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# Pemphigus – A Review

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**ABSTRACT:**
Pemphigus is defined as chronic mucocutaneous autoimmune disease with the clinical feature of blisterswhich initially appear in the oral cavity and later in the skin and the oral mucosa. The dental professionals play an vital role in diagnosing the disease. Early diagnosis and treatment determine the treatment course and prognosis of the diseaseincidnce. Pemphigus has three major subtypes: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus and rare condition of IgA pemphigus. While IgG autoantibodies are characteristically raised against thedesmoglein 1 and desmoglein 3, which are cell–cell adhesion molecules found in desmosomes. Diagnosis and management is based on clinical manifestations and confirmed with histological features and immunochemical testing. The current first-line treatment is evidently systemic corticosteroids and adjuvant therapies, including immunosuppressive agents, intravenous immunoglobulin and plasmapheresis. This review highlights the major points about pemphigus its pathophysiology,histology and its treatment.

**KEYWORDS:**
Vesiculo bullous lesion,Pemphigusvulgaris,lesion,blisters,desmoglei ns,oralcavity,autoimmune.

## I. INTRODUCTION:

Vesiculobullous lesions are defined as a group of oral cavity disorders, characterized by the formation of vesicle or bullae formation. And it is uncommon to see vesicle and bullae intra orally because due to constant masticatory pressure vesicles and bullae get ruptured and it becomes severe ulcers and erosions[1].The binding of circulating autoantibodies and the induction of an inflammatory reaction in the area of target structures are lead to loss of adhesion with subsequent intra- or subepidermal blister formation[3]. Pemphigus includes a group of autoimmune blistering diseases of the skin and mucous membrane also. It is characterized by intradermal blisters and immunologically by circulating autoantibodies directed against the cell surface of keratinocytes. Pemphigus refers to a family of rare acantholytic autoimmune dermatoses of the mucocutaneous membranes in which acantholysis, or the loss of cell-to-cell adhesion, causes potentially lethal bullae and cause erosion formation. Multiple subtypes of pemphigus disease have been identified based on their distinct clinical features and pathophysiology, including pemphigus vulgaris (PV), pemphigus foliaceus (PF), IgA pemphigus, and paraneoplastic pemphigus (PNP).(ali). This is a review of the literature on etiology, pathogenesis, clinical features,pathogenesis as well as the various diagnostic criteria and the therapeutic options of Pemphigus[6].

## EPIDEMIOLOGY:

Pemphigus is the most common type of vesiculobullous lesion in Europe, the United States and Japan; it preferentially affects women than men, and most of the patients are 50–60 years of age at disease onset[7]. In pemphigus vulgaris, epidemiological studies evaluating different European regions suggest that incidence of pemphigus tends to be lower at higher latitudes than at lower latitudes[7]. Similarly to other autoimmune diseases, Pemphigus is more prevalent among women. The male/female ratio ranges from 1:1.5 in Israel and Iran to 1:4 in Tunisia. Pemphigususually occur at between 40 and 60 years of age. An increased frequency in the elderly and children has been observed[8]. An uncontrolled study demonstrated the frequency of non-Hodgkin's lymphoma and leukemias in Pemphigus cases was 50% higher than expected[8] .Ashkenazi Jews and people from India and the Middle East have higher rates risk of the disease (Pisanti et al. 1974). It is equally distributed among genders[9].

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**ETIOLOGY:**

Pemphigus results from an autoimmune process in which IgG serum antibodies are produced against normal desmosomal adhesion molecules on cell membrane of keratinocytes .The serum antibodies responsible for PV are always IgG type[10]. Numerous studies are demonstrated the contribution of genetic factors to the development of this disease, with reports of its relationship with MHC genes, and research is ongoing into other candidate genes[10].

**Classification Of Pemphigus Subtypes:**

**PEMPHIGUS VULGARIS:**

Caused by humoral autoimmune response; the three subtypes are:

Mucosal-dominant type (limited cutaneous involvement): blisters in the deep layers of the oral mucosa, owing to anti-desmoglein 3 IgG autoantibodies [7].

Mucocutaneous type (both mucosal and cutaneous involvement): blisters in the deep layers of the oral mucosa and epidermis, owing to anti-desmoglein 3 and anti-desmoglein 1 IgG autoantibodies, respectively[7].

