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56th INTERNATIONAL CONGRESS

organizzato da  certificata ISO 9001:2000 

RIMINI 1st-3rd June 2007
PALACONGRESSI DELLA RIVIERA DI RIMINI

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In: 50° Congresso Nazionale Multisala SCIVAC, 2005 – Rimini, Italia

Immune-mediated Skin Diseases

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Autoimmune skin diseases are characterized by a specific humoral or cell-mediated immune response against the body's own tissues. There are a number of autoimmune diseases that may occur in veterinary dermatology, but most of these are extremely rare. However, dogs and cats with discoid lupus erythematosus or pemphigus foliaceus are presented regularly in small animal practice and we will focus predominantly on these two diseases.

Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is one of the more frequently encountered autoimmune skin diseases in dogs and humans and has been reported in cats. In humans, 10% of all patients with DLE proceed to develop systemic lupus erythematosus (SLE). Luckily, this does not seem to happen in small animals, only rarely will a patient with DLE develop systemic signs. However, it is possible occasionally and thus needs to be considered. SLE is an uncommon, multisystemic immune disorder of dogs cats and humans (it has also been reported in horses).

Pathogenesis

The exact pathogenesis of DLE is not elucidated in dogs and cats. However, a subset of dogs with clinical signs definitely deteriorates when exposed to UV light and improves on UV protection, thus it is safe to assume that UV rays play a role in at least some of the patients with DLE. Another subset of animals does not seem to be influenced at all by changes in UV exposure. Breed predispositions exist for Collies, Shetland sheepdogs, German shorthaired pointers, Siberian Huskies and Brittany Spaniels. Thus, genetic factors seem to play a role in the disease. Histopathologically, there is a spectrum of changes as well, but plasma cells are more prominent in dogs than humans (where lymphocytes are the major inflammatory cells).

Clinical signs

Discoid lupus erythematosus in early stages is characterized by depigmentation, erythema and scaling of the nose. The rough cobblestone-like architecture of the planum nasale changes into a smooth surface. Depigmentation of the skin around the eyes and the lips is observed less commonly. Erosions, ulceration and crusting are changes occurring later and may extend from the planum nasale and nostrils up to the dorsal and lateral part of the haired muzzle. These changes may be encountered around the eyes as well as on the pinnae. Scarring may occur in severe and chronic cases.

Diagnosis

Biopsy of skin lesions is the diagnostic procedure of choice. You want to choose nonulcerated lesions, because the site of action, the dermo-epidermal junction, is gone as well as the epidermis, if you biopsy an ulcer. Ideally, a greying area is chosen because the depigmenting is actively going on and the histopathological findings are most diagnostic, while the depigmented areas are already 'burnt out'. For discoid lupus erythematosus two to three punch biopsies are taken. I typically choose 6mm punches for the nose and 8mm for the dorsal muzzle in most dogs and 4mm punches for the nose and 6mm for the dorsal muzzle in cats and toy breeds. For cutaneous changes on the trunk or legs I always use 8mm punches or excisional biopsies. A typical finding in formalin-fixed samples is interface dermatitis (inflammation at the dermo-epidermal junction).

Samples fixed in Michel's solution classically reveal immunoglobulin deposits at the basement membrane (lupus line). However, these findings have also been reported in samples from the nose and foot pads of normal dogs and are not necessarily specific for LE.

Pemphigus

The pemphigus complex includes four subtypes recognized in human medicine, pemphigus vulgaris, vegetans, erythematosus and foliaceus. In all of these subtypes, the immune system for various and often unknown reasons starts to produce antibodies against parts of the desmosomes, the little connections holding adjacent keratinocytes together. These (auto-) antibodies are called pemphigus antibodies.

The antibodies in the different subtypes are directed against different antigens of the desmosomes expressed in different layers of the epidermis. Thus, the location of the forming vesicles within the epidermis and the resultant clinical signs vary. Once the antibody is bound to the part of the desmosome which forms the antigen, the complex is "swallowed" by the cell and elicits intracellular reactions leading to the release of plasminogen activator. The subsequent plasminogen activation results in the production of plasmin, a protease that destroys the desmosomes and leads to acantholysis (the process, where keratinocytes lose their intercellular bridges and "round up"). These acantholytic cells are located as single cells in vesicles formed by the destruction of the intercellular connections.

