Autoimmune Skin Diseases

Paul Bloom, DVM, DACVD, DABVP
Allergy, Skin and Ear Clinic for Pets
Livonia, MI

Pemphigus

Pemphigus foliaceus (PF) is the most common form of pemphigus and is probably the most frequently diagnosed autoimmune skin disease (AISD) affecting cats and dogs. In general, PF is a disease of young to middle aged animals. Any dog may develop PF but Chow Chows and Akitas have a higher incidence in the author's practice.

Historically, the owner may report that the lesions wax and wane or are progressive. The progression of the disease may be slow, especially cases with only facial involvement, or the dog may develop acute eruptions (most commonly associated with generalized disease). With the generalized form the dogs frequently will be febrile, may have limb edema and have constitutional signs. Pruritus with any form varies from non-existent to moderately intense.

There are 3 primary distribution patterns of PF -facial (most common) form which involves the bridge of the nose, nasal planum, periorbitally, pinnae (especially in cats); a footpad form (cats may present only with paronychia) and a generalized form where lesions usually begin on the face and then spread.

Because there is involvement of the hair follicles, multi-focal to diffuse alopecia is frequently present. The primary lesions of PF are large nonfollicular pustules (there are also follicular pustules present). The pustules that are present in a bacterial pyoderma usually involve the ventral abdomen and/or trunk and are much smaller than those seen with PF. Other lesions include epidermal collarettes, yellow brown crusts and erosions.

Differential diagnosis would include any pustular, crusting and scaling disease such as: pemphigus erythematosus; zinc responsive dermatosis (especially with foot pad involvement); metabolic epidermal necrosis (especially with foot pad involvement); bacterial and fungal (dermatophytosis) infections; demodicosis, DLE (facial/nasal form); erythema multiformae; mycosis fungoides; Leishmaniasis; and sebaceous adenitis.

Diagnosis

A cytologic prep of a pustule or crust should be performed. Microscopic findings would include acantholytic keratinocytes, either individually or in clusters, surrounded by NON-degenerative neutrophils and/or eosinophils- bacteria should not be seen. Histopathology is the only definitive means to diagnose pemphigus. An intact pustule (or if none are present, a crusted lesion) should be biopsied. Infectious diseases that produce proteases, such as a bacterial pyoderma or a dermatophyte infection (Trichophyton mentagrophytes), can breakdown the intracellular glycoproteins (desmoglein) leading to acantholysis. Because these infectious diseases mimic PF histologically, you should request special stains for both bacteria (gram stain) and fungi (GMS, PAS) anytime a there is a histopathologic diagnosis of PF.

Prognosis

PF may be drug related, either drug-induced or drug-triggered. The drug-induced form PF is caused by a drug and upon removal of the drug, sometimes with a short course of immunosuppressive treatment, the disease resolves. Drug-triggered PF occurs when a drug stimulates a genetically predisposed individual to develop PF. Typically, this form of PF must be managed long term, similar to idiopathic PF. Currently there is no way to identify which cases of drug related PF are drug induced and which ones are drug triggered. In fact there is no test that can be used to predict how well a case of PF will respond to treatment.

A study at NCSU revealed that 6 of 51 dogs (11.7%) with PF were weaned off all medication and stayed in remission for >1 year. Recognizing that PF is a sunlight aggravated disease, it was interestingly the dogs in this study were from areas (NC or Sweden) with high UV light exposure. In this report the dogs took 1.5–5 months of therapy before the disease was in remission. The drug(s) were then slowly tapered and then all therapy was stopped. The total duration of immunosuppressive therapy varied between 3 and 22 months. These dogs stayed in remission for the entire follow up period (1.5–6 years after treatment). Supporting this finding is a study from the University of Pennsylvania that reported that 10% of their cases went into long-term remission after weaning off medication.

This study performed at the University of Pennsylvania suggests that dogs with PF survived longer when given antibiotics (usually cephalexin) in addition to their immunosuppressive regimen. This is in contrast to the author's clinical observation that if dogs with PF do develop a concurrent pyoderma it only occurs AFTER being placed on immunosuppressive therapy. Supporting the author's observations is a study from CSU that reported that there was no difference in survival when antibiotics were part of the initial treatment. In the study from University of Pennsylvania the survival rate was approximately 40% with 92% of the deaths occurring by 1 year. Other researchers have reported having a long-term survival rate of approximately 70%.