**PARANEOPLASTIC PEMPHIGUS:**

Cutaneous type (cutaneous involvement alone): blisters in the deep layers of the epidermis owing to anti-desmoglein 1 and pathogenically weak antidesmoglein 3 autoantibodies[7].

**PEMPHIGUS FOLIACEUS:**

It is caused by humoral autoimmune response; no apparent mucosal involvement, blisters in the superficial layers of the epidermis owing to anti-desmoglein 1 IgG autoantibodies[7].

Caused by both humoral and cellular autoimmune responses; mucosal and cutaneous blisters owing to anti-desmoglein 3 and/or anti-desmoglein 1 IgG autoantibodies in combination with interface dermatitis (vacuolization of basal cells, apoptosis of keratinocytes, dyskeratotic cells (cells with abnormal keratinization) and inflammation at the dermal–epidermal junction) or severe oral lichenoid reaction owing to self-reacting T cells[7].

**PEMPHIGUS VARIANTS :**

**Pemphigus vegetans** is a variant of pemphigus vulgaris with fungoid vegetations (eroded areas which do not heal as usual but form papillomatoses growth of epidermis) characterized by anti-desmoglein 3 IgG autoantibodies[7].

**Pemphigus erythematosus**: a variant of pemphigus foliaceus with localized involvement, mainly on the face and upper part of the chest and back, mediated by anti-desmoglein 1 IgG autoantibodies • Fogoselvagem: an endemic form of pemphigus foliaceus found in rural areas in Brazil that is characterized by anti-desmoglein 1 IgG autoantibodies[7].

**Herpetiform pemphigus**: a subtype characterized by small vesicles and pustules and mainly anti-desmoglein 1 IgG autoantibodies [7].

**Drug-induced pemphigus[7].**

**PATHOGENESIS:**

Central to the pathogenesis of pemphigus is the presence of immunoglobulin (Ig) antibodies against proteins on the cell surface of the keratinocytes[5].There are cell surface components known as desmoglein proteins which are components of the desmosomes in between keratinocytes. Keratinocytes cells make up the layers of the epidermis. Particularly, in the stratum spinosum (called spinosum (Beutner and Jordon 1964) because the "spines"—which are desmosomes—can be seen between conjoining cells in this epidermal layer), desmosomes contribute to the mechanical strength and integrity of and between cells, as well as cellular differentiation (Garrod and Chidgey 2008)[9]. Antibodies to the two most common desmogleins—1 and 3—attack the epitope structure of these desmosomes and cause damage.The immunoglobulin subclass of these autoantibodies is IgG4 (Ding et al. 1999; Bhol et al. 1995). A type 2 hypersensitivity reaction takes place in which antibodies attach and destroy cell surface receptors. This leads to loss of integrity between keratinocytes in the stratum spinosum and loss of intercellular connectivity; it is referred to as acantholysis[9] . The basic pathophysiology of pemphigus is the inhibition of the adhesive function of desmogleins by autoantibodies, which leads to formation of blisters[8].

**CLINICAL FEATURES:**

**PEMPHIGUS VULGARIS:**

Pemphigus Vulgaris is a subtype of pemphigus disease is mucosal involvement in the form of painful blisters are leads to erosions that predominate in the oropharyngeal mucous membranes[5].Newer agents such as intravenous immunoglobulin therapy, rituximab, immunoadsorption using the Glo- Baffin adsorber system and immunoadsorption for rapid removal of desmoglein-reactive autoantibodies[11].

Pemphigus Vulgaris involves two main subgroups: the mucosal-dominant type, which produces mucosal erosions, but has minimal skin

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involvement, and the mucocutaneous type, which produces diffuse mucosal involvement in addition to cutaneous blisters and erosions[5]. The flaccid nature of the blisters seen in Pemphigus Vulgaris are secondary to the intraepidermal acantholysis caused by anti-desmoglein antibodies. PV lesions are often Nikolsky sign-positive, signifying that mechanical pressure applied to a blister with little force results in shearing of adjacent skin[5].

