Proceedings of the 33rd World Small Animal Veterinary Congress

Dublin, Ireland - 2008

Next WSAVA Congress:

Reprinted in IVIS with the permission of the Congress Organizers
Autoimmune dermatoses (AIDs) are a group of infrequent but not uncommon skin disorders. The origin of an auto-immune disease normally arises from a breakdown in self tolerance due to interference with normal control mechanisms. Traditionally, the basic immunological defects best recognized include:

- malfunction of T suppressor cells
- by-passing of T suppressor cell function
- inappropriate activation of polyclonal B cells
- auto-antigen modification, e.g. trauma to tissues etc
- cross-reacting antigens e.g. drugs/microbial antigens.

However, small groups of researchers have made some novel findings in relation to disease pathogenesis and treatment options over the last 10 years. Most of this work has concentrated on determining the antigens involved and the response to novel therapeutic strategies. The most recent information is highlighted in italics in the text below.

Areas of on-going debate in disease pathogenesis include:

- What is the role of allergy in AIDs e.g. flea allergic dermatitis?
- What is the true incidence of drug-induced disease?

**Pemphigus complex**

There are four distinct clinical forms of disease. The pathogenesis is thought to involve an auto-antibody produced to the glycocalyx of the keratinocyte. The antigens involved are heterogeneous, and may differ from one form of the disease to the next. When antibody binds to the antigen on the cell surface, it is thought to internalise and bind with intracellular lysosomes. This leads to release and activation of a specific proteolytic enzyme which diffuses extracellularly and breaks down the glycocalyx. There is then a breakdown of the bridging network between neighbouring cells, with the development of micro-vesicles or blisters. The vesicle represents fluid accumulation, with sloughed off keratinocytes. Histologically, the lesion is referred to as acantholysis and the cells are called acanthocytes. It is a Type II hypersensitivity reaction, with no inflammatory cells or complement activation being required. Additional factors may be involved, particularly in a predisposing role, e.g. ultraviolet light and drug reactions etc. A genetic predisposition is seen in some breeds.

**Clinical signs**

Some signs are common to all four different forms of pemphigus and relate to the initial lesion type.

Differences do exist in lesion location, severity and occasionally in the type of lesion. Pemphigus complex is a vesico-bullous, erosive to ulcerative skin disease. The vesicles, which are common in humans, are rarely seen in dogs/cats due to the thinness of the canine/feline epidermis as compared to humans.

**P. vulgaris**

One of the more common forms seen clinically. Can occur at any age. The typical lesions are seen in the mouth and at mucocutaneous junctions, although lesions can occur elsewhere on the skin. The erosions/ulcers may show evidence of epidermal collarettes, and may be secondarily infected. The nikolsky sign may be present. Pruritus and pain are variable. The main cutaneous antigen targeted in canine P. vulgaris is Desmoglein 3. Circulating autoantibodies to this fraction are commonly found in affected dogs (as well as in dogs with paraneoplastic pemphigus). More recent studies have demonstrated that the autoantibodies in P. vulgaris up-regulate the expression of c-myc (a pivotal proto-oncogene) that subsequently predisposes to increased cell proliferation. This new information opens the way to new treatment strategies that modulate c-myc signalling cascades.

**P. foliaceus**

Rare form. May represent a benign form of P.vulgaris (similar sites). The lesions, however, are somewhat different in that they become verrucose or warty in appearance, and are frequently secondarily infected. Again, pruritus and pain are variable. The main cutaneous antigen targeted in canine P. vegetans is Desmoglein 1, not Desmoglein 3 as in humans.

**P. vegetans**

Probably the form most commonly seen clinically. Certain breeds appear predisposed. Lesions may consist of vesicles/bullae or more commonly erosions/ulcers. These lesions quickly become secondarily infected. The common sites include the body trunk (particularly hind limbs), face, ears, feet (including pads), mucocutaneous junctions and nasal region. It is normally not seen in the oral cavity. If severe, anorexia and depression may develop. Desmoglein 1 is only a minor autoantigen in P. foliaceus. The main autoantigen remains unknown at this point in time.

**P. erythematous**

Not as common. It may represent a benign form of P.foliaceus. Lesions are commonly seen on face (nose, eyes) and ears. German shepherds and collies are over-represented. The clinical signs are similar to before, but nasal/ocular depigmentation and erosion/ulceration are often dominant features.
Diagnosis
The diagnosis of the various forms of pemphigus rests on a combination of the following:
- History and clinical signs
- Biopsy - lesions of acantholysis etc.
- Immunofluorescence studies - can demonstrate the antibody in situ in some cases. Can also demonstrate circulating autoantibodies using indirect methods on substrates such as salt-split canine skin or bovine oesophagus.
- Routine bloods are usually unrewarding.

Bullous pemphigoid
Vesico-bullous, ulcerative skin disease, where the initiating pathology is based at the level of the dermo-epidermal junction, i.e. the basement membrane (b.m.) zone. The auto-antibody attacks this junction and thus the vesicles or bullae develop sub-epidermally. Another difference between this and pemphigus complex is that complement fixation and neutrophil/eosinophil chemo-attraction are involved in the pathogenesis of bullous pemphigoid.

