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DERMATOLOGY SECRETS: PEMPHIGUS FOLIACEUS IN CATS

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Pemphigus foliaceus (PF) is the most common autoimmune dermatosis in cats. True incidence in the general population is not known; however, 2-10% of feline cases presenting to dermatology referral services are diagnosed with PF. Although most common in young adult cats, 2-5 years of age, the age of onset is highly variable, ranging from less than one year to greater than 17 years. Cats as young as 12 weeks can be affected. There is no apparent sex or breed predisposition. PF has been reported in most breeds, including Siamese, Himalayan, Persian, Maine Coone, Somali, Ragamuffin, Scottish Fold, and American Blue.

PATHOGENESIS OF DISEASE

What is known about PF in cats is extrapolated from the equivalent disease in humans and dogs. PF is an autoimmune disease, characterized by the presence of autoantibodies against desmoglein I (dsg I), an adhesion molecule that links keratinocytes with other keratinocytes in the epidermis. The precise mechanism of pustule formation is not known, but likely involves attachment of antibody to dsg I on the keratinocytes, internalization of the antibody-antigen unit, activation and release of proteolytic enzymes, resulting in loss of intercellular cohesion. Keratinocytes that become disconnected from their neighbors assume a round shape rather than the classic polygonal shape seen in normal epidermis. This is known as acantholysis. During this process there is fixation of complement, release of potent chemotactic factors, resulting in the arrival of large numbers of neutrophils. Neutrophil-derived inflammatory mediators contribute to lesion formation and clinical disease; however, mouse studies have demonstrated that neither complement fixation nor the presence of neutrophils is necessary for acantholysis to occur.

The precise trigger for formation of autoantibodies against dsg-1 is not known. In humans there is a contagious disease resembling PF, known as fogo sevalgum. Fortunately this disease is limited to certain jungle valleys in South America. PF autoantibodies may also be formed secondary to adverse drug eruptions and neoplasia. If a drug trigger is identified and avoided, then clinical disease should self resolve, otherwise patients with idiopathic autoantibodies require immune suppressive therapy to prevent ongoing disease.

CLINICAL PRESENTATION

The classic lesion for PF is a pustular eruption. However, because pustules are fragile and transient, they rapidly rupture and coalesce to form crusts, erosions, alopecia, and purulent exudate. Single site involvement is rare; more typically patients develop lesions in multiple areas. The most common site for lesion formation is the head, particularly the nasal planum, periocular and preauricular skin, and pinnae. In a recent study the head was the initial site of disease in one-third of cats, and eventually the head became involved in 80% of all cases. Pinnae seem especially prone to forming pustules, crusts, and erosions. After the ears and face, paws are the next most likely area of involvement, followed by

ventrum, dorsum, and tail. Paw lesions most typically involve the claw folds, with heavy purulent exudate and honey-yellow crusts extruding from the area around the claw. Interdigital skin, pads, and junction of pad with haired skin are also common. Periaerolar (nipple) involvement has been reported as well. The majority of cases (94%) have a bilaterally symmetrical distribution. Pruritus is also a common feature; reported in 80% of cases; however, severity of pruritus is variable. Lethargy is seen in half of all cases; with fever and anorexia present in approximately one-third of patients.

One presentation that can cause confusion is purulent exudate from only the clawfolds, but not any other locations on the body. Typically multiple digits on multiple paws are involved at presentation. This clinical sign should be considered a classic indication for PF in cats, but is frequently misdiagnosed as bacterial infection or dermatophytosis. Humans get multidigit dermatophytosis infections of their nails, because we wear shoes. Cats don't wear shoes, and a severe multiple site infection with purulent exudate would indicate systemic immune compromise. If multiple claws have purulent exudate, think pemphigus, not dermatophyte or bacteria.

DIAGNOSIS

The principle differential diagnoses for a pustular crusting dermatosis of haired skin include bacterial folliculitis, dermatophytosis, *Notoedres cati*, *Cheyletiella*, *Otodectes*, demodicosis, and cutaneous drug eruption.

A cytologic sample from intact pustules is ideal for initial evaluation. Since intact pustules are transient and rare in cats, the yellow-crust adhered to eroded epidermis is the most common lesion seen. Choose a newly erupted area that is less likely to be affected by secondary bacterial colonization and self-trauma. The pinnae and top of head are often good locations to start. Peel back a crust to reveal shiny, possibly blood tinged, eroded epidermis. Impression smears of both the erosion and the underside of the crust should be made and stained with Diff-Quik for examination. Unstained specimens can be submitted to a clinical pathologist for evaluation as well. In cats with profound paronychia, the purulent exudate from the clawfold should also be collected for cytology.