Cats may have a better prognosis than dogs with this disease. In the same report from the University of Pennsylvania, only 4/44 cats treated died (from their disease or therapy) during the study period. In the author's practice, survival at 1 year also exceeds 90%. In addition, a significant number of the cats are eventually able to have all medications discontinued without suffering a subsequent relapse.

Treatment

Managing any AISD takes frequent rechecks and alertness to complications associated with immunosuppressive therapy such as demodicosis, dermatophytosis and bacterial pyoderma. Interestingly the author has rarely seen a dog with PF that had a secondary pyoderma at initial presentation. It is more common to develop after beginning immunosuppressive therapy. If a patient was controlled and then has a relapse or if the patient has been improving and suddenly worsens, there are 2 possibilities. The PF (which does wax/wane) is flaring up OR that the dog developed a secondary infection due to immunosuppression. If the new lesions are folliculocentric you must also rule the big 3 folliculocentric infections – bacteria, demodex and dermatophyte. Skin scrapings, Wood's light examination (screening test) and impression smears are the minimum data based that should be performed when a dog is presented with these lesions. Whether or not you need to do a fungal culture at this time depends on the how frequently you see dermatophytosis in your practice and what is seen on cytology (acantholytic keratinocytes, cocci, demodex mites). If dermatophytosis is commonly seen in your practice then a fungal culture should be performed. Otherwise a fungal culture and a repeat skin biopsy can be considered second tier tests to be performed if the case doesn't respond to appropriate therapy (eg antibiotics)

In addition to the treatment options listed below, shampoo therapy should be included for symptomatic treatment of the crusting dermatitis. Pending biopsy results, if intracellular cocci are seen on cytology the author will dispense cephalexin (10-15 mg/# bid-tid), unless there is a suspicion that it is a case of cephalexin induced PF. If only extra cellular cocci are seen, then topical shampoo therapy with a antiseptic (eg chlorhexidene, benzoyl peroxide, etc)

Treatment must be individualized for each patient since there is no "best" treatment that works in all PF patients. This is why monitoring the progress of the disease closely by PHYSICALLY examine the dog or cat is critical for successful management of PF. It is especially important to recheck the patient prior to any adjustment in medication. When devising a treatment plan, be sure to consider the severity of the disease so that the treatment side effects are not worse than the disease itself.

There may be regional differences in how aggressively PF needs to be treated. Some of this may be due to the differences in the gene pools of the patients. But since PF is a sunlight aggravated disease, it also may be related to the differences in sun exposure. Regardless of the locale, sun avoidance should be part of the treatment for PF.

Because diet has been implicated as a cause of PF (endemic) in humans, the author will review the dietary history and consider dietary modification if the initial response to therapy is poor

Vitamin E (400-800 IU bid) and essential fatty acids may be used as part of the treatment since these nutrients have anti-inflammatory properties and anti-oxidant activities.

Glucocorticoids (GC) are the main stay of therapy for AISD. They may be applied topically or administered systemically depending on the severity of the disease and the amount of the body involved. Since some cats can't metabolize inactive prednisone to the active form, prednisolone, ONLY PREDNISOLONE should be used in cats. In dogs either prednisone or prednisolone may be used. The author has seen cases of feline PF, which were well controlled on prednisolone, but when prednisone was dispensed relapsed, only to go back into remission once the cat was placed back on prednisolone- all at the exact SAME dosage and frequency.

For localized disease the author will apply a potent topical steroid product bid until clinical remission (not to exceed 21 days) and then tapered slowly over the next few months. Be sure to have the owners wear gloves when applying this product. If this treatment is unsuccessful the one of the following systemic therapies will be instituted.

In dogs with more extensive disease or those that fail topical therapy, prednisone or prednisolone is administered at 1 mg/# bid for 4 days then ½ mg/# bid for another 10 days. The dog is rechecked every 14 days. If the disease is in remission, the dose is decreased 25% at each recheck examination. The author defines "remission" as the absence of any active lesions (no pustules and any crusts that are present are easily removed with the underlying epidermis appearing pink rather than erosive). DON'T TAPER THE DOSE TOO QUICKLY. The goal is to maintain the dog on 0.25 mg/# or less every other day of prednisone/prednisolone. If this is not achievable, then azathioprine is added to the therapy (see below). Some dermatologist will use the combination therapy from the onset, but because at least 75% of the dogs in the author's practice can be maintained on just GC and there are additional risks and costs associated with this drug the author considers this a second tier therapy. Only if the dog fails to respond to GC, or can't be managed with every other day administration, will the author add azathioprine to the therapy.

