Pemphigus

📸§ pemphigus, 📸§ pemphigus01, 📸 pemphigus02, 📸¬ pemphigus03, 📸¬ pemphigus04

Before the introduction of corticosteroids, pemphigus was uniformly fatal. Today it is treatable, but significant management problems relate to appropriate early diagnosis and control of the adverse effects of immunosuppression.

There are 2 main types of pemphigus:

- pemphigus vulgaris
- pemphigus foliaceous.

In pemphigus foliaceous, IgG antibodies act against **desmoglein 1 (Dsg1)**
In pemphigus vulgaris the attack is on **desmoglein 3 (Dsg3) +/- desmoglein 1 (Dsg1)**.

These antibodies to desmosomal proteins ar**e causal**: if you inject them into another host, they cause blisters. They are not an epiphenomenon.

To understand the clinical features of these two diseases we need to understand the biology of these desmogleins (key desmosomal proteins), in particular three facts:

1. Different desmogleins co-expressed in the same cells can compensate for the loss of the other.
2. The pattern of expression of Dsg1 and Dsg3 is different within skin.
3. The pattern of expression of Dsg1 and Dsg3 differs between skin and mucosae.

Dsg1 is present throughout skin, but is expressed most highly in the superficial layers. By contrast, Dsg3 is expressed in skin in the basal and immediately suprabasal layers, but **not** in the superficial layers. If there are antibodies to Dsg1, as you see in pemphigus foliaceous, inactivation of Dsg1 leads to superficial blisters. This is because Dsg1 is the only one of the two Dsg expressed in the superficial layers of skin, and so **Dsg3 cannot compensate**.

If you have antibodies to Dsg3 only, then Dsg1 in skin can compensate for its lack of function: there is little or no blistering of skin. If however you have antibodies to Dsg1 and Dsg3 then blisters of skin result, and the result is pemphigus vulgaris: there is nothing left to do the 'compensating'.

The situation in the mucosae is different.

In the mucosae, there is very little Dsg1 expression and Dsg3 is expressed in **all layers**. Antibodies or inactivation of Dsg1 therefore produces no mucosal phenotype (pemphigus foliaceous). However, antibodies to Dsg3 will cause mucosal blisters (📸§ mucosal disease) and, as discussed above, few or no skin blisters (mucosal dominant pemphigus vulgaris). However if you have antibodies to both Dsg1 and Dsg3 then you will have mucosal and extensive skin disease (mucocutaneous pemphigus vulgaris)

Note: some of the images in dermnet.com are wrong: for instance images labelled foliaceous show mucosal disease (incorrect)

Pemphigus of either type can occur at any age but it is most common in middle age. It is more common in some genetic ancestral groups such as certain Jewish populations.

Fogo selvagem— a rate variant of pemphigus foliaceous
There is a fascinating epidemiological pattern of pemphigus foliaceous seen in Brazil which suggests that arthropods may be important as a vector for an infective agent that precipitates the disease. This disorder is known as fogo selvagem (flaming fire). The name gives you an idea of one of the main symptoms of pemphigus foliaceous, burning pain.

Clinical Features of pemphigus

Because blisters in both pemphigus foliaceous (and vulgaris) are superficial, they are easily missed because they break easily (see 📸§ image). Patients may just present with erosions and crusts and be misdiagnosed as having eczema (📸§ image). This is a particular problem in pemphigus foliaceous, because the blisters are even more superficial that in vulgaris.

Mucosal involvement in pemphigus vulgaris may involve the eyes, mouth, pharynx,larynx, oesophagus as well as the genitalia.

The **Nikolsky sign** is usually positive: if you rub apparently normal skin, a blister develops.

In pemphigus foliaceous the rash is common on the scalp, the face, chest and upper back. It is easily misdiagnosed as seborrhoeic dermatitis (because there is scaling, crusting, redness but no obvious blisters).

Diagnosis of pemphigus

- biopsy of the blister will show acantholysis (separation of keratinocytes from each other)
- a peri-lesional biopsy will confirm IgG intercellular staining within the epidermis (the exact location depends on whether it is pemphigus foliaceous or vulgaris). 📸† Here is an image of positive vulgaris IF.
- Indirect immunofluorescence against circulating antibodies are usually present and correlate to some extent with disease activity.
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Treatment of pemphigus

- Large doses of systemic corticosteroids are required and immunosuppressive sparing agents such as azathioprine or mycophenolate are frequently used.
- Drug treatment may be tapered off as circulating antibodies decline.
- Patients who do not respond to the above may be treated with intravenous immunoglobulin, anti CD-20 antibodies (anti B cells) or cyclophosphamide.
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Pemphigus like syndromes can present as part of a **paraneoplastic phenomenon.** They are characterised by an atypical clinical course and a failure to respond to conventional treatment.

Dermatologists have various neuroses about missing a diagnosis (or at least this one does…….). One hazard with blistering disorders, especially in pemphigus, is to not realise there is a primary blistering disorder, because scaling and crusting predominate. Your (sometimes) smug colleague tells you a week later: "remember that patient you saw last week and who you thought had 'mild eczema, Prof?". "I've admitted them, and started them on high-dose steroids, pending the results of the immunofluorescence." Duh!