

Episode #30 – Pemphigus February 12, 2021

Pemphigus

Pemphigus is a group of rare B-cell-mediated autoimmune diseases of the stratified squamous epithelia in which acantholysis (the loss of cell adhesion) causes flaccid bullae[1] and erosions of the skin and mucous membranes (e.g., oral cavity, nose, throat, eyes, and genitals). Although rare, they are potentially life-threatening diseases that are associated with high morbidity and mortality, if not properly treated. Pemphigus is a chronic, noncontagious disorder, which is best controlled by early diagnosis and treatment.

Pemphigus is a term originally derived from the Greek word, 'pemphix', meaning bubble or blister. It describes a group of blistering disorders characterized by antibodies directed against desmoglein 1 and desmoglein 3. Desmoglein is the "glue" that attaches adjacent epidermal cells (keratinocytes) via attachment points called desmosomes. The antibodies cause acantholysis and the epidermis to become detached. Fluid then fills the clefts to form intraepithelial bullae or blisters. [1] [2] [3] [4]

Pemphigus versus pemphigoid

Pemphigoid is a rare, autoimmune blistering disease of the skin and mucous membranes, similar to pemphigus. However, pemphigoid primarily affects the skin, especially in the lower abdomen, groin, and flexor surfaces of the extremities. It may also look like hives or eczema without blisters. Pemphigoid affects the layers between the epidermis and dermis creating deep tense blisters that do not break easily. Whereas, pemphigus affects the epidermis and causes lesions and blisters that are easily ruptured. Also, the autoantibodies (anti-BPA-2 and anti-BPA-1) of pemphigoid are directed against the basal layer of the epidermis and mucosa, while the antibodies of pemphigus affect desmoglein 1 and 3.

There are two major forms of pemphigoid: pemphigoid bullous pemphigoid and cicatricial pemphigoid also known as mucosal membrane pemphigoid. The type of pemphigoid depends on which antibodies are produced and in which layer of the skin blisters occur. Pemphigoid is most common in older adults and may cause death. [5] [6] [7]

[1] Flaccid bullae – blisters that rupture easily

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Incidence of pemphigus

Pemphigus has been reported to occur worldwide. Its incidence varies from 0.5-3.2 cases per 100,000 population. Estimates of the number of new cases diagnosed each year ranges from as high as 5 per 100,000 to as low as one per million, depending upon the type of pemphigus and the ethnicity of the affected population. [8] [9]

Epidemiology of pemphigus

Pemphigus can occur at any age including young adults and children, but often affects people in middle or older age, with the highest incidence in the 5th and 6th decade of life. It affects people of all races and cultures. Pemphigus occurs approximately at the same rate in women and men. Studies have shown that some populations may be at greater risk for certain types of pemphigus. For instance, people of Jewish descent (e.g., Eastern European Jews) and those from India, Southeast Europe, and the Middle East are at greater risk for pemphigus vulgaris, while pemphigus foliaceus is more common in North America, Turkey, South America (e.g., rainforests of Brazil), and North Africa. [4] [8] [10] [11]

Etiology of pemphigus

In most cases, it is unknown what triggers this autoimmune disorder. A large body of evidence supports the role of genetic factors in pemphigus. Thus, pemphigus is considered a polygenic disease and although sporadic forms only rarely affect more than one family member, an increased prevalence of low titres of disease-associated autoantibodies in healthy first-degree relatives of individuals with pemphigus have been reported. However, genetic factors alone are insufficient for pemphigus onset, and triggering environmental factors may have a role. For example, certain drugs, especially those containing a thiol group such as penicillamine (a metal-chelating agent) and captopril (an angiotensin-converting enzyme inhibitor), might interfere with the biochemistry of the keratinocyte membrane or the immune balance and, therefore, promote acantholysis in pemphigus. Nonetheless, there are no case-control studies that corroborate this potential link. Other environmental factors under investigation include viruses (e.g., herpes simplex virus), dietary factors, and physiological and psychological stressors. [4]

Types of pemphigus

There are several different types of pemphigus depending on where the blisters form. The two main types are pemphigus vulgaris and pemphigus foliaceus. Other varieties include pemphigus vegetans, immunoglobulin A (IgA) pemphigus, paraneoplastic pemphigus, and drug-related pemphigus.

Pemphigus vulgaris (PV) – the most common type of pemphigus, accounts for more than 80% of cases. It occurs almost exclusively in middle-aged or older people. The primary lesion of PV is a soft blister filled with clear fluid that appears on healthy or irritated skin. These blisters form in the deeper portion of the epidermis, directly above the basal cell layer. The blisters are fragile and usually form in the oral cavity first,

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followed by cutaneous blisters that may come and go. Blisters are usually nonpruritic; however, ruptured blisters may be painful and limit a person's daily activities. PV does not cause permanent scarring unless there is an infection associated with the lesion. Complications due to infections can be serious and the damaging nature of the blisters can cause loss of body fluids and protein. PV is a potentially life-threatening disease, with a mortality rate of approximately 5-15%.