**BULLOUS PEMPHIGOID:**

Bullous pemphigoid is a subepidermal blistering skin disease that cause usually occurs in the elderly population and is characterized by large tense blisters with immunopathological findings of linear deposits of C3 and IgG at the basement membrane zone[3]. The oral lesions that tend to rupture to form painful, eroded surfaces. The common sites in the oral cavity include palate, floor iof the mouth, tongue and buccal mucosa. Desquamative gingivitis may also be observed[11]. The treatment options most frequently used are systemic corticosteroids alone or in combination with other immunosuppressive agents[11] .

**PEMPHIGUS FOLIACEUS:**

It presents as a superficial variant of pemphigus that is caused by aantibodies against desmoglein 1. Patients with Pemphigus foliaceus typically present with cutaneous lesions without mucosal involvement. Cutaneous lesions in Pemphigus foliaceus characteristically involve scattered superficial blisters that devolve into crusted erosions on an erythematous base. These thin and delicate crusted like erosions have been described as “bran-like” or resembling “cornflakes” structures

Patients with Pemphigus foliaceus complains of pain or a burning sensation in areas whereas skin lesions are present.Symptoms are typically milder than those seen in pemphigus vulgaris. Systemic symptoms are such cause fever, nausea, or vomiting, are usually absent only. Subgroup of Pemphigus foliaceus include endemic Pemphigus foliaceus, which presents with clinical symptoms similar to the idiopathic form of the disease, but it is connected to an environmental or endemic source (i.e., black flies (Simulium species)), and pemphigus erythematosus (Senear-Usher syndrome), which describes a localized variant of Pemphigus foliaceus with a malar distribution reminiscent of the “butterfly” rash of systemic lupus erythematosus . Drug-induced pemphigus can occur as Pemphigus foliaceus or Pemphigus Vulgaris secondary to medication use[5].

**MUCOUS MEMBRANE PEMPHIGOID:**

Mucous membrane pemphigoid is a chronic autoimmune subepithelial disease It primarily affects the mucous membranes ofpatients over the age of 50 years, resulting in mucosal ulceration and subsequent scarring[11]. It is also known as cicatricial pemphigoid, benign mucous membrane pemphigoid, ocular pemphigus, childhood Pemphigoid, and mucosal pemphigoid.When it affects gingiva exclusively, it is referred clinically as gingivosis or desquamative gingivitis[3]. The antigens associated with mucous membrane pemphigoid are most commonly seen in the lamina lucida portion of the basement membrane. In the oral cavity, gingiva is the most frequently affected site which presents as erythema, sloughing and occasional bullae formation. Positive ofNikolsky’s sign, which shows as a desquamation manifests clinically as desquamative gingivitis. The untreated lesions may have periods of exacerbation and remission; but lesions may also be seen for long durations with minimal improvement when treatment is administered[11].

**PARANEOPLASTIC PEMPHIGUS:**

Paraneoplastic pemphigus (PNP), is also known as paraneoplastic autoimmune multiorgan syndrome (PAMS), Clinically it represents as heterogeneous autoimmune bullous dermatosis that occurs secondary to an underlying neoplasm. Patients with Paraneoplastic pemphigus typically suffer from cutaneous lesions after the onset of mucosal lesions. The morphology of these lesions has variable presentations, including bullous pemphigoid-like, pemphigus-like, erythema multiforme-like, lichen planus-like, and graftversus-host disease-like. Progressive respiratory failure, with clinical features of bronchiolitis obliterans, is often cited as the most common cause of mortality in patients with PNP[5]. The oral mucosa shows multiple areas of erythema and diffuse irregular ulceration affecting virtually any oral mucosal surface. If the lesions remain untreated, they persist and worsen. In this area, a cicatrizing (scarring) conjunctivitis develops, similar to that seen with cicatricial pemphigoid[3].

**IgA PEMPHIGUS:**

IgA pemphigus are seen raretype of pemphigus disease defined by IgA antibodies that target one and only transmembrane adhesion proteins in the epidermis area. It has been linked to various autoimmune and inflammatory malignancies and disease states, including HIV infection, Sjogren syndrome, rheumatoid arthritis, and inflammatory bowel disease also. . Skin lesions

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in patients with IgA pemphigus initially appear as tense vesicles on erythematous bases that later transform into pustules The most frequently affected cutaneous sites, in patients with IgA pemphigus, include the flexural areas of the proximal extremities and the trunk; however, the scalp, postauricular areas, and intertriginous areas may also be affected. Most often, patients diagnosed with IgA pemphigus are not affected by systemic symptoms such as fever or weight loss[5].