For cats, ONLY prednisolone is used and in fact only prednisolone is stocked in the author's pharmacy- this is to avoid the inadvertent administration of prednisone to a cat. The dose for cats is 1 mg/# bid for 14 days. From that point forward the management of the cat with prednisolone is the same as the dog. If the disease is not controlled with prednisolone then CHLORAMBUCIL (see below) is added to the therapy NOT AZATHIOPRINE!!!

If an animal fails to respond to prednisolone other immunosuppressive agents (see below) will be added to the therapy

Animals on chronic GC, regardless of dose should have a CBC, serum chemistry profile, urinalysis and urine CULTURE (monitoring for asymptomatic bacteriuria) every 6 months. The recommendation for performing a urine culture, even with a normal urinalysis, is best exemplified in 2 reports. In these reports, dogs had been receiving steroids for a minimum of 6 months. The incidence of UTI ranged from 21%-39%. In addition, pyuria was not identified in 48% of the samples that yielded growth. There was

not a correlation between the incidence of UTI and the frequency of drug administration (eg alternate-day versus daily), the type of GC or dosage administered or the duration of therapy (minimum 6 months). Lastly, clinical signs of UTI ranged from 0-32% of the cases. These 2 studies support the recommendations of performing urine cultures on dogs who receive steroids for at least 6 months whether or not they are symptomatic of a UTI. Also it stresses the need for a urine culture whether the urinalysis is normal or not since urine sediment analysis alone was not an adequate means of detecting urinary tract infections in these dogs

Azathioprine (AZA) is an antimetabolite that is a competitive inhibitor of purine. Purine is necessary for DNA formation, so in the presence of AZA, defective DNA is formed preventing cell replication. It has a lag phase of four to six weeks before it reaches its full effectiveness. The drug is administered concurrently with GC. The initial dose of azathioprine is 1.0 mg/# sid. Once remission is achieved, and the dog is either off of GC, or the lowest dose of GC has been obtained, AZA is then tapered every 60-90 days. Usually the author will decrease the frequency, not the dose of azathioprine, first decreasing it to every other day and then if the disease is still in remission, to every 72 hours. A CBC, platelet count, serum chemistry profile are performed every 14 days for 2 months, then q 30 days for 2 months then q 3 months for as long as the dog is on azathioprine. Potential adverse effects include anemia, leukopenia, thrombocytopenia, hypersensitivity reactions (especially of the liver) and/or pancreatitis. AZA should not be used in cats- it may cause irreversible bone marrow suppression.

Chlorambucil (CAL) is used in cats and in dogs who failure to respond to azathioprine or can't tolerate it. The protocol/precautions/monitoring for CAL is the same as w/AZA. The induction dose is 0.1-0.2 mg/KG/day.

Because tetracycline and niacinamide (T/N) have a variety of anti-inflammatory & immunomodulating properties the combination has been used in treating a variety of immune mediated skin diseases, such as discoid lupus erythematosus, vesicular cutaneous lupus erythematosus (idiopathic ulcerative dermatosis of collies and Shelties), lupoid onychodystrophy, pemphigus erythematosus, German Shepard Dog metatarsal fistulae, sterile panniculitis, sterile periadnexal granulomatous dermatitis (idiopathic sterile granuloma-pyogranuloma syndrome), vasculitis, dermatomyositis and cutaneous histiocytosis. The author used to use this combination for any of the previous mentioned diseases if the disease is relatively mild. If any of these diseases fail to respond well to immunosuppressive therapy, T/N may also have been added to the therapy in dogs. Since the unavailability of tetracycline, the author has replaced it with either doxycycycline or minocycline. Currently the author uses subantimicrobial doses of doxycycline. This has 2 advantages- 1 has minimum impact on oral and intestinal bacterial resistance and secondly makes the product cost effective. The dose is 2 mg/kg sid. At this dose the author has not seen the side effects that have occurred with tetracycline (anorexia, vomiting and diarrhea). The dosage for niacinamide in dogs <10 kg is 250 mg, q 8 hours and for dogs >10kg - 500 mg q 8 hours. If there is clinical response, which may take a few months, the niacinamide is slowly decreased from tid, to bid to sid while maintaining sid doxycycline. Side effects are rare but when they occur as usually due to niacinamide. These side effects include vomiting, anorexia, lethargy, diarrhea and elevated liver enzymes. The author has not tried the low dose doxycycline in cats yet but will try 10 mg sid (1/2 of a 20 mg tablet crushed in the food). When administering doxycylcline be sure to use a liquid form or administer a pill in a meat bolus followed immediately with food. ESOPHAGEAL STRICTURES have occurred as a sequele to doxycycline use in cats!!!

