Pemphigus foliaceus: review of clinical signs & diagnosis in dogs and cats

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Classification and clinical signs of pemphigus in dogs and cats

Pemphigus can broadly be classified into superficial and deep forms

Pemphigus foliaceus
The most common autoimmune skin disease of dogs and cats.
Lesions progress from erythematous macules to papules to pustules to crusts.
N.B. Compared to pyoderma, PF pustules are usually more numerous, larger, may have irregular, highly erythematous borders and may coalesce.
Distribution is usually facial/pedal or may be generalised (Figure 1).

Figure 1 - Lesion distribution patterns in pemphigus foliaceus

Pemphigus erythematosus
Probably a photosensitive form of pemphigus foliaceus primarily restricted to the face.

Panepidermal pustular pemphigus (pemphigus vegetans)
May be a variant of PF, although the pustules may be deeper.
Lesions are similar to PF but may become verrucose.
Lesions are clinically the same as facial PF.

Pemphigus vulgaris
The rarest form of pemphigus.
Lesions are erosions and ulcers of the muco-cutaneous junctions and oral cavity. Vesicles are rarely seen due to the fragility of the canine epidermis. If they are seen, it is likely to be in the oral cavity.

Paraneoplastic pemphigus
Rare form of pemphigus.
Has been seen in association with tumours such as thymic lymphosarcoma, mammary carcinoma, Sertoli cell tumour.
Histologically, the lesions can show features of both PV and erythema multiforme.
**Drug-induced pemphigus**
Some cases of PF are thought to have been induced by drugs.

**Pemphigus of chronic disease**
Some authors believe that dogs that have suffered from other skin diseases for prolonged periods of time (allergy, chronic pyoderma) may develop pemphigus later in life. There is currently no evidence to support this anecdotal observation.

**Diagnosis of pemphigus**
As with other skin diseases, the diagnosis of autoimmune skin diseases relies on history, physical examination and diagnostic tests (cytology and histopathology).

**History**
The history of dogs and cats with autoimmune skin diseases is usually non-specific. Due to the severity of many of these diseases, owners usually present their animals as soon as the disease appears. With some autoimmune skin diseases such as pemphigus foliaceus, the lesions may appear in waves and go through periods of waxing and waning. Systemic manifestations such as lethargy and anorexia are variable. Some people believe that dogs that have suffered from recurrent skin disease (especially allergic disease and pyoderma) for a long time can ultimately develop a form of pemphigus foliaceus. A true cause and effect has yet to be proven.

**Physical examination**
The main objectives of the physical examination are to determine:
1. The nature of the skin lesions – are they superficial and pustular/crusting or are they deep and erosive/ulcerative.
2. The distribution of the skin lesions – are they confined to certain body regions such as the face or mucocutaneous junctions or are they generalised.
3. Are there any other abnormalities such as joint swelling, anaemia etc.

Based on the physical examination alone, it is possible to draw up a list of differential diagnoses that includes or excludes some of the above auto-immune skin diseases, as well as other, non immune-mediated diseases. However, without further diagnostic tests, it is not possible to make a specific diagnosis.

**Diagnostic tests**
The two most useful tests in the diagnosis of autoimmune skin diseases are cytology and histopathology.

**Cytology**
Cytological examination should be performed in all cases of suspected autoimmune skin disease. In cases of pemphigus foliaceus (and the clinically similar variants), cytology can be virtually diagnostic because of the presence of acantholytic keratinocytes (Figure 2). In all autoimmune skin diseases, cytology can help to confirm the presence of secondary bacterial infection or other differential diagnoses.
Biopsy and Histopathology

Although cytology is a very useful test that can be performed in the clinic, it is essential to biopsy all cases of suspected autoimmune skin diseases. With the appropriate samples it may be possible to make specific diagnoses of pemphigus foliaceus, pemphigus erythematosus, panepidermal pustular pemphigus, pemphigus vulgaris, and cutaneous lupus. It is not possible to distinguish between bullous pemphigoid, mucous membrane pemphigoid, linear IgA bullous dermatosis and epidermolysis bullosa acquisita on histopathology.

When taking biopsies from autoimmune skin diseases, the following tips may help to get diagnostic results:

- Biopsy punches are acceptable for the majority of lesions but ellipse biopsies may be preferable for large bullae or ulcers.
- Always take at least five biopsies.
- For pustular/crusted lesions, try and biopsy pustules. If none are present, biopsy papules or macules – they may contain microscopic pustules. If you have to biopsy crusted lesions, make sure that the crusts are submitted along with the skin.
- If you suspect pemphigus foliaceus but there are no primary lesions, clip the fur off an area of skin and wait for 24-48 hours. New lesions may develop in the clipped area (or other areas).
- If ulcers are biopsied, sample the junction between normal and ulcerated skin. Make sure that the biopsy is orientated so that the pathologist sections the skin the right way.
- If there are ulcerative lesions, rub an unaffected area of skin with a pencil eraser for about a minute. If there is dermo-epidermal weakness, this can artefactually create a new lesion to biopsy.
- If the first set of biopsies are non-diagnostic but you still suspect an autoimmune disease, biopsy the animal again.

Histopathological changes in the skin

The key histopathological findings of the various diseases can be summarised as follows:

- Pemphigus foliaceus – Intracorneal or subcorneal pustules containing neutrophils and acantholytic keratinocytes; surface neutrophilic crusts containing degenerated acanthocytes.
- Pemphigus erythematosus – Epidermal changes as for pemphigus foliaceus, but with lichenoid or interface changes at the dermo-epidermal junction. These may include hydropic degeneration of basal cells, basal cell apoptosis, abnormal appearance of the basement membrane and a sub-epidermal infiltrate of mononuclear cells, mainly lymphocytes.
- Pemphigus vulgaris – Suprabasilar acantholysis leads to cleft formation above the basal cell layer of the epidermis. The basal cells may remain attached to the basement membrane like a row of tombstones.
- Paraneoplastic pemphigus – this disease has features of both PV and erythema multiforme i.e. suprabasilar cleft formation with apoptosis at multiple layers throughout the epidermis.

Other tests that should be performed when a skin disease is suspected to be auto-immune include fungal culture (in suspected cases of PF), bacterial culture and sensitivity (in suspected cases of PF and if rods are seen on cytology), skin scrapings to rule out demodicosis, and a routine haematology and biochemistry panel to allow monitoring of therapy and to look for evidence of systemic involvement.
Immunofluorescence and immunohistochemistry

These techniques allow detection of the autoantibodies directed against skin targets. However, they are not widely available in commercial histopathology labs, although they have been used extensively in research. The principles underlying these tests are illustrated below.

Direct immunofluorescence

1. Skin section taken from a dog with autoimmune skin disease
2. Tissue section
3. Autoantibody or complement components to be detected (already bound to diseased skin)
4. Specific antibody labelled with fluorescent marker is added
5. Fluorescent marker visualised under UV light microscope

Indirect immunofluorescence

1. Skin, lip, oesophagus section taken from a normal dog
2. Tissue section
3. Serum from a dog with autoimmune skin disease containing autoantibodies to skin components is added
4. Specific antibody labelled with fluorescent marker is added
5. Fluorescent marker visualised under UV light microscope

Immunohistochemistry

1. Tissue section taken from an animal with skin disease (autoimmune or tumour)
2. Tissue section
3. Autoantibody or tumour-specific protein to be detected (already bound to, or part of, diseased skin)
4. Specific antibody labelled with enzyme marker is added
5. Enzyme reaction with substrate allows visualisation of specific proteins under microscope