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# Pemphigus: Complete Literature on Symptoms, Pathogenesis & Treatment

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**ABSTRACT** *Pemphigus is a group of rare autoimmune diseases. Such diseases occur when the body's immune system attacks healthy cells. Mucous membranes are found in the mouth, nose, throat, eyes, and genitals. Pemphigus is a group of potentially life-threatening diseases characterized by cutaneous and mucosal blistering. There is a fairly strong genetic background to pemphigus with linkage to HLA class II alleles. Certain ethnic groups, such as Ashkenazi Jews and those of Mediterranean origin, are especially liable to pemphigus. Pemphigus vulgaris (PV), the most common and important variant, is an autoimmune blistering disease characterized by circulating pathogenic IgG antibodies against desmoglein 3 (Dsg3), about half the patients also having Dsg1 autoantibodies. Oral lesions are initially vesiculobullous but readily rupture, new bullae developing as the older ones rupture and ulcerate. Systemic corticosteroids remain the mainstay of therapy for pemphigus. Their use has transformed what was almost invariably a fatal illness into one whose mortality is now below 10%. Unfortunately, the high doses and prolonged administration of corticosteroids that are often needed to control the disease result in numerous side effects, many of which are serious or even life-threatening*

**Introduction**

The autoimmune bullous dermatoses fall into 2 main groups: diseases of the dermoepidermal junction, which are due to abnormalities at the interface between the dermis and the epidermis (of which pemphigoid is one example) and intraepithelial dermatoses, which include the various forms of pemphigus. n pemphigus, autoantibodies form against desmoglein.(1) Desmoglein forms the "glue" that attaches adjacent epidermal cells via attachment points called desmosomes. When autoantibodies attack desmogleins, the cells become separated from each other and the epidermis becomes "unglued", a phenomenon called acantholysis. This causes blisters that slough off and turn into sores. In some cases, these blisters can cover a significant area of the skin.(2)

Originally, the cause of this disease was unknown, and "pemphigus" was used to refer to any blistering disease of the skin and mucosa.(3) Pemphigus affects the skin and may also affect the mucosae of the mouth, nose, conjunctivae, genitals, esophagus, pharynx, and larynx; it is found mainly in middle-aged and elderly patients. Pemphigus is a group of autoimmune disorders in which there is damage to desmosomes by antibodies directed against the extracellular domains of the cadherin-type epithelial cell adhesion molecules—the desmogleins (Dsg) with immune deposits intra-epithelially, and loss of cell-cell contact (acantholysis), leading to intra-epithelial vesiculation.(4) Pemphigus is a group of autoimmune blistering diseases that may be classified into the following types(5):

- Pemphigus vulgaris, of which there several forms:
- Pemphigus vegetans
- Pemphigus vegetans of Hallopeau
- Pemphigus vegetans of Neumann
- Pemphigus foliaceus, of which there several forms:
- Pemphigus erythematosus or Senear-Usher Syndrome

- Endemic pemphigus foliaceus with its three variants, Fogo Selvagem, the new variant endemic pemphigus Foliaeus and Tunisian endemic pemphigus foliaceus
- Paraneoplastic pemphigus
- IgA pemphigus, of which there several forms:
- Subcorneal pustular dermatosis
- Intraepidermal neutrophilic IgA dermatosis
- Drug induced pemphigus

**Pemphigus Vulgaris**

Pemphigus vulgaris (PV) is the most common form and frequently involves the mouth.(6) The main importance of PV is that it typically runs a chronic course, almost invariably causing blisters, erosions, and ulcers on the oral mucosae and skin. Essentially all patients with pemphigus vulgaris have mucosal membrane erosions, and over half also have cutaneous blisters and erosions. Mucosal lesions usually predate skin lesions by many months. The bullae of pemphigus vulgaris develop in the deeper portion of the epidermis, just above the basal cell layer, while more superficial and flaccid subcorneal bullae are seen in pemphigus foliaceus.(7) Mucous membrane lesions usually appear as painful erosions. Intact blisters are rare; rupture occurs early since the mucous membranes have no keratin layer. Although scattered or extensive erosions may be seen anywhere in the oral cavity, the most common sites are the buccal and palatine mucosa. Extensive involvement may result in decreased intake of food and liquids.(8)

**Paraneoplastic Pemphigus**

Apart from PV, the other important variant affecting the mouth is paraneoplastic pemphigus (PNP), usually associated with lymphoproliferative disease, though one case with oral squamous carcinoma has been reported. Oral lesions may be the sole manifestation and have also been seen in all reported cases of paraneoplastic pemphigus.(9)

**Other Variants**

Oral lesions have been seen in less common pemphigus variants, especially in most cases with IgA pemphigus (intraepithelial IgA pustulosis [IEAP]), and in some cases of pemphigus associated with inflammatory bowel disease. In contrast, other types of pemphigus—such as pemphi-

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gus foliaceus (PF) and erythematosus and pemphigus vegetans—only rarely affect the oral mucosae.