Clinical signs

Lesions of pemphigus vulgaris are characteristically seen in the oral cavity (80% of the cases have oral ulcers or vesicles at the time of diagnosis), other mucous membranes and the groin and axillae. German Shepherds may have lesions on ears and nose only. Lymphadenopathy, anorexia, lethargy and fever as well as secondary pyoderma (and sepsis) are frequently present. These pets are sick, look disgusting and feel miserable. Age, sex and breed predispositions are not known. If the lesions seem to show papillomatous vegetations, pemphigus vegetans may be present. However, many veterinary dermatologists don't believe in this entity.

Pemphigus foliaceus is the most common immune-mediated skin disease (together with discoid lupus erythematosus). It can affect adult dogs of any age, the mean age in a bigger study was 4.2 years. Akitas, Chows and Dobermans are some of the more commonly affected breeds.

The disease usually begins on the ears and the face. Depigmentation of the planum nasale and/or crusty lesions of the dorsal muzzle, periocular areas and pinnae are the first signs. Feet, foot pads and groin are affected commonly. In some dogs, hyperkeratotic footpads (with occasional sloughing) are the only clinical signs. Generalisation may occur after weeks to months. Pruritus, pain and lethargy may be seen in some cases. The Nikolsky sign may be present (if you rub the dull end of a pencil on the skin laterally, you create a blister with the produced shearing forces). Paronychia (with often a caseous, brownish material accumulating in the nail fold) and nipple involvement is frequent in cats. One of the classical clinical clues for pemphigus foliaceus (especially in cats) is crusting on the inside and nonhaired center of the pinnae. **Pemphigus erythematosus** is clinically indistinguishable from early pemphigus foliaceus with facial involvement only. It is thought of as a benign "cross over" between lupus erythematosus and pemphigus foliaceus. Pemphigus erythematosus is characterized by a positive antinuclear antibody titer, sometimes a lichenoid infiltrate on biopsies (see below) and typically is limited to the face.

Diagnosis

Biopsy is the diagnostic test of choice. It is usually performed after skin scrapings have been negative, no evidence of fungi or bacteria has been found on cytology or antibiotic therapy improved the patient, but pustules and crusts without microorganisms are still evident on reexamination.

Multiple biopsies should be taken (I usually take four to five samples) and you must choose your sites carefully. Ideally you want to take intact pustules. If you have a small pustule (less than half the size of your punch) you may use a sharp, new (!) biopsy punch. If the pustule is a little larger, you will probably rupture the diagnostic pustule you searched so hard for. In these cases I use a scalpel blade and perform an excisional biopsy. In many cases it is hard to find an intact pustule. Don't give up too soon, I spend up to ten minutes searching the whole animal for a diagnostic lesion. The second best lesion to biopsy is a papule, a little red bump not yet crusted. And last, you may include some really crusty lesions with the thick crust still attached to the biopsy.

Give the pathologist your differential diagnosis list and ask the laboratory to "please cut the crusts in" as they may contain important clues. In some cases, rebiopsies are necessary as initial samples may be nondiagnostic despite all of the clinician's efforts. On a classic biopsy intraepidermal or subcorneal pustules are filled with neutrophils, acantholytic cells and occasionally eosinophils. The dermis underneath is characterized by a mild to moderate superficial perivascular dermatitis. Pustules can also be found in the follicular walls. More often than not numerous acantholytic cells in the crusts are your only diagnostic clue.

In some publications you will read about direct and indirect immunofluorescence. Indirect immunofluorescence screens the serum of patients for the pemphigus antibodies mentioned above, this test is important in human medicine but not that useful in dogs and cats. Direct immunofluorescence shows antibodies bound to the intercellular space in the epidermis (it looks like a green fluorescent net in a black sea) of a histopathological sample. The sample must be either frozen or stored in Michel's solution, formalin-fixed samples cannot be used. Recently, immunohistochemistry has been utilized to stain these antibodies in formalin-fixed tissue in some laboratories. Direct immunofluorescence and immunohistochemistry are somewhat controversial, false negatives and false positives have been reported (for example cases of chronic solar skin damage have been tested positive). I have used these tests very rarely in the past and we currently do not use them at all. I would only recommend these tests if you are familiar with the laboratory and know how diagnostic and reliable these tests are for that specific laboratory.

Prognosis

The prognosis for pemphigus foliaceus as well as pemphigus erythematosus is fair, even though life long immunosuppressive treatment is necessary in most cases. The same holds true for pemphigus erythematosus. Sometimes partial remission with only few residual crusts is achieved with comparatively low doses of immunosuppressive drugs and complete remission requires much higher maintenance doses. It may be reasonable and safer for the patient to maintain the disease at partial remission in these particular cases. Pemphigus vulgaris has a guarded to poor prognosis.

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