Clinical signs
Certain breeds appear predisposed, e.g. collies. Common sites include the mouth, mucocutaneous junctions and different parts of the body trunk (axilla and groin in particular). Many cases have lesions in the mouth. The foot-pads may be involved. Clinical signs are similar to those for the pemphigus complex, but ulceration may be more severe.

Diagnosis
- History and clinical examination
- Biopsy - sub-epidermal lesions
- Immunofluorescence tests - direct immunofluorescence testing for antibodies and complement at the BM zone. Indirect methods attempted as well.

Systemic lupus erythematous (SLE)
The aetiology of this disease appears to be multifactorial. Auto-antibodies are formed against numerous different cell types, not just skin. There are many theories on how skin lesions arise in this condition. One of the more popular theories suggests that UV light penetrates down to the basement membrane cells, and alters the keratinocyte surface to allow expression of previously hidden antigens (in cytoplasm or nucleus). Predisposed breeds include German shepherd, collies and shelties.

Clinical signs
Somewhat variable compared to before; systemic and cutaneous. Vesicles/bullae and ulcers seen on face, ears, nose, distal limbs and feet. Secondary pyoderma and seborrhoeic skin disease are occasionally present. Pruritus is variable, but on occasions can be marked. There may be ulceration or hyperkeratosis of the food pads.

Diagnosis
- History and clinical signs
- Haematology/biochemistry and urinalysis e.g. anaemia, thrombocytopenia, proteinuria etc.
- Serology test for ANA (anti-nuclear antibodies)
- LE (lupus erythematosus) cells on smears
- Skin biopsy - interface dermatitis
- Immunofluorescence tests - antibodies and complement deposited at BM zone

Discoid lupus erythematosus (DLE)
Considered by many authors to be a benign form of SLE. There are no systemic signs present. Lesions are usually confined to the face, although there can be exceptions to this rule. Early clinical signs include depigmentation, erythema and slight excess scale over the nasal region. These lesions may subsequently ulcerate. UV light frequently causes deterioration in this condition. Breed predispositions include German shepherds, collies, shelties and huskies.

Diagnosis
- History and clinical examination.
- Skin biopsy - interface dermatitis. Lesions seen near b.m. zone, and around dermal blood vessels and adnexal structures.
- Immunofluorescence tests - antibody and complement deposited at b.m. zone.

Cold agglutinin disease
Certain proteins can be precipitated from blood by cooling, e.g. cryoglobulins, etc. These globulins can be monoclonal or polyclonal, and can be associated with disease processes as diverse as infections, autoimmune diseases and neoplasia. The effect of precipitation of these proteins is to cause vascular pathology through obstruction, thrombosis, stasis of blood vessels etc. As well as globulins, other proteins such as fibrinogen can also be involved. It involves a type II hypersensitive reaction, and has been associated with lead poisoning in dogs and upper respiratory tract infections in cats.

Clinical signs
As the autoantibodies involved are cold reacting, cold agglutinin disease generally affects the extremities, i.e. paws, nose, etc. Skin lesions involve erythema, necrosis, purpura and ulceration. Exposure to cold is typically a relevant factor in the history. There may be signs of anaemia present.

Diagnosis
- History and clinical signs.
- Serology - cold-reacting autoantibodies (cold agglutinins)
- Haemagglutination on a slide at cold temperatures, e.g. 0°C, which can then be reversed by heating up to 37°C.
Skin biopsies may reveal necrosis/ulceration; secondary infection may be present.

Other diseases
Recent reports in the literature have alluded to an autoimmune component to variants of the above diseases such as exfoliative cutaneous lupus erythematosus (CLE) in German short-haired pointers, and vesicular CLE in collies and shelties.

Treatment
- Avoid exposure of the animal to cold.
- Follow the general principles outlined below.

General treatment of autoimmune dermatoses
The therapeutic approach to a case of auto-immune skin disease will be significantly influenced by the severity of the condition, and whether or not the disease process is confined to the skin. Many different treatment strategies can be attempted, but much of the emphasis rests with conventional pharmacotherapy. First line agents include:
  - Systemic glucocorticoids/topical hydrocortisone sprays (e.g. Cortavance)
  - Azathioprine
  - Gold therapy (chrysotherapy)
  - Chlorambucil (some authors even use cyclophosphamide)
  - Cyclosporine/other calcineurin inhibitors (e.g. topical tacrolimus)

Miscellaneous drugs
- Interferons
- Vitamin E
- Tetracycline and nicotinamide
- Mycophenolate mofetil - inhibits purine biosynthesis. Response varies according to different reports - 50% at best. Often needs to be combined with glucocorticoids.
- Human Igs - have worked in haemolytic anaemia cases etc. No controlled studies in dogs yet.

Additional strategies for controlling autoimmune disease
- If pyoderma or scaling disorders are present, appropriate use of antimicrobial and anti-seborrheic agents.
- If UV light is an eliciting or complicating factor, then the use of appropriate sun-block preparations and avoidance of peak-time exposure to UV light should be instigated. Tattooing has largely fallen out of fashion, due to the danger of ink eliciting a foreign-body type reaction.