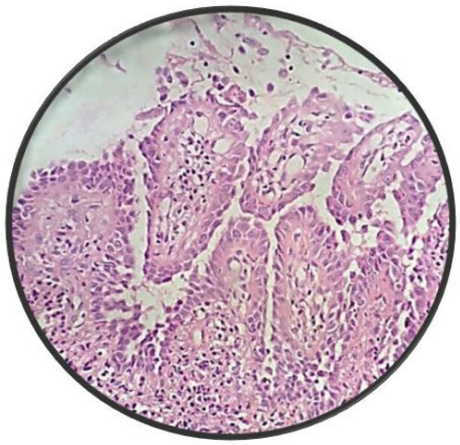

Figure 4: High power view showing the acantholytic Tzanck cells within the epithelium.

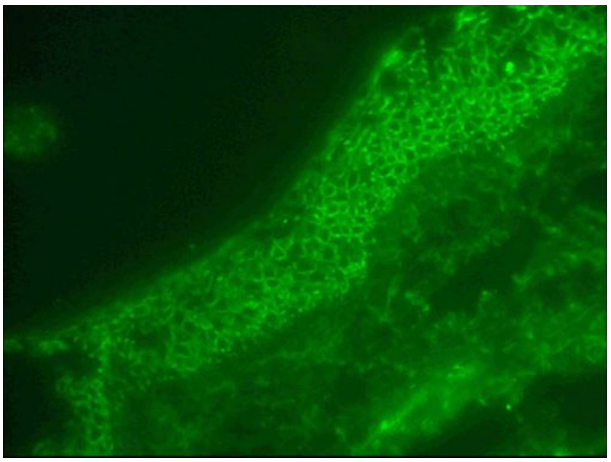

Figure 5: Intercellular deposition of IgG in the squamous epithelium.

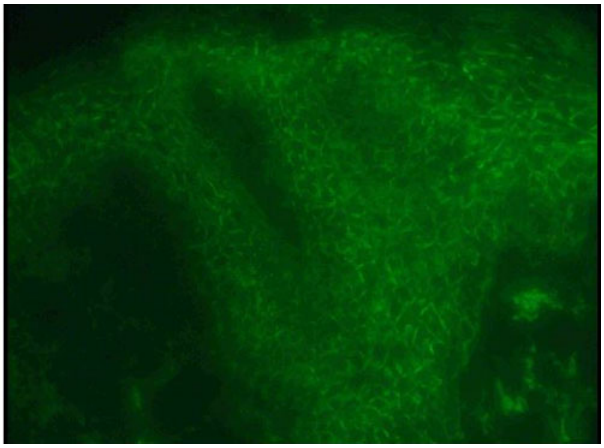

Figure 6: C3 deposition in the squamous epithelium.

DISCUSSION

The term "Pemphigus" was named by Wichman in 1791. It belongs to a group of chronic autoimmune blistering diseases affecting the skin and mucous membrane [6].

It is a rare condition affecting males and females in the 4th to 5th decade of life [7]. The pathogenesis of pemphigus vulgaris was given by Beutner and Jordon in 1964. They found that patients with pemphigus have autoantibodies to intercellular antigens within the malpighian epithelia. Autoreactive IgG was identified as the cause for acantholysis and bulla formation in pemphigus vulgaris through in vitro studies on human skin and disease-associated IgG passive transfer experiments in mice. Desmoglein 1 and Desmoglein 3 are the calcium dependent intercellular adhesion proteins that form the desmosomes. They belong to the cadherin family of proteins and are responsible for anchoring keratin intermediate filaments to the cell membrane of epidermal cells [8].

Pemphigus occurs as a result of autoantibodies which are directed against the units of epithelial desmosomes. Skin and oral mucous membrane show variable expression of Dsg-1 and Dsg-3. Desmoglein 1 is predominantly expressed in the superficial epidermal cells while Dsg-3 is expressed in the basal layers of the epidermis. Desmoglein 3 expression predominates over Dsg-1 in the oral mucous membrane. Thus, the integrity of the oral epithelium is exclusively dependent on Dsg-3, which is targeted by the autoantibodies in cases of pemphigus vulgaris affecting the oral cavity [9].