Cyclosporine A (CSA), a calcineurin inhibitor, has been used orally at a dose of 5 mg/kg sid in cases of PF with poor results in dogs. Recently the author has used CSA at 5 mg/kg sid- bid with success either as monotherapy or as steroid sparing agent. Others report that using at 5–10 mg kg every 24 hours along with ketoconazole 5 mg kg every 24 hours has increased the treatment success rate. In a retrospective study of cases in which either CSA or chlorambucil was used concurrently with steroids (steroids alone were ineffective) the author concluded that CSA appeared to be as effective as chlorambucil for controlling feline PF when used in combination with steroids.

Recently topical tacrolimus has been reported to be effective in the treatment of facial PF and PE. The author has limited experience with this product.

Sulfasalazine (SSZ) is a sulfa that has both anti-inflammatory and/or immunomodulatory properties due to its prostaglandin synthetase and leukotriene inhibition. In the past it has been used for the treatment of colitis but more recently it has been used for neutrophilic vasculitis. SSZ is metabolized by colonic bacteria to 5-aminosalicylic acid (5ASA) and sulfapyridine (SP). SP is well absorbed, metabolized in the liver, and excreted by the kidney while 5-ASA is much less well absorbed. Because SSZ is metabolized to aminosalicylic ("aspirin") this drug should be used cautiously in cats. The biggest concern with this medication is the possibility of developing irreversible keratoconjunctivitis sicca. This appears to be an idiosyncratic reaction that occurs more in smaller dogs but may occur in any dog. It is essential that you warn the owner that if the eyes become red or they notice an ocular discharge or squinting to contact you immediately so that you can do tear testing. Other side-effects associated with this drug include anemia, KCS and hepatotoxicity so a CBC, serum chemistry profile and Schrimer tear test are performed every 14 days for 2 months, then q 30 days for 2 months then q 3 months for as long as the dog is on SZA. In cases of neutrophilic vasculitis that fail SZA treatment w/dapsone may be effective, however, dapsone appears to be more toxic than SZA. The dose is 20-50 mg/kg tid (maximum 1 gm/dose), usually beginning with 20-30 mg/kg tid. Once the disease is in remission, the dose is slowly tapered

Specific treatment approach- for mild cases of facial PF (or cases of pemphigus erythematosus), a topical glucocorticoid is used. For generalized forms, or in cases with severe facial and/or footpad involvement, prednis(ol)one should be used as described above.

As long as the disease is in remission at each recheck, the steroids are tapered as previously described. If the disease is not in remission at the first 14 day recheck or it can't be kept in remission with steroids at a dose of <0.25 mg/# q 48 hrs, then either azathioprine (dogs) or chlorambucil (cats) is added to the treatment.

If the disease is not responding to the above treatment, CONFIRM that the diagnosis is correct (be sure to have ruled out dermatophytosis, demodicosis and bacterial pyoderma) then , changing to either dexamethasone or triamcinolone may be helpful. Use 0.05-0.1 mg/# bid of either drug, as the starting dose, and then taper as previously discussed.

As a "rescue" treatment for refractory cases of PF, high dose GC pulse therapy has been reported to be successful. Pulse therapy is followed by ½ mg/# bid of prednisolone and then taper as described previously. There are 2 protocols for pulse therapy:

1. 11 mg/kg of methylprednisolone sodium succinate (mixed w/250 ml of D5W) IV sid x 3-5 days
2. 10 mg/kg once daily for 3 days of prednisone ORALLY

Lymphoplasmacytic lichenoid dermatitis

Historically discoid lupus erythematosus (DLE) was considered an auto-immune disease whose symptoms were localized to the skin. Diagnosis was made using the same approach as in cases of PF- signalment, detailed history, physical findings, histopathology changes and response to therapy. In the dog, DLE is the 2nd most common autoimmune skin disease**Error! Bookmark not defined.**. The author has never recognized it in a cat. It has been suggested that there is no age predilection, but in the author's experience it seems to be more common in young to middle aged-dog. Collies, Shelties, German shepherd dogs, Siberian huskies and Brittany spaniels are at risk breeds**Error! Bookmark not defined.**.