Mucous membranes of the oral cavity are involved in almost all cases of PV. For example, 80-90% of individuals with PV develop oral lesions and in 60% of cases oral lesions are the first sign. Lesions may occur anywhere on the oral mucosa, but the buccal mucosa is the most commonly affected site followed by involvement of the palatal, lingual, and labial mucosa. Gingiva is the least commonly affected site. However, when the gingiva is involved, desquamative gingivitis is the commonest manifestation of the disease[2].

Intact bullae are rare in the mouth because of the fragility of the lesions. The bullae easily rupture leading to painful erosions. The erosions are ill-defined, irregularly shaped, and slow to heal making eating difficult. This may lead to dehydration, malnutrition, and weight loss. Other mucosal surfaces may be involved, including the esophagus, which can further cause odynophagia[3] and/or dysphagia[4]. The erosions in the oral cavity may also spread to involve the larynx, resulting in subsequent hoarseness. In juvenile PV, stomatitis is the presenting complaint in more than 50% of cases.

If oral PV is recognized in its early stages, treatment can be initiated to prevent the progression of the disease to skin involvement. Diagnostic delays of greater than six months are common in cases of oral PV. Considering that the oral cavity may be the only site of involvement for a year or more, this may lead to delayed diagnosis and inappropriate treatment. [3] [8] [12] [13] [14]

Pemphigus foliaceus (PF) – is a less severe type of pemphigus. Blisters may form on the scalp and face first and then spread to the chest and back. Blisters do not occur in the oral cavity. Blisters are usually pruritic, nonpainful, superficial, and form crusts. PF can also cause loose, moist scales on the skin. PF has the following six subtypes: pemphigus erythematosus also known as Senear-Usher syndrome, pemphigus herpetiformis, endemic pemphigus foliaceus, endemic pemphigus foliaceus with antigenic reactivity characteristic of paraneoplastic pemphigus (but with no neoplasm), immunoglobulin A (IgA) pemphigus foliaceus, and drug-induced pemphigus foliaceus. [6] [15]

Pemphigus vegetans – is a variant of PV that occurs as a result of polymicrobial superinfection of lesions. It is characterized by vegetating lesions in the inguinal folds

[2] When pemphigus presents with gingival manifestations, the condition is considered a non-plaque-induced gingival disease classified under autoimmune diseases of skin and mucous membranes. https://aap.onlinelibrary.wiley.com/doi/10.1002/JPER.17-0163
[3] Odynophagia – pain with swallowing
[4] Dysphagia – difficulty with swallowing

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(mainly in the groin and under arms) and oral cavity and by the presence of autoantibodies against desmoglein 3. It causes hyperpigmented vegetative plaques with pustules and hypertrophic granulation tissue at the periphery of the lesions. Pemphigus vegetans is the rarest form of pemphigus comprising less than 1-2% of all pemphigus cases. [3] [16]

IgA pemphigus – the least harmful type, is caused by the IgA antibody binding to epidermal cell proteins. It may resemble PF or may appear as small pustules. [5]

Paraneoplastic pemphigus (PNP) – is a very rare type of pemphigus associated with certain forms of cancer. Painful blisters form on the vermillion of the lips and in the oral cavity, especially on the lateral borders of the tongue. Sores of the oral cavity, lips, and esophagus are almost always present and skin lesions of different types occur. PNP may affect the lungs, leading to a fatal outcome. Sometimes the diagnosis of the disease will prompt doctors to search for a hidden tumour. If the tumour is benign, the disease will usually improve if the tumour is surgically removed. [4] [5]

Drug-related pemphigus – also known as drug-induced pemphigus, is caused by some medications including penicillamine[5], ACE inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). [17]

Diagnosis of pemphigus

Diagnosis of pemphigus is based on clinical features and confirmed with histological testing, direct and indirect immunofluorescence, and enzyme-linked immunosorbent assays (ELISAs).

Clinical manifestations – chronic multiple oral ulcers, flaccid bullae, and a positive Nikolysky and/or Asboe-Hansen sign can assist with a provisional diagnosis. A positive Nikolsky sign[6] occurs when firm sliding pressure with a finger separates normal-appearing epidermis and produces an erosion in individuals with active blistering. The Asboe-Hansen sign[7] occurs when lateral pressure on the edge of a blister spreads the blister into clinically unaffected skin. However, note that these signs are not specific for pemphigus and are found in other blistering diseases.