**HISTOPATHOLOGICAL FEATURES:**

The diagnosis of pemphigus is confirmed by histological and immunopathologic investigations. Histopathology shows a lesional skin shows a subepidermal blister. The inflammatory infiltrate is an eosinophilic predominance. Mast cells and basophils early in the disease course. Tzanck smear shows a reactive inflammatory cells[3]. Microscopically the vesicle or bullae formation is intraepithelial[12].

The classic histological feature seen in PV is acantholysis which is the loss of cell to cell contact in the epithelial cell layers. Development of intercellular edema within the epithelial layers, dissolution of the intercellular bridges and the widening of intercellular spaces, lead to separation between the cells and the formation of blisters just above the basal cell layer[3].

There is asuprabasilar split formed by the intraepithelial vesicle or bullae just above seen on the basal layer. 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[12].

**Pemphigus vulgaris** - Suprabasilaracantholysis with retention of basal keratinocytes along the basement membrane ("tombstoning")[5].

**Pemphigus foliaceus** - Acantholysis within upper epidermis, adjacent or within the granular layer, leading to a subcorneal cleft If significant eosinophils are present, consider drug-induced pemphigus[5].

**Paraneoplastic pemphigus** - Suprabasilaracantholysis, keratinocyte necrosis, and interface change[5].

**IgA pemphigus** - Subcornealpustulardermatosis type: subcornealvesiculopustules with minimal acantholysis Intraepidermal neutrophilic dermatosis type: intraepidermalvesiculopustules with variable acantholysis[5].

**DIFFERENTIAL DIAGNOSIS:**

Autoimmune diseases: bullous pemphigoid, mucous membrane pemphigoid, lichen planuspemphigoides, anti-p200 pemphigoid, epidermolysisbullosaacquisita, linear IgA bullous dermatosis and bullous lupus erythematosus[7].

Infectious diseases: staphylococcal scalded skin syndrome, bullous impetigo and acute herpetic stomatitis[7].

Genetic diseases: Hailey–Hailey disease[7].

Others: aphthous stomatitis, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, severe drug eruption, lichen planus, graft-versus-host disease, Grover disease (transient acantholytic dermatosis), seborrheic dermatitis and subcornealpustular dermatosis[7].

**DIAGNOSTIC PROCEDURES:**

1.Nikolsky'stest[1].
2.Tzanck test[13,14].
3. Direct immunofluoresence test[1].
4. Indirect immunofluoresence test[1].
5. Salt split technique[1].
6. Elisa and western blot technique test[1].

**TREATMENT:**

Commonly used treatments areinclude corticosteroids and immunosuppressive drugs. Newer agents such as intravenous immunoglobulin therapy, rituximab, immunoadsorption using the Glo- Baffin adsorber system and immunoadsorption for removal of desmoglein-reactive autoantibodies. Patients with mild oral disease are should be treated with topicaland intra-lesional steroids. These include systemic corticosteroids, antimetabolites, antibiotics, and dapsone[11].

## II. CONCLUSION:

Pemphigus is a family of rare bullous disorders that affects the mucous membranes. Pemphigus vulgaris and Pemphigus folliaeceus are classically characterized by flaccid bullae that correlate with the histopathologic finding of acantholysis. Therapeutic options, such as anti-CD20 therapy, have improved the prognosis of patients with pemphigus and decreased morbidity which isbassociated with conventional immunosuppression[5].Corticosteroids remain the gold standard treatment. . Multicenter studies need to be incorporated to establish the common definitions and guidelines, and to determine optimal multistep algorithmic treatment regimens of pemphigus and, contribute in reducing duration of therapy and good standard of life for the patients[6].

The pemphigus group of diseases are classified as autoimmune diseases since they are manifested by the development of autoantibodies against intercellular substances. Viral infection act as predisposing factor in the production of autoantibody. It also can be aggravated by other environmental factors such as foods, infections, neoplasms, and drugs. Most commonly, drugs that belong to the thiol group, such as captopril, penicillamine and rifampicin, have been associated with the disease affects[6].

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