Nasal Planum and Paw Pad Diseases

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Pemphigus Foliaceus

Pemphigus foliaceus is an autoimmune skin disease that can affect both dogs and cats. Although the incidence of disease in general practice is unknown, it comprises approximately 2% of cases seen in specialty practice.

Pemphigus foliaceus targets a component of desmosomes in the epidermis; desmosomes are essential for cell adhesion in epithelial tissues. Once the desmosome is broken down, then separated keratinocytes round up as **acantholytic** cells. (Not acanthocytes which is a change noted in red blood cells). The disease can be idiopathic but can also be drug induced or drug triggered. Drug induced refers to induction of disease by a drug. In drug triggered disease, the pet has a predisposition to the disease, but the drug then facilitates development of signs. Certain neoplastic conditions can also trigger disease; therefore, when a diagnosis of pemphigus foliaceus is made, it is very important to obtain a thorough drug history and to recommend diagnostic testing, especially in older or systemically ill patients. Sunlight exposure may exacerbate flares.

The disease is typically seen in middle aged to older dogs but can be appreciated in young animals as well. Chow Chows, Akitas and English Bulldogs may have a predisposition for the disease, with Cocker Spaniels, Labradors and Dachshunds being overrepresented.

Cats have a median age of onset of 5 years old with no known sex or breed predilection.

The disease generally starts on the head, face and ears and is bilaterally symmetrical. Lesions may spread to include the trunk, limbs, and paw pads. In some cases, lesions can be limited to the paw pads. Mucus membranes are typically unaffected in pemphigus foliaceus but can be affected in other forms of pemphigus. Pruritus may or may not be present. Pemphigus foliaceus is a pustular disease, but due to the fragility of the pustules, generally dogs and cats will present with diffuse crusting. Erosions, ulcers, alopecia, and erythema may also be present. The lesions can resemble pyoderma; however, the pattern of distribution differs from a typical pyoderma, as that does not typically start on the face and ears.

Because of normal grooming habits, pustules are less common in cats in comparison to dogs. Like dogs, oftentimes cats will present with crusted lesions which start on the head, face and pinnae and are bilaterally symmetrical. It can then spread to the trunk and limbs. Crusted paronychia and disease around the nipples can also occur.

In addition to dermatological lesions, animals can present with lethargy, fever, and anorexia. The lesions may or may not be pruritic; they can be acute and rapid or slowly progressive. In some instances, waxing and waning can be appreciated which may impact diagnosis.

A tentative diagnosis of pemphigus foliaceus can be made by clinical presentation, history, and cytological findings. Cytological examination should reveal neutrophils +/- eosinophils and acantholytic cells with the absence of bacteria. However, bacteria can be present as a secondary infection, and so the presence of it does not negate the possibility of pemphigus foliaceus. As with any other dermatological disease, secondary infections can occur and can complicate the diagnosis. Deep skin scrapings should also be performed to rule out demodicosis. Biopsy is necessary to confirm the diagnosis as other diseases, namely staphylococcal pyoderma and dermatophytosis (*Trichophyton* spp.) can also cause acantholysis. I usually will perform both aerobic bacterial and fungal cultures at the same time as the biopsy, but not everyone recommends this practice. Even with histopathology, it can be challenging in rare cases to differentiate between infectious causes and pemphigus foliaceus; having a concurrent culture can be beneficial. If possible, any bacterial infections should be treated prior to biopsy. However, if the pet is showing signs of systemic illness, sometimes a biopsy needs to be obtained as quickly as possible so that therapies can be started. Regardless, it is always important to try to obtain numerous biopsy samples using the largest biopsy punch possible (minimum of 6 mm in most cases). If taking biopsies of pinnae, footpads or nasal planum, sometimes a 4 mm punch is the largest sample which can be obtained. When obtaining samples, take the whole lesion. Do not attempt to biopsy part normal part abnormal skin. If a biopsy of a crusted lesion is taken, include the crust with your sample. Do not throw it away. Some pathologists even recommend peeling crusts off by themselves and including it in the formalin jar. In some instances, the crust will contain the diagnosis. Communicate with your pathologist and describe the lesions, your cytology findings, and the presentation. This will help them have a better understanding of the case.

Typical histopathology findings in pemphigus foliaceus include subcorneal pustules which span multiple hair follicles, acantholytic cells in rafts and non-degenerate neutrophils and / or eosinophils.

Other therapies, including glucocorticoids, should not be started prior to biopsy, as they can interfere with getting an accurate diagnosis.

The question of the significance of eosinophilic infiltration in dogs was analyzed in a 2010 retrospective study (Vaugh DF, Hodgin GL, Berstein JA.) Eosinophilic infiltrate was more likely found in dogs with concurrent disease, dogs who had adverse effects associated with immunosuppressive therapy and in dogs with a history of allergic dermatitis.

In some instances of pemphigus foliaceus, vasculopathic changes can be appreciated on histopathology. A recent retrospective study reviewed clinical presentation, treatment response and outcomes in dogs with vasculopathic changes and pemphigus foliaceus. The results of the study suggested that dogs with pemphigus foliaceus and vasculopathic changes

were more likely to have signs of systemic illness. Dogs with vasculitis took longer to achieve remission and were more likely to have adverse effects from medications. (Chou Z, Petersen A, Rosser E, et al.)

Once a diagnosis of pemphigus foliaceus is made, it is important to obtain blood work and urine analysis both as a screen for underlying disease but also to obtain a baseline level prior to starting therapies. In a pet with signs of systemic illness, other diagnostic tests may also be obtained, including imaging. It is also important to consider the possibility of drug triggers, discontinuing any medications which were started within 2 months of developing clinical signs.

