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Oral blistering diseases

Blisters arising in the mouth may be due to the autoimmune diseases, pemphigus and bullous pemphigoid. These are characterised by autoantibodies directed against the adhesion molecules of the skin and mucous membranes.

Oral pemphigus

Pemphigus is a term originally derived from the Greek term, *pemphix*, meaning bubble or blister.

It describes a group of blistering disorders characterized by antibodies directed against intercellular substance, which is found between keratinocytes. Keratinocytes are the cells that make up epidermis (skin) and epithelium (mucous membrane). The antibodies cause the keratinocytes to separate from each other. Body fluid fills the clefts to form blisters.

There are three main types of pemphigus:

- [Pemphigus vulgaris](#)
- [Pemphigus foliaceus](#)
- [Paraneoplastic pemphigus](#)

Pemphigus vulgaris accounts for about 70% of cases, with an incidence of about 0.1 to 0.5 per 100,000 of adult population. Pemphigus vulgaris is more common in patients of Ashkenazi Jewish descent and those of Mediterranean origin. Men and women are equally affected, with the mean age of onset being 50 to 60 years. However it may also affect children and the elderly.

Clinical presentation

Pemphigus vulgaris involves mucosal surfaces in 50–70% of patients. Oral vesicles (small blisters) are rarely seen intact as they break down rapidly and become shallow irregular erosions (sores) that later ulcerate. Widespread erosions may be seen, particularly over the buccal mucosa (inner aspect of cheeks) or palate. Involvement of the gums can lead to a form of desquamative gingivitis. Pemphigus may also affect other mucosal surfaces i.e. the nose, eyelids, genitals and anus.

Paraneoplastic pemphigus typically first affects the lips but may result in oral erosions or lichenoid lesions (these are lesions that resemble oral lichen planus). This type of pemphigus is due to antibodies produced by a benign or malignant tumour. The most common benign tumour associated with paraneoplastic pemphigus is thymoma, followed by Castleman tumour, a rare and complex type of lymphoma. The most common associated malignant tumour (cancer) is non-Hodgkin lymphoma, followed by chronic lymphocytic leukemia.

What is the cause of pemphigus?

The cause of pemphigus remains unknown. However, there is a genetic predisposition. In 1964, autoantibodies against keratinocyte surfaces were described in patients with pemphigus. Certain major histocompatibility complex (MHC) class II molecules, in particular alleles of human leukocyte antigen DR4 (DRB1*0402) found in Jews of Eastern European origin, and human leukocyte antigen DRW6 (DQB1*0503), are common in patients with pemphigus.

Pemphigus sometimes occurs in patients that suffer from other autoimmune diseases, particularly myasthenia gravis and thymoma.

Pathological features

The characteristic histological findings in a [biopsy](#) of pemphigus are:

- A split within the epidermis above the basal layer
- Rounded up and floating keratinocytes (acantholysis)
- Basal cells separated from one another and standing like a row of tombstones on the floor of the blister
- Basal cells remaining attached to the basement membrane

Direct immunofluorescence of the biopsy reveals immunoglobulin IgG and complement factor C3 binding to the cell surface in the mid and lower or entire epidermis.

Biopsy findings can help differentiate pemphigus vulgaris from pemphigus foliaceus, in which the clefting occurs higher up in the epidermis.

The clefting arises because the antibodies bind to proteins called desmogleins, breaking up the plates that stick the keratinocytes together (these are called desmosomes). This results in the keratinocytes separating from each other (acantholysis).

- Desmoglein-3 is the primary target antigen in pemphigus vulgaris
- Desmoglein-1 is the exclusive target antigen in pemphigus foliaceus

The autoimmune antibodies immunoglobulin g1 (IgG1) and immunoglobulin G4 (IgG4) can also be detected by a skin antibody blood test (indirect immunofluorescence). It is positive in 80–90% of patients with active pemphigus. Disease activity correlates with antibody titre (concentration) in most patients.

Management of pemphigus

Pemphigus has been associated with a high mortality and morbidity. Conventional therapy consists of high-dose [systemic corticosteroids](#), immunosuppressive agents and [intravenous immunoglobulin](#). Rituximab and epidermal growth factor have also been used effectively.

The advent of systemic corticosteroids reduced the mortality rate from 70 – 100% to a mean of 30%. The most common causes of death in pemphigus nowadays are adverse reaction to drugs and infections.

Oral pemphigoid

Pemphigoid is characterized clinically by the presence of large, tense blisters or bullae. These arise under the epidermis (subepidermal).

Three major forms exist:

- [Bullous pemphigoid](#)
- [Mucous membrane or cicatricial pemphigoid](#)
- [Gestational pemphigoid](#)

These diseases have clinical, pathological and immunological similarities but the exact relationship to each other is not fully defined.

Bullous pemphigoid

Bullous pemphigoid is a chronic, autoimmune, subepidermal, blistering skin disease that may involve mucous membranes. It is by far the most common autoimmune blistering disease and mostly affects the elderly, although it may occur at any age including during childhood. Men and women of all races are equally affected.

Clinical presentation

Blisters (bullae) may be preceded for days, weeks or months by:

- Red areas
- Dry eczema-like patches
- Urticarial lesions

The blisters may be localised to one site or generalised. They may contain clear (serous) or blood-stained (haemorrhagic) fluid. They are usually scattered but may form arcs, circles and snake-like patterns. The blisters may rupture to form erosions, but these occur less easily than in pemphigus.

The blisters most often arise in the armpits, inner thighs, groins, abdomen, elbow creases and lower legs. Usually the only mucous membrane affected is the mouth in 10–35% of patients. Pemphigoid is generally less severe and painful, and less easily ruptured than pemphigus.

Bullous pemphigoid can persist for months or years with periods of spontaneous remission.

What is the cause of bullous pemphigoid?

The cause of bullous pemphigoid is not known. Genetic factors may play a part, as the human leukocyte antigen (HLA) haplotype, DQB1*0301, is more prevalent in patients with bullous pemphigoid.

Direct immunofluorescence of a skin biopsy in bullous pemphigoid reveals antibodies in a fine linear distribution along the basement membrane just underneath the epidermis. These IgG4 autoantibodies are directed against the hemidesmosomal antigens BP230 (BPAg1) and BP180 (BPAg2). Hemidesmosomes are the structures that stick the basal cells to the underlying dermis.

The autoantibody reaction activates inflammatory mediators and complement factors. These attract inflammatory cells that release enzymes called proteases, which degrade hemidesmosomal proteins and lead to blister formation. The inflammatory cells at the basement membrane usually include eosinophils.

The management of bullous pemphigoid

Treatment depends on the extent and severity of the skin or mucous membrane disease. Once the disease develops, it tends to progress. Spontaneous remission is rare.

Most patients are managed with [systemic steroids](#) in varying doses. Because these may be required for months or years and have serious side effects, other agents may also be prescribed. These include:

- [Topical steroids](#)
- [Tetracycline](#) / nicotinamide
- [Azathioprine](#)
- [Cyclophosphamide](#)

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Related information

References:

On DermNet NZ:

- [Blistering skin conditions](#)
- [Pemphigus vulgaris](#)
- [Pemphigus foliaceus](#)
- [Paraneoplastic pemphigus](#)
- [Bullous pemphigoid](#)
- [Mucous membrane or cicatrical pemphigoid](#)
- [Gestational pemphigoid](#)

Other websites:

Books about skin diseases:

See the [DermNet NZ bookstore](#)

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DermNet does not provide an on-line consultation service.

If you have any concerns with your skin or its treatment, see a [dermatologist](#) for advice.

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