**Pathogenesis of Pemphigus**

Inevitably, any one or more of the desomosomal proteins can be defective or damaged, and this can result in loss of cell-cell adhesion leading to the clinical result of vesiculation, erosions, or ulcers which characterize pemphigus. Pemphigus vulgaris is an autoimmune disorder in which there is deposition of mainly IgG class antibodies intercellularly as well as damage to desmosomes by antibodies directed against the extracellular domains of cadherin-type epithelial cell adhesion molecules, particularly desmoglein 3.(4)

Since oral epithelium expresses largely Dsg 3 but skin expresses Dsg 1 as well as Dsg 3, damage by antibodies to Dsg 3, as in PV, results in oral lesions at an early stage, whereas skin integrity is maintained by Dsg 1; however, if Dsg 1 antibodies appear, cutaneous lesions appear to result and the disease tends to be more severe.

The precise mechanism of the acantholysis after pemphigus IgG binds to Dsg 3 on the cell surface is unknown but may involve proteinases.(10, 11) PV- IgG causes a transient increase in intracellular calcium and inositol 1,4,5-trisphosphate concentration, and subsequent activation of protein kinase C (PKC) in cell lines. Plasminogen activation and apoptosis may also be involved. Late development of Dsg 1 antibodies in PV correlates with disease progression(12); the appearance of antibodies against Dsg1 heralds involvement of skin and mucosae other than oral.(13)

**Antigens Other Than Desmoglein**

Pemphigus autoimmunity may not be limited to antidesmoglein antibodies. Non desmoglein antibodies induce pemphigus-like lesions in neonatal mice. Non-Dsg PV IgGs also cause gross skin blisters with PV-like suprabasal acantholysis and staining perilesional epithelium in a fishnet-like pattern, indicating that the PV phenotype can be induced without anti-Dsg 3 or anti-Dsg 1 antibody.(14)

**Cellular Immunity in Pv**

Although the PV autoantibodies are pathogenic, the role of the cellular immune system in acantholysis is unclear. Although CD4 T-cells that recognize the extracellular domain of these desmosomal cadherins are present, any role for these is as yet undefined. There is only a sparse cellular infiltrate around the basement membrane zone, but autoreactive T-cell responses to Dsg 3 may be critical to the pathogenesis, since antibody production generally requires T-cell help, and the strong association with distinct HLA class II alleles suggests the involvement of CD4+ T-lymphocytes.(14)

**Diagnosis of Pemihigus**

Pemphigus defines a group of autoimmune interepithelial blistering diseases that are characterized by loss of normal cell-cell adhesion (acantholysis), and by the presence of pathogenic (predominantly IgG) autoantibodies reacting against epithelial adhesion molecules. Pemphigus is further divided in two major subtypes: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). However, several other disorders such as IgA pemphigus, IgE pemphigus, pemphigus herpetiformis, drug induced pemphigus, Senear Usher syndrome and endemic pemphigus foliaceus exist; recognized by a dermatologist from the appearance and distribution of the skin lesions. It is also commonly diagnosed by specialists practicing otolaryngology- head and neck surgery, periodontists, oral and maxillofacial surgeons and eye doctors, as lesions can affect the eyes and mucous membrane of the oral cavity. Intraorally it resembles the more common diseases lichen planus and mucous membrane pemphigoid. Definitive diagnosis requires examination of a skin or mucous membrane biopsy by a dermatopathologist or oral pathologist. The skin biopsy is taken from the edge of a blister, prepared for histopathology and examined with a microscope. The pathologist looks for an intraepidermal vesicle caused by the breaking apart of epidermal cells (acantholysis). Thus, the superficial (upper) portion of the epidermis sloughs off, leaving the bottom layer of cells on the "floor" of the blister. This bottom layer of cells is said to have a "tombstone appearance".(3)

**Treatment(15)**

Pemphigus defines a group of autoimmune interepithelial blistering diseases that are characterized by loss of normal cell-cell adhesion (acantholysis), and by the presence of pathogenic (predominantly IgG) autoantibodies reacting against epithelial adhesion molecules.[12]Pemphigus is further divided in two major subtypes: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Intraorally it resembles the more common diseases lichen planus and mucous membrane pemphigoid. Definitive diagnosis requires examination of a skin or mucous membrane biopsy by a dermatopathologist or oral pathologist. The skin biopsy is taken from the edge of a blister, prepared for histopathology and examined with a microscope. The pathologist looks for an intraepidermal vesicle caused by the breaking apart of epidermal cells (acantholysis). Thus, the superficial (upper) portion of the epidermis sloughs off, leaving the bottom layer of cells on the "floor" of the blister. This bottom layer of cells is said to have a "tombstone appearance".

Definitive diagnosis also requires the demonstration of anti-desmoglein autoantibodies by direct immunofluorescence on the skin biopsy. These antibodies appear as IgG deposits along the desmosomes between epidermal cells, a pattern reminiscent of chicken wire. Anti-desmoglein antibodies can also be detected in a blood sample using the ELISA technique. Half of people with pemphigus have mouth lesions alone during the first year but develop skin lesions later.

**Conclusion**

PV is a rare chronic autoimmune cutaneous–mucosal disease that is often diagnosed late, even when oral lesions occur. If not treated promptly, the disease has a high morbidity rate, and it may be fatal in 5% to 10% of cases. The diagnosis is confirmed through pathological examination and direct immunofluorescence testing in the healthy perilesional mucosa. The therapeutic regimen, based on corticosteroid therapy as well as adjuvant treatments, helps to decrease painful symptoms.

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