Histopathology – lesion biopsy specimens from all types of pemphigus demonstrate acantholysis, which can progress to the formation of intraepithelial blisters. In PV, a 'tombstone effect', which is the presence of residual basal keratinocytes at the basement membrane zone, might be seen at the site of the floor of the blister. Although the epidermal blisters are classically non-inflammatory, in both PV and PF, a slight eosinophilic or neutrophilic infiltration can be occasionally seen in the upper dermis and epidermis. The features of PNP might vary depending on the morphology of the clinical lesion.

[5] Penicillamine is used to treat conditions such as Wilson's disease (an inherited condition that causes copper to build up in the body), cystinuria (an inherited condition which can lead to kidney stones), and rheumatoid arthritis**.**

[6] Nikolsky sign – a finding named after Dr Piotr Nikolsky, who first described this sign in 1896.

[7] Asboe-Hansen sign is named after Gustav Asboe-Hansen (1917-1989), a Danish physician.

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Direct immunofluorescence – the perilesional biopsy specimen is treated to detect desmoglein autoantibodies in the tissue. The presence of these antibodies indicates pemphigus. Direct immunofluorescence microscopy is the most reliable and sensitive diagnostic test for all forms of pemphigus.

Indirect immunofluorescence or antibody titre test — this measures desmoglein autoantibodies in the blood serum. It may be used to obtain a more complete understanding of the course of the disease.

Serological tests – the molecular specificity of circulating pemphigus autoantibodies can be analysed using highly sensitive and specific enzyme-linked immunosorbent assays (ELISAs) with recombinant autoantigens. The desmoglein ELISA has 96–100% sensitivity and specificity for disease diagnosis, indicating that nearly all persons with pemphigus have anti-desmoglein antibodies and that anti-desmoglein antibodies largely do not occur in healthy individuals.

Upper digestive endoscopy – maybe performed on individuals with oral lesions to determine if esophageal lesions are present. [4] [5] [8] [12] [18] [19] [20]

Differential diagnosis

Differential diagnosis may include:

- Autoimmune diseases – bullous pemphigoid, mucous membrane pemphigoid, lichen planus pemphigoides, anti-p200 pemphigoid, epidermolysis bullosa acquisita, linear IgA bullous dermatosis, and bullous lupus erythematosus
- Infectious diseases – staphylococcal scalded skin syndrome, bullous impetigo, and acute herpetic stomatitis
- Genetic diseases – Hailey-Hailey disease
- 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 subcorneal pustular dermatosis [4]

Morbidity and mortality of pemphigus

PV and PF are associated with considerable morbidity and mortality. Mortality has substantially decreased to 1.6–12% since the regular use of corticosteroids and adjuvant immunosuppressants was introduced, but is approximately 2–3-fold higher in individuals with pemphigus than in the general population. The most frequently reported causes of death include respiratory tract infections, septicaemia, cardiovascular disease, and peptic ulcer disease. Besides corticosteroid-related comorbidities (e.g., infections, Cushing syndrome [hypercortisolism], adrenal insufficiency, and osteoporosis), pemphigus has been correlated to other autoimmune diseases, such as autoimmune thyroid diseases (e.g., Graves disease and Hashimoto thyroiditis), rheumatoid arthritis, and type 1 diabetes mellitus.

The prognosis of PNP is poor. Mortality is as high as 90%, with 1-year, 2-year, and 5-year overall survival rates of 49%, 41%, and 38%, respectively. The disease is often

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fatal owing to the presence of underlying neoplasms, such as non-Hodgkin lymphoma, chronic lymphocytic leukaemia (both of which account for about two-thirds of paraneoplastic pemphigus-associated neoplasms in Europe, Japan, and the United States), Castleman disease (the most common paraneoplastic pemphigus-associated neoplasia in Chinese and paediatric patients), thymoma, epithelial carcinoma or other malignancies, but mortality might also result from associated infections or bronchiolitis obliterans. [4]

Treatment of pemphigus

Treatment includes steroids to reduce inflammation, immunosuppressive drugs, immunotherapy, and antibiotics to treat associated infections. Treatment may consist of three phases: control, consolidation, and maintenance. The control phase involves intense therapy until no new lesions develop. In the consolidation phase, therapy continues until existing lesions have cleared. In the maintenance phase, medications are gradually reduced to the lowest possible dose that prevents the development of new lesions.

Different medications may be used alone or in combination depending on disease severity. Medications may include:

- Corticosteroids – topical corticosteroids (e.g., creams, rinses, custom-made trays for localized application) may be enough to manage mild pemphigus; however, many individuals need systemic oral corticosteroids.
- Immunosuppressants – e.g., azathioprine, methotrexate, mycophenolate, cyclophosphamide, and cyclosporine.
- Rituximab – a monoclonal antibody targeted against $CD20^+$ B cells (the cells responsible for making pemphigus antibodies). It is administered via injection and may be used if other medications are causing serious side effects or are ineffective. Its effects last six to nine months.