Pemphigus antigen Desmoglein 4 and other non-Desmoglein antigens like human α-9-acetylcholine receptor that regulates keratinocyte adhesion and keratinocyte annexin like molecules binding acetylcholine termed pemphaxin and catenin are also considered to play a role in its etio-pathogenesis. Acantholysis and suprabasal spilt within the epithelium is triggered by a thin separation at the desmosomal junctions [10].

Different theories are established to understand the pathogenesis of pemphigus vulgaris. They are the desmoglein compensation theory, multiple hits hypothesis, the antibody induced apoptosis theory, basal cell shrinkage hypothesis, and the apoptolysis theory [11].

Desmoglein compensation theory

Amagai et al. in 1999 stated this theory based on the distribution of Dsg-1 and Dsg-3 in the skin and mucosa. According to this theory the presence of any type of desmoglein is appropriate to sustain the integrity of the epidermis and mucosa.

Desmoglein 3 is preferably expressed in the parabasal region of the epidermis and oral epithelium, whereas Dsg-1 in the superficial portion of the epidermis. Therefore patients who develop autoantibodies directed against Dsg-3 with or without the involvement of Dsg-1 will show suprabasal intraepithelial clefting in histopathological examination and clinically show blisters of the oral mucosa. Patients who develop autoantibodies against Dsg-1 will show superficial intraepithelial clefting of the epidermis histopathologically, but oral mucosa will not be affected. This concept has proved the basic pathophysiology of pemphigus and has been extensively used in diagnosis and assessment of efficacy and prognosis. However, this theory cannot explain the epidermal-blister formation satisfactorily [12].

"Multiple hits" hypothesis

Recent evidences suggest that besides anti-Dsg-1 and anti-Dsg-3 antibodies, patients also develop antibodies against other desmosomal proteins like desmocollins, plakins, and non-desmosomal proteins such as cell-membrane receptors like nicotinic acetylcholine receptor, pemphaxin, thyroperoxidase, and other annexins. Volker et al. noted that desmocollin-3 (Dsc-3) expression is seen throughout the basal, spinous, and lower granular layer. Blocking of the function of Dsc-3 with a monoclonal antibody led to the formation of intraepidermal blisters. Non-desmosomal autoantigens such as pemphaxin, an α9-acetylcholine receptor, also contribute to pemphigus vulgaris. It was found that some patients develop antimitochondrial antibodies. These antibodies could penetrate keratinocytes and react with mitochondrial proteins. These data suggest that pemphigus is a complex disease, initiated by at least three classes of autoantibodies which are directed against desmosomal, mitochondrial, and other keratinocyte autoantigens [13].

Basal cell shrinkage hypothesis

There is a change in the cytoskeletal structure of the keratinocytes which results in partial collapse and shrinkage of the cells due to binding of pemphigus antibodies to the keratinocytes. Separation of keratinocytes occurs because they shrink more than they are bound together by the desmosomes and not because of a primary defect in the function of desmosomes. The shrinkage is limited to basal cell layer because the cells are

less rigid and shrink more easily when there is alteration of their cytoskeleton [14].

Apoptolysis theory

Grando et al. in 2009 suggested a unique term, "apoptolysis," which relates the suprabasal acantholytic and cell death pathways to basal-cell shrinkage. The principal difference between apoptolysis and apoptosis is that the basal cells shrink but do not die which gives a "tombstone" appearance to the pemphigus lesions.

Many researchers stated that pemphigus vulgaris IgG-induced caspase-8 activation and acantholysis can be prevented by anti-FasL antibody, which suggested that the acantholysis and apoptosis of keratinocytes in pemphigus are interrupted by the same set of apoptotic enzymes. This new concept illustrates the distinctive pattern of cellular damage and detachment in pemphigus [12].

