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IMMUNE-MEDIATED AND PARANEOPLASTIC DERMATOSES IN CATS

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IMMUNE-MEDIATED DERMATOSES

Immune-mediated dermatoses are uncommon diseases that result from formation of autoantibodies to keratinocyte antigens (pemphigus complex), epidermal-dermal junction antigens (bullous pemphigoid), or antigen-antibody immune complex formation (lupus erythematosus). Although rare these diseases are associated with significant morbidity and mortality, requiring early recognition, definitive diagnosis, and aggressive management.

PEMPHIGUS COMPLEX

Pemphigus diseases are immune-mediated diseases caused by autoantibodies targeting adhesion molecules in the epidermis. Three variants have been described in cats: pemphigus foliaceus (PF), pemphigus vulgaris (PV), and pemphigus erythematosus (PE). Of these pemphigus foliaceus is the most common; an entire session is devoted to this topic. The difference in disease presentation arises from different adhesion molecules being targeted. The target of PF (desmoglein I) is a molecule found in the superficial layers of the skin, paw pad, and nasal planum. Clinical lesions are therefore superficial. Typical initial lesions consist of fragile, sterile pustular eruptions that rapidly rupture and degenerate into honey-yellow crusts and shallow erosions. The epidermis underlying the crusts usually appears shiny. In contrast, the target of PV antibodies (desmoglein III) is prominent in deeper levels of the epidermis and mucous membranes. As a result the classic lesions of PV are deep ulcerations of the oral cavity, lips, nostrils, eyelids, perineum, and anus. Affected cats are usually systemically ill. Pemphigus erythematosus is named such because histopathologically PE shares features of pemphigus and lupus erythematosus. Lesions tend to be more mild, limited to the face and ears, and are believed to be exacerbated by sunlight exposure (like lupus).

Diagnosis is based on histopathology and consistent clinical signs. Since PF is predominately a pustular to crusting dermatosis, primary differential diagnoses are pyoderma, dermatophytosis, demodicosis, and Notoedres. Cytology from intact pustules or newly formed crusts reveal neutrophils, acantholytic keratinocytes (rounded up cells that have separated from their neighbors deeper in the epidermis), and the absence of bacteria. Histopathologically, pustules are seen in or just beneath the stratum corneum or the epidermis and hair follicles. For PV, any erosive-ulcerative disease of the oral mucosa warrants biopsy on initial presentation. The ideal sample is an intact vesicle, however because of their fragile and transient these are very rare. Biopsies of ulcers rarely yield a diagnosis, rather aim for erythematous areas adjacent to ulcers. In PV, the histopathologic diagnosis is based on epidermal clefts just above the stratum basale. Acantholytic cells are present in the cleft, or more classically basal cells separate from neighbors but remain attached to the basement membrane, giving the appearance of a "row of tombstones." Leukocytes are less abundant in PV than in PF. Histopathologically, PE is characterized by intraepidermal pustules (like PF) and

accumulation of lymphocytes along the dermal-epidermal junction (like lupus erythematosus).

Treatment consists of immune suppression by corticosteroids or steroids in combination with chlorambucil, gold salts, cyclosporin, or other adjunctive therapy. Start with high immunosuppressive doses until no new lesions are being formed, and older lesions are healing (2-4 weeks), and then very gradually decrease steroid dosages over the course of 6-12 months. Most patients require prolonged maintenance therapy from several years to life. The most common error in management is attempting to wean the patient too rapidly. This results in relapse of clinical disease necessitating return to very high doses. With each cycle of remission and relapse, lesions become less responsive to treatment. In general the prognosis for PF and PE is good, with 85-90% survival. PV carries a grave prognosis, but too few cases are reported in the literature to provide accurate descriptions of outcome.

BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is a very rare autoimmune disease characterized by autoantibodies against vital adhesion molecules in the basement membrane zone. These molecules are critical for the attachment of the epidermis to the dermis. Autoantibody attack and subsequent inflammatory response, results in cleft formation between the epidermis and dermis. Patients present with vesicles or bulla that rapidly rupture to form deep ulcerations; lesions tend to be localized to the oral cavity, lips and pinna, but can occur anywhere. Even minor trauma to the skin predisposes the patient to lesion formation. Application of lateral pressure adjacent to an ulcer results in sheering away of the epidermis from the dermis (Nikolsky's sign).

Diagnosis is based on clinical and histopathologic features; however knowledge and use direct/indirect immunofluorescence for this disease is growing. Currently the dermatologists at North Carolina State are leading research efforts in BP; if you suspect BP contact NC State for additional advice on sample collection and submission.

Too few cases have been reported to provide a predictable prognosis. Treatment typically involves immunosuppressive doses of prednisolone (4-6mg/kg/day) until lesions resolve; followed by gradual reduction in dose to an every other day life-long, maintenance therapy.