Other therapies include:

- Intravenous immune globulin (IVIg) – a blood product prepared from the pooled plasma of donors that may be given over the course of several days. The mode of action of IVIg is not well understood although the general thought is that IVIg helps to eliminate circulating immune complexes.
- Plasmapheresis – also called plasma exchange, is a therapy that removes the responsible antibodies from the blood. [10] [21]

Low level laser therapy

Low level laser therapy (LLLT)[8] or photobiomodulation therapy has been investigated for the management of pemphigus lesions because of its anti-inflammatory, analgesia, and tissue repair effects. [22]

Minicucci et al. (2012) reported two cases of PV where systemic treatment combined with LLLT for the oral and cutaneous lesions were administered. Prompt analgesic

[8] Refer to Episode #24 – FAQs for more information on low level laser therapy

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effect in the oral lesions and accelerated healing of the oral and cutaneous lesions was observed. The authors proposed that LLLT should be considered as an adjuvant therapy in oral and skin disorders in individuals with PV. [23]

Pavlic et al. (2014) reviewed the available literature on the effects of LLLT in the treatment of pemphigus. The authors concluded that LLLT was efficient in the treatment of recalcitrant oral pemphigus lesions, either used alone or as an adjunct to conventional treatment modalities. However, they stated that these results should be interpreted with caution since there were no solid evidence-based proofs to provide the guidelines for the treatment of PV with LLLT. They recommended the need for further long-term randomized controlled clinical studies in order to give any solid recommendations on the use of LLLT in the treatment of PV. [24]

Yousef et al. (2017) conducted a pilot study to evaluate the efficacy of LLLT in the treatment of pemphigus cutaneous lesions. Ten patients with pemphigus vulgaris were enrolled in the trial. The criteria for inclusion in the study were a minimum of two unresponsive ulcers or erosions after undergoing a minimum of one-month treatment for pemphigus with prednisolone and azathioprine. The participants underwent laser and routine treatments simultaneously on one side of their body while the other side did not receive LLLT. The number of laser therapy sessions was 3 sessions per week for 2 weeks. The lesions that received laser therapy demonstrated a decrease in mean qualitative wound score as compared to routine therapy. The researchers concluded that application of LLLT simultaneously with conventional therapy could result in improved healing of ulcers especially in patients who do not respond to conventional treatment or who are suffering from recalcitrant lesions. [25]

Andrade Pontes et al. (2020) reported a clinical case of a female patient with severely painful erosions on the lip and intraoral mucosa as a result of pemphigus vulgaris. LLLT was utilized, which resulted in improvement in pain and regression of the oral lesions. The authors concluded that LLLT effectively treated the oral lesions of pemphigus vulgaris, reduced pain, and improved the patient's quality of life. [21]

Oral health considerations[9]

Considerations are based on severity of the lesions and whether or not the condition is in remission.

- Oral lesions can interfere with proper nutrition intake impacting wound healing. A balanced diet, avoiding spicy, hot, or abrasive foods, is recommended to minimize trauma to the tissues. Hydration is important.
- Painful lesions impact oral self care, combined with a soft diet can lead to an increased incidence of dental caries and periodontal disease. Frequent appointments are necessary to assess the oral condition, provide gentle debridement, and reinforce meticulous daily homecare (e.g., utilizing ultrasoft toothbrushes, mild flavoured toothpastes without sodium lauryl sulfate [SLS], alcohol-free mouth rinses).

[9] Refer to CDHO Pemphigus Factsheet for information on oral management implications https://www.cdho.org/Advisories/CDHO_Factsheet_Pemphigus.pdf

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- Oral prophylaxis should be performed prior to initiation of systemic or topical therapy.
- Monitor for effects of corticosteroid and immunosuppressive treatment (e.g., oral candidiasis) and treat accordingly.
- Hand scaling is recommended to cause minimal disruption to the tissues.
- Polish teeth with nonabrasive pastes, avoid harsh abrasives and air polishing. [20] [26] [27] [28] [29] [30]

Take home messages

Timely recognition and therapy of oral lesions is critical as it may prevent cutaneous involvement. If treatment is instituted promptly, the disease is easier to control and the potential for an early remission of the disorder is improved.

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Client resources

Canadian Skin Patient Alliance
https://www.canadianskin.ca/en/

Canadian Pemphigus and Pemphigoid Foundation
http://pemphigus.ca/

International Pemphigus & Pemphigoid Foundation
https://www.pemphigus.org/

RareConnect
https://www.rareconnect.org/en

Genetic and Rare Diseases Information Center (GARD)
https://rarediseases.info.nih.gov/guides/pages/96/patients-families-and-friends

National Institute of Arthritis and Musculoskeletal and Skin Diseases – Overview of Pemphigus
https://www.niams.nih.gov/health-topics/pemphigus/advanced

Additional Resources

Pemphigus, CDHO factsheet, June 20, 2017
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