Clinical findings include depigmentation, erythema, erosions, crusts and alopecia. When the nasal planum is first affected there is loss of its normal cobblestone appearance and it develops a slate gray appearance. Depigmentation, erythema, erosions and crusts may occur over time. DLE usually begins on the nasal planum and may process to involve the bridge of the nose. It may also involve the lips, periocular region, pinnae, and genitalia. Dogs affected with DLE are not clinically ill.

Differential diagnoses may include mucocutaneous pyoderma, pemphigus complex, cutaneous drug reaction, erythema multiformae, cutaneous lymphoma, uveodermatologic syndrome, SSC, solar dermatitis/collie nose and systemic fungal infections

Mucocutaneous pyoderma (MCP) (the author feels a better name is "antibiotic responsive dermatitis" since bacteria are not seen histologically) is a crusting disease that may affect the lips, nasal planum (exclusively), the bridge of the nose, periocular region, genitals or anus. Clinically it is indistinguishable from DLE. There is no identifiable cause for this disease and the diagnosis is based on the signalment (adult dog, most commonly in German Shepard Dogs (or mixes)), clinical appearance and distribution of the lesions and most importantly response to antibiotic therapy.

In the past MCP was differentiated from DLE based on histopathologic findings. DLE was diagnosed when a lichenoid lymphocytic to lymphoplasmacytic interface dermatitis with hydropic degeneration and/or individual necrotic keratinocyte involving the basal cell layer, pigmentary incontinence and a thickened basement membrane was present. Mucocutaneous pyoderma would be diagnosed histologically when a lichenoid plasmacytic to lympho-plasmacytic infiltration was present without an interface change and without basal cell damage. HOWEVER, this criterion has been called into question with a study that reported that histologically mucocutaneous pyoderma and DLE are indistinguishable! In that study, dogs were separated, based on histologic findings, into 3 groups, ones with lymphocytic lichenoid interface dermatitis with hydropic degeneration; ones with plasmacytic lichenoid dermatitis, and lastly ones with a mixture of the first 2 patterns- lymphoplasmacytic lichenoid, interface dermatitis with hydropic degeneration. The authors then evaluated whether the group responded to antibiotics or immunomodulating therapy. There was no statistical difference when histopathologic features were compared between the 2nd and 3rd groups! The author now believes that all cases of canine nasal dermatitis should have a 30 day course of cephalexin prior to immunomodulating therapy- in fact prior to biopsy a 3-4 week course of a cephalosporin is appropriate and may establish a diagnosis without needing to biopsy the lesion!

A better way to approach cases of nasal dermatitis that presents clinically as the "typical" DLE is to recognize that this is a reaction pattern rather than a disease. This reaction pattern (lymphoplasmacytic lichenoid dermatitis) may be antibiotic responsive or may require immunomodulating therapy. Since the biopsy findings will be identical in both cases, a 30 day trial of a cephalosporin prior to biopsy should be administered. This is the same approach I would apply to those cases of "DLE" that involve other areas, such the perivulvar region or in cases of chelitis.

Diagnosis

Dogs with DLE are clinically healthy and are normal hematologically and serologically (including a negative ANA). Historically the histopathologic changes consistent w/DLE included a lymphocytic to lymphoplasmacytic lichenoid interface dermatitis w/hydropic degeneration of basal keratinocytes. Scattered apoptotic keratinocytes may also be present. Failure to respond to a 30 day course of a cephalosporin is also required for the diagnosis.

Treatment

When treating dogs with DLE it is important to avoid aggressive therapy since it is primarily a cosmetic disease. Occasionally the lesions seem to bother the dog because of pruritus. It is therefore important to treat cases in proportion to the severity of the

symptoms. Be sure that the therapy is not worse than the disease. The author treats this disease in a stepwise progression with each step added to the previous therapy except where noted. The steps are as follows: Cephalexin 10-15 mg/# bid- tid for 30 days (since DLE and MCP are indistinguishable); if the dog does not respond to the cephalexin, then the cephalexin is discontinued and the following treatment is begun, sun avoidance, sun screens and vitamin E and omega 3 fatty acids. Niacinamide and doxycycline are as begun as previously described. If after 60 days the dog doesn't respond to this treatment the next step is topical GC (beginning with a moderately potent GC). If after 60 days there is no response then stop the doxycycline and niacinamide and begin systemic prednisone (anti-inflammatory doses) that is slowly weaned over a period of months to achieve the lowest possible dose.