LUPUS ERYTHEMATOSUS

Lupus erythematosus results from antigen-antibody immune complex deposition along the basement membrane zone and other interface zones of the skin or other organs. Tissue damage is caused by response by the normal immune system to the antigen-antibody complexes. Two forms of lupus erythematosus exist: discoid and systemic.

Discoid lupus erythematosus (DLE) is limited to the skin and does not progress to involve other organ systems; sometimes DLE is also known as cutaneous lupus erythematosus. The cause for immune-complex formation is not known, but UV light, vaccines, and genetic factors are hypothesized. Even if it is not the trigger, UV light certainly exacerbates clinical disease. Clinically lesions are worse in photosensitive areas such as the face and pinna; however, lesions can form in less sun exposed areas, such as paw pads. Lesions consist of crusts, erosions, and ulcerations as inflammation along the dermal-epidermal junction disrupts the overlying epidermis. Diagnosis is based on clinical features and histopathologic features consistent with lupus

erythematosus. There is no pathognomonic diagnostic pattern on histopathology, so don't be shocked by a non-committal pathology report. Typical lesions are characterized by a lymphocytic-plasmacytic infiltrate hugging the dermal-epidermal junction, with individual keratinocyte necrosis (apoptosis) and hydropic degeneration. Because secondary pyoderma can bring inflammatory changes to the area, antibiotic therapy prior to biopsy may enhance the pathologist's ability to assist with the diagnosis. Treatment involves avoidance of sunlight and topical or systemic corticosteroids. Tacrolimus topical ointment or systemic cyclosporin may also prove useful in the management of this disease; however, reports on use of these drugs in feline cases is lacking.

Systemic lupus erythematosus (SLE) is an exceptionally rare, but life-threatening, disease in cats. SLE is characterized by immune-complex deposition in multiple organ systems. The most consistent clinical signs are fever, anemia, glomerulonephritis, and polyarthritis. Cutaneous lesions are present in only 20% of feline cases in the literature. Skin lesions may resemble those of DLE or consist of necrotizing lesions or deep ulceration secondary to vasculitis. Inflammation of the claw bed (paronychia) or sloughing of claws (onychomadesis) is also reported. Diagnosis is based on clinical signs, biochemical profile, CBC, and urinalysis (sterile urine with significant proteinuria). If skin lesions are present biopsy should always be performed; histopathology is typically similar to DLE (dermal-epidermal inflammation), but may also demonstrate vasculitis. In cats with polyarthritis, arthrocentesis is recommended for cytologic evaluation of synovial fluid. A positive anti-nuclear antibody titer is also supportive of a diagnosis; however, other systemic inflammatory diseases can result in a positive ANA, so the test is not definitively diagnostic for SLE. Because SLE results from antigen-antibody immune complexes, a hunt for an antigen source should always be performed. Response to immunosuppressive therapy is variable to poor.

PARANEOPLASTIC DERMATOSES

Paraneoplastic syndromes are defined as pathologic conditions that result from neoplasia, but are not directly caused by expansion or invasion of the primary tumor or metastases. The most classic example is Cushing's syndrome, which is characterized by distinctive clinical disease resulting from a pituitary or adrenal neoplasm. Cutaneous paraneoplastic diseases are a subset of paraneoplastic syndromes characterized by specific dermatologic responses to non-cutaneous neoplasia. Basically these diseases are cutaneous markers for internal neoplasia; therefore, recognition of clinical presentation of paraneoplastic dermatoses increases the index of suspicion for internal tumors, hopefully leading to earlier diagnosis and therapy. In human medicine, there are numerous well characterized syndromes, including acanthosis nigricans, tripe palm, Sweet's syndrome, exfoliative erythroderma, necrolytic migratory erythema, and paraneoplastic pemphigus. Fewer conditions have been described in the veterinary literature; however, those that occur in cats are extraordinary and worthy of recognition by feline practitioners.

PARANEOPLASTIC ALOPECIA

This peculiar dermatologic disease, associated with pancreatic carcinoma, was first described in the literature in 1994. Since then it has also been reported in two cats with biliary carcinoma. The hallmark clinical presentation is acute, progressive, symmetrical alopecia limited to the medial aspect of the limbs and ventral aspects of cat extending from chin to tail. Hair epilates very easily leaving behind remarkably shiny skin. Presentation is dramatic, and once seen seldom forgotten. The time course is variable, developing as rapidly as 2 weeks, or follows a slowly progressive course over 6-10 months. Secondary *Malassezia* overgrowth on affected skin is common. In addition to skin lesions, paw pads may become painful, dry, crusted, and fissured or may develop painful, moist, erythematous lesions. Cutaneous signs may be accompanied by weight loss, inappetance, vomiting, diarrhea, and lethargy.