Pemphigus vulgaris is generally seen in patients with certain HLA genotypes that generate B-cells which are responsible for the specific autoantibodies. These B-cells are activated by a complex interaction with CD4+ T helper 2 (Th2) cells and the over-activation of these Th2 cells leads to the autoantibody production that is essential for pemphigus vulgaris. IL-4 secreted by Th2 cells plays an important role in pemphigus and the humoral immune response. It promotes the production of antibodies by primed B cells and an isotype switching from IgG1 to IgG4 antibodies which have been shown to be important in the active form of pemphigus vulgaris. IL-4 also perpetuates the disease by causing naïve CD4+ T cells to differentiate into Th2 cells. The formation of autoantibodies and epitope binding is enough to cause loss of adhesions between desmosomes which leads to the separation of keratinocytes which is related to disease activity. Other components of the immune system such as complement or cytotoxic T cells are not required for the activation of the disease. Based on this pathogenesis, treatment for pemphigus is directed mainly on the prevention of antibody production and prevention of isotype switching from an IgG1 to IgG4 [15].

Pemphigus vulgaris is generally first manifested in the oral cavity and then may spread to the skin or other mucous membranes [16].

The buccal mucosa, gingiva, tongue, hard and soft palate are the sites involved. Pemphigus vulgaris lesions are initially manifested as extremely painful erosions of the oral mucosa. These painful erosions lead to impaired food uptake which causes progressive weight loss. Hoarseness of the voice may be seen in laryngeal involvement. In the early stages, oral lesions may be misdiagnosed as recurrent aphthae, erosive lichen planus, or herpetic gingivostomatitis.

In rare instances gingiva may be the only affected site. Gingival lesions which appear as extensive erythema and erosions have been termed as desquamative gingivitis, although use of the term is not usually recommended as it is descriptive and nonspecific in nature [17].

Other mucous membranes less frequently involved are the nasal mucosa, esophagus, conjunctiva, vagina, labia [18]. In the present case the patient reported a history of genital lesions.

Pemphigus vulgaris may also show involvement of the nail apparatus. In a study, nail involvement occurred in circa 13% of patients with pemphigus vulgaris. Nail alterations included paronychia, nail discoloration, periungual hemorrhages, onychorrhexis, and onycholysis [19].

Pemphigus is characterized histologically by intra-epithelial cleft formation and acantholysis [1]. The production of IgG autoantibodies against the cell membrane proteins, the desmogleins of the keratinocytes results in acantholysis [3].

Acantholysis is described as the loss of coherence among epidermal cells due to the breakdown of intercellular bridges. The cells are intact, rounded but are no longer attached to each other which results in intra-epidermal clefts, vesicles, and bullae. Acantholysis can be classified into two types: primary and secondary. In primary acantholysis, there is dissociation and disintegration of desmosomes which leads to separation of keratinocytes. This may be due to direct injury to desmosomes or due to the hereditary defects in their assembly. This is the key pathogenetic finding in pemphigus group of diseases. Secondary acantholysis describes acantholysis which is secondary to alteration or damage to the keratinocytes. This can occur by different factors like in several benign and malignant skin diseases such as herpes simplex, herpes zoster, etc. [12].

In the early stages of the disease there is wrinkling of apparently healthy skin under pressure and subsequent exposure of the lesion, which is called direct Nikolsky's sign. The primary lesion is a thin-walled bulla ranging several centimeters in size and which contains clear fluid. It develops on both normal and erythematous skin. Under pressure it releases its content through the surrounding epidermis and further increases in size. This is described as indirect Nikolsky's sign [20].

Diagnosis of pemphigus can generally be established with histopathological examination of an incisional biopsy. However, the gold standard for diagnosis is direct immunofluorescence which is more specific [17].