Cytologic preparations should be evaluated with the 10x, 40x (high dry), and 100x (oil-immersion) objectives. At lower magnification, cytology typically reveals a sea of neutrophils populated by islands of "acantholytic" keratinocytes. Acantholytic keratinocytes are undifferentiated cells from the deeper, "living" layers of the epidermis, and are very rarely seen on surface cytology under normal circumstances. These cells have detached from their neighbors, rounded-up, and floated to the surface among the neutrophils. Occasionally rafts of acantholytic keratinocytes are seen. Acantholytic keratinocytes typically appear as round or ovoid cells with a healthy appearing nucleus, cytoplasm, and cell membrane. The cytoplasm usually stains a uniform blue or occasionally pink. Cells are 3-5 times larger than the surrounding neutrophils. They may resemble discrete "round" cells. Although, these cells can be present in severe pustular bacterial or fungal infections, PF samples frequently contain dozens of acantholytic keratinocytes. Any more than 2 or 3 acantholytic keratinocytes should be considered strongly suggestive of PF. High magnification with the oil-immersion lens may be needed to evaluate for bacteria in the sample. Bacteria should be absent from samples taken directly from intact pustules and minimal from samples taken

under newly formed crusts. Also note that the neutrophils largely ignore the bacteria, which are usually found in the background rather than phagocytosed by leukocytes.

Since therapy for PF involves long term immunosuppressive drugs, empirical treatment based on history and cytology is not recommended. A biopsy should always be performed to confirm the diagnosis. For histopathology intact pustules are the ideal specimen for diagnosis; however, recently developed crusts with minimal secondary excoriation or infection is a good second choice. Do not prepare area prior to biopsy as this will reduce diagnostic value by scrubbing away cells of the crust and superficial epidermis. Be sure to place all crusts in formalin as these may also contain diagnostic cells. A minimum of 3 punch biopsies should be collected; ideally 5-6 samples are submitted to the pathologist for a diagnosis. PF is defined histopathologically by the presence of intact or degenerative pustules (crusts) in the stratum corneum or subcorneal layer. Pustules contain predominately neutrophils and acantholytic keratinocytes. Occasionally these cells adhere to each other in small rafts. Eosinophils may be found infiltrating the lesions as well. Since the surface pustules are fragile and easily ruptured by grooming, intact pustules may be best seen in the hair follicle epithelium. In some cases no intact pustules are seen and the diagnosis is based on the presence of neutrophils and acantholytic keratinocytes in the crusts.

TREATMENT

Once a diagnosis is made, then initial therapy is immune-suppression combined with management of secondary bacterial infections. The most common approach is to use glucocorticoids as the sole therapy. Success has been achieved with triamcinolone (0.4 – 0.8 mg/kg/day), prednisolone (4 – 6mg/kg/day), methylprednisolone (3 – 5 mg/kg/day) or dexamethasone (0.4 – 0.6mg/kg/day). In a recent review of 44 cases of feline PF, remission was achieved in 15/15 cats treated with triamcinolone, but only 8/13 cats treated initially with prednisone or prednisolone. The triamcinolone group also had fewer reported adverse effects and required fewer changes in therapeutic protocol than the prednisone group. Both triamcinolone and dexamethasone have longer duration of action than prednisolone, necessitating eventual decrease to every third day therapy. Regardless of which steroid is used initially the patient should be rechecked every two weeks until no new lesions are seen. As long as new lesions are forming, remission has not been achieved. If initial therapy fails, switch to a different glucocorticoid. In individual cases, one steroid may work better than another. Dexamethasone is effective clinically, but my personal impression is that dexamethasone is more diabetogenic than the other steroids, and has a higher incidence of cutaneous fragility as a complication. A partial explanation of this is the longer half-life of dexamethasone, and the difficulty in reducing dosage to an every third day dose. Repositol glucocorticoids, such as Depo-medrol, have no place in the management of immune-mediated diseases. Induction is typically followed by repeated relapses as therapeutic tissue levels drop more

rapidly than what can be achieved with steady decrease in oral prednisolone therapy.

If steroid as a sole therapy is ineffective, then a second agent can be added to the glucocorticoids. Chlorambucil with prednisolone is the most commonly used combination therapy; some dermatologists start cases with this protocol from the beginning. Chlorambucil is an alkylating, immunomodulating agent given at 0.1mg/kg/day or 0.2mg/kg every other day. Principal adverse reactions include nausea, inappetence, and idiosyncratic myelosuppression. CBC, Chemistry, urinalysis, body weight, and appetite should be monitored every two weeks during induction therapy, and every 6-12 weeks during maintenance. Less commonly used second agents include gold salts and cyclosporin. Gold salt (chrysotherapy) is given as an intramuscular injection, 1.0 mg/kg once weekly. Once remission is achieved the interval between injections is extended. Gold salts have been associated with myelosuppression, and must never be given simultaneously with other potentially myelosuppressive agents; an adequate washout period between drugs is essential. Cutaneous drug eruptions can also occur. Gold salts are retained in high levels in the tissues; consequently adverse reactions are prolonged. Cyclosporin (5-25 mg/kg/day) is anecdotally effective in some cases, and ineffective in others. If responsive, Cyclosporin may significantly decrease the reliance of systemic glucocorticoids. Anorexia, vomiting, and gingival hyperplasia are the most common adverse reactions. Recently several cases have been published reporting fatal toxoplasmosis in cats receiving cyclosporin. Both recrudescence of dormant tissue cysts and acute acquisition and subsequent fatal systemic toxoplasmosis have been described. Toxoplasmosis can be a concern with any systemic immune suppressive therapy.