The pattern is uniquely striking, but differential diagnosis should include hyperadrenocorticism, hyperthyroidism, dermatophytosis, demodicosis, telogen defluxion, and alopecia areata. Skin biopsy, fungal culture, skin scraping, chemistry, CBC, urinalysis, T4, ACTH stimulation, and diagnostic imaging of the abdomen are indicated. Histopathologic findings include a nonscarring alopecia, marked follicular atrophy, miniaturization or telogenization. The epidermis may be thickened, but the stratum corneum is absent or compact. The loss of stratum corneum accounts for the shiny appearance of the skin, but the cause of this loss is not known; one author speculates that the layer is removed by excessive grooming. *Malassezia* spp. may be seen colonizing the surface of the epidermis. Exploratory laparotomy and biopsy of the pancreas are necessary for definitive diagnosis.

Pancreatic carcinoma is a severe, life-threatening neoplasia. The majority of cases have distant metastasis at the time of diagnosis. Eight-five percent of reported cases died of their disease or were euthanized within 8 weeks of the onset of clinical signs. One case with a solitary pancreatic tumor experienced regrowth of hair following surgical resection. Interestingly, in this case, cutaneous signs recurred 18 weeks later prompting a search for metastatic disease, which unfortunately was found.

THYMOMA-ASSOCIATED EXFOLIATIVE DERMATITIS

In humans, exfoliative dermatitis or exfoliative erythroderma is a paraneoplastic syndrome that occurs secondary to lymphoma or leukemia. In cats this condition has been described in association with thymoma, rather than lymphoma. Clinical presentation is characterized by non-pruritic scaling and erythema on the head and pinna that progress to generalized involvement. With time scaling worsens and alopecia predominates. Waxy accumulations form in the ear canals, in the claw beds, and between digits. Pruritus may result secondary to yeast overgrowth on the altered skin. Principle differential diagnoses include dermatophytosis, *Cheyletiella*, demodicosis, erythema multiforme, lupus erythematosus, cutaneous drug eruptions, and epitheliotropic T-cell lymphoma. Biopsy reveals a histopathologic pattern characterized by interface dermatitis, areas of hydropic degeneration in the basal layer, individual keratinocyte necrosis, and marked increase in thickness of stratum corneum. Inflammatory infiltrate at the dermal-epidermal junction is present, but not excessive; lymphocytes are the predominant cell type. Thoracic radiographs reveal a mass in the cranial mediastinum with or without pleural

effusion. Needle aspirate or biopsy is necessary to confirm the diagnosis.

The pathologic mechanism for dermatologic disease is unknown. Changes likely result from aberrant cytokine production or other immunologic event associated with neoplastic thymic lymphocytes. The presence of lymphocytic infiltrate and apoptotic keratinocytes support this theory

Few cases of this syndrome have been published; however one that received treatment of the thymoma by surgical resection had complete resolution of dermatologic signs and remained disease free at 14 months. In cases of feline thymoma without dermatologic change, tumors that are non-invasive at time of surgery have a median survival time of 2 years is achieved. In cases with local invasion (15%) or patients with incomplete resection, survival much beyond surgery is uncommon. This underscores the importance of recognizing the cutaneous marker for internal disease as early diagnosis and therapy may result in remission.

ACQUIRED CUTANEOUS HYPERFRAGILITY SYNDROME

Cutaneous hyperfragility is a life-threatening dermatosis characterized by marked epidermal and dermal thinning; sometimes the entire thickness of skin is only 2-3 cell layers. The result of this change is spontaneous full-thickness tearing. Fortunately, tears are painless for the cat and hemorrhage is absent. The size of tears depends on the type of trauma occurring; small 1-2 cm may resemble fish-mouth lesions of cutaneous asthenia, but much larger lesions extending over 20-30% of the body can also occur. Wounds are unmistakable as the skin is only a few cell layers thick; occasionally the skin is so thin it is mistaken for an epidermal collerette or other scaling disorder and wounds are made larger while trying to peel away the "adherent scale." Attempts to repair lesions are usually unsuccessful as the damaged skin heals very poorly; more often than not, new tears are made by the surgeon attempting to close the open wound. Euthanasia is a reasonable response to very large wounds with no chance of healing.

The precise pathomechanism for cutaneous hyperfragility is not known, but likely involves atrophy of fibroblast and absence or blockage of response to normal growth factors. The condition has been associated with severe metabolic disease, including spontaneous hyperadrenocorticism secondary to pituitary neoplasia. The syndrome has also been associated with a single case of cholangiocarcinoma. Non-neoplastic causes include diabetes mellitus (perhaps peripheral insulin resistance from undiagnosed pituitary disease), hepatic lipidosis (same), or most commonly iatrogenic disease resulting from excess use of corticosteroids or megestrol acetate. Unfortunately hyperfragility may not be reversible even with management of primary disease or withdrawal from external steroids.

RECOMMENDED READING

1. Turek MM Cutaneous paraneoplastic syndromes in dogs and cats: a review of the literature. *Vet Dermatol* 14:279-296. 2003.
2. Scott DW, Miller WH, Griffin CE: Muller and Kirk's Small Animal Dermatology, 6th ed, WB Saunders Philadelphia, 2000.