Immunofluorescence (IF) is a laboratory staining technique which demonstrates the presence of antibodies bound to antigens in the tissues or circulating body fluids. These methods supplement the clinical findings and histopathology for the diagnosis of immuno-bullous disorders. When the antigen reacts directly with a fluorescein-conjugated antibody specific for the material sought within the tissue, it is called as the direct technique, while indirect immunofluorescence is a two-step serological procedure for detecting the circulating antibodies in the body fluids [21].

A direct immunofluorescence test intents to detect the localization of IgG autoantibodies and C3 complement within the tissue of the pemphigus patients. A fluorescence

is characteristically seen within the intercellular regions of the epithelium. This gives a fishnet or chicken mesh appearance. It is of importance to examine the perilesional tissue under direct immunofluorescence as tissue obtained from actual lesion might give false-negative result as a result of internalization of the immune reactants on the cell surface. Indirect immunofluorescence gives an estimate of the amount of circulating autoantibodies in the patient's serum [17].

The criteria for the diagnosis of pemphigus are the presence of appropriate clinical lesion, histopathological picture of acantholysis in biopsy specimens, and identification of autoantibodies in the tissue or serum, or both [22].

Cytological examination (Tzanck smear) for rapid demonstration of acantholytic keratinocytes in the spinous cell layer is useful. Acantholytic cells have rounded central nucleus and abundant eosinophilic cytoplasm which are preferably stained by hematoxylin and eosin. Immunohistochemical examination is based on the detection of antigen-antibody complex. Markers for the detection of intercellular IgG and C3 can be used in pemphigus vulgaris. ELISA is a very sensitive and specific approach for detecting IgG anti-Dsg-1 (mucocutaneous PV) and anti-Dsg-3 (mucosal PV) autoantibodies in more than 90% of patients when employing recombinant Dsg-1 and Dsg-3. It is a quantitative method with a good correlation to clinical severity that could be useful for patient follow-up. Serological tests like immunoblotting and immunoprecipitation are also available, but due to their complexity and cost these tests are not very useful in clinical practice. They are used more for research purpose [23].

Pemphigus vulgaris can be distinguished from other similar conditions by biopsy and direct immunofluorescence. Biopsies are best taken from intact vesicles and bullae less than 24 hours old. Pemphigus vulgaris shows a suprabasilar split in histopathology. The diagnosis is confirmed by the characteristic deposition of IgG and other C3 antibodies that bind to cell surface of perilesional skin or mucosa. Other blistering diseases like bullous lichen planus and mucous membrane pemphigoid show sub-epithelial split in histopathology. Indirect immunofluorescence is helpful to distinguish pemphigus from pemphigoid patients and also aids in the follow-up of pemphigus patients [24]. Paraneoplastic pemphigus is generally seen in association with neoplasms like B-cell lymphoma, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia [25]. There may be substantial inflammatory cell infiltration of the early lesions in paraneoplastic pemphigus unlike the other forms [26].

If proper investigations are not carried out and left untreated pemphigus can be a fatal disease as there is loss of the epidermal barrier function which leads to loss of body fluids and secondary bacterial infection [27].

CONCLUSION

This article describes a case of pemphigus vulgaris and reviews the literature with a focus on its pathogenesis. Pemphigus vulgaris is an autoimmune blistering mucocutaneous disease with a genetic predisposition. The severity of the disease is variable. Oral manifestations of pemphigus vulgaris are generally the first and sometimes the only sign of the disease. A dentist should therefore be familiar with this disease and consult an oral pathologist for facilitating proper storage and transportation of the biopsy tissue in a suitable medium. This will facilitate accurate diagnosis, better treatment planning, and a good prognosis. Early diagnosis and appropriate treatment is essential to reduce the morbidity and mortality associated with this disease. Newer diagnostic tests are an adjuvant to histopathological diagnosis. A proper history and dermatological examination is a must to rule out other skin or mucosal lesions.

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Author Contributions

Priya Nimish Deo – Conception of the work, Acquisition of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Revati Shailesh Deshmukh – Conception of the work, Acquisition of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.