Once remission is accomplished, then immune-suppressive therapy is gradually diminished in dose and frequency until the lowest maintenance therapy is achieved. This is the trickiest part of therapeutic decision making. The most common mistake is decreasing therapy too rapidly, resulting in relapse and the subsequent need to return to induction doses. Resist the temptation to get to lower doses faster to spare the patient from the adverse effects of high-dose glucocorticoid therapy; the end result is longer periods on higher doses of steroids than if doses were reduced more gradually from the beginning.

There is no standard guideline for reducing steroid dosages that works for all patients. The best approach is to think of the total glucocorticoid dose in a 48 hour period; decrease this dose by 10-25% every 2-4 weeks until the patient is on a once every other day dose. Once this is achieved, each reduction occurs every 3-6 months. See table 1 thru 3 for an example. If using combination therapy with chlorambucil, decrease chlorambucil to every other day first, then gradually reduce the glucocorticoid on the day the patient receives chlorambucil. The eventual goal is steroid one day, chlorambucil the next; thus giving the patient a day off each drug, while never missing some form of immune suppressive agent.

Table 1: First 3 months of Prednisolone (4mg/kg/day) with Chlorambucil (0.1mg/kg/day) for a 5kg cat.

Drug	Time	Induction		4 weeks		6 weeks		8 weeks		12 weeks	
	Date	Odd	Even	Odd	Even	Odd	Even	Odd	Even	Odd	Even
Pred	AM	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	5mg
	PM	10mg	10mg	10mg	10mg	10mg	5mg	10mg	--	10mg	--
Chlor	AM	0.5mg	0.5mg	--	1mg	--	1mg	--	1mg	--	1mg

Table 2: Months 3-15: Step downs are every 2 weeks until you are on a single dose every other day of pred. Note that do not change the total amount of prednisolone during this period, rather shift it all to the morning dosage. Once you are alternating prednisolone and chlorambucil step downs occur once every 3-6 months!

Drug	Time	16 weeks		18 weeks		20 weeks		36 weeks		60 weeks	
	Date	Odd	Even	Odd	Even	Odd	Even	Odd	Even	Odd	Even
Pred	AM	10mg	--	15mg	--	20mg	--	15mg	--	10mg	--
	PM	10mg	--	5mg	--	--	--	--	--	--	--
Chlor	AM	--	1mg	--	1mg	--	1mg	--	1mg	--	1mg

Table 3: Months 15-36: very slow step downs. Things are going great!

Drug	Time	15-18 months		18-24 months		24-30 months		30-36 months		Maybe never	
	Date	Odd	Even	Odd	Even	Odd	Even	Odd	Even	Odd	Even
Chlor	AM	7.5mg	--	5mg	--	5mg	--	2.5mg	--	--	--
	PM	--	--	--	--	--	--	--	--	--	--
Azath	AM	--	1mg	--	1mg	--	0.5mg	--	0.5mg	--	--

PROGNOSIS

In most cases, the prognosis for PF is good, although owners should be aware that the majority of cats require life-long therapy. In a retrospective study of 44 feline PF cases with sufficient follow-up information, only 4 cats died or were euthanized due to disease or complications of therapy. This is highly favorable compared to similar reviews of canine cases, which report 15 – 60% fatality, most due to unacceptable complications of steroid therapy. The more favorable prognosis in cats probably results from less frequent, or less noticeable, adverse drug reactions. In the same retrospective, only 27% of cats relapsed during therapy, although 45% required modification in therapy due to lack of remission, adverse effects, or relapse. Three cats (7%) maintained remission without needing long-term maintenance therapy; of these two cats were believed to have drug-induced PF, and therefore did not have an ongoing disease.

RECOMMENDED READING

1. Preziosi DE, et al. Feline pemphigus foliaceus: a retrospective analysis of 57 cases. *Vet Dermatol* 2003, 14:313-321.
2. Rosenkrantz WS. Pemphigus: current therapy. *Vet Dermatol* 2004, 15:90-98.
3. Scott DW, Miller WH, Griffin CE: Muller and Kirk's Small Animal Dermatology, 6th ed, WB Saunders Philadelphia, 2000, pp. 678-693.