Treatment of pemphigus foliaceus consists of immunosuppressive therapies, with corticosteroids being the mainstay of therapy. Prednisone / prednisolone are usual therapies, but other options can include methylprednisolone or more potent steroids such as dexamethasone or triamcinolone. In cats, some retrospective studies have suggested triamcinolone may be beneficial. Using these medications can increase risks for adverse side effects. I personally start therapy with 2 mg/kg prednisolone / prednisone in most cases. If there is no response, then I explore other corticosteroids.

Studies have also explored pulse dosing using higher doses of prednisone in dogs. Using this therapy, dogs are dosed at 10 mg/kg for 3 days and then the prednisone is decreased to less than 2 mg/kg. Higher doses can be repeated, but not more than weekly. The dosing protocol could improve time to remission. (Bizikova P, Olivry T.)

Since treatment in most cases is lifelong and given the risks of side effects with corticosteroids, secondary steroid sparing drugs such as azathioprine, mycophenolate motefil, cyclosporine, chlorambucil, or doxycycline / niacinamide are generally started as well. Azathioprine should never be used in cats! It is important to do appropriate monitoring with bloodwork and urine analysis when using these medications as they can have significant side effects.

For animals with focal disease, using topical agents such as topical corticosteroids or tacrolimus 0.1% are also valid choices.

In cases of severely refractory disease, intravenous human immunoglobulin has been used as a treatment option. In a recent case series, Adequan was utilized as an adjunctive steroid sparing agent. Anecdotally, this treatment has been described as beneficial in other dogs as well. (Simpson A, Rosychuk R, Schissler J, et al.). One case report is available in which Oclacitinib was beneficial in the treatment of a cat with pemphigus foliaceus, and one abstract reviewing its usage in a dog. (Carrasco I, Martinez M, Albinyana G.; Cordero M, Lopez-Marquez C, Sheinberg G et al.) More research would be needed to assess its true efficacy.

It is important to monitor patients with pemphigus foliaceus as you would any other autoimmune disease; this means frequent monitoring and recheck cytology, +/- skin scrapings. When tapering medications, it is important not to exceed 20-25% reduction in steroid dose more frequently than every 2 weeks and recheck exams are needed prior to tapering in most

cases. In my experience, a frequent cause of treatment failure is when medications are tapered too aggressively. I personally try not to taper both corticosteroids and adjunctive therapies concurrently. But each case needs to be assessed independently.

These cases can be challenging and require frequent follow up. Prognosis is guarded until the pet goes into remission. Referral is recommended in many cases.

Vasculitis

Cutaneous vasculitis is a term used to describe an inflammatory response directed toward blood vessel walls. Although vasculitis is frequently used as a diagnosis, it is not a definitive diagnosis but rather a cutaneous reaction pattern associated with multiple causes, which can include concurrent disease (infections, food hypersensitivity, neoplasia, tick disease) or precipitating factors (vaccines, drugs). However, it can also be idiopathic.

The pathomechanism of vasculitis is not fully understood but is thought to be related to Type II and Type III hypersensitivity reactions with the latter being the more significant.

Clinical presentation can include palpable purpura, erythematous / purpuric plaques, hemorrhagic bullae, wheals, papules, pitting edema, ulcers, or crusting. Purpuric and erythematous lesions don't blanche on diascopy. (Diascopy is performed by pressing a clear microscope slide over an erythematous lesion. If the lesion blanches with pressure, then it is due to vascular engorgement. If it does not blanche, then there is hemorrhage into the skin.) Lesions usually present on the dependent areas of the body and on areas of pressure, including the apex of the pinnae, tail tip, scrotum, and the paw pads.

Some animals will show signs of systemic illness, including anorexia, depression, and fever with some showing signs of pain, myopathy, polyarthropathy and neuropathy.

Treatment involves identifying the underlying cause, including a thorough drug and vaccine history, CBC, serum chemistry, urine analysis, diagnostic imaging, tick titers, +/- an elimination diet trial.

Diagnosis is confirmed via histopathology. As histopathologic changes can be subtle and can be dependent on the stage of disease, it is important to use a dermatopathologist and advise them of your clinical suspicion of vasculitis. With a general pathologist, the subtle lesions associated with vasculitis can be easily missed.

Identifying and treating the underlying cause is necessary, if one can be determined. For drug triggered cases, discontinuing the inciting medication is important; the drug should also be avoided in the future. For less severe cases, using a combination of doxycycline / niacinamide (**not niacin**) or pentoxifylline is sufficient. In more severe cases, prednisone / prednisolone may need to be considered, and in refractory cases, adding secondary immunosuppressive agents,

such as cyclosporine, azathioprine or chlorambucil may be necessary. In cases where other underlying disease or drug triggers cannot be identified, or if there is a clinical suspicion of allergy, an elimination diet trial should be performed.

Ischemic Dermatopathy

Ischemic dermatopathies are a group of vasculopathic skin diseases which result from loss of blood supply from vasculitis or vasculopathy resulting in atrophy of recipient tissues.

Subtypes of ischemic dermatopathy include juvenile dermatomyositis, non-familial dermatomyositis, post rabies vaccines, generalized vaccine induced ischemic dermatopathy, or adult onset ischemic dermatopathy.

Treatment of ischemic dermatopathy depends on the cause, but typically pentoxifylline and Vitamin E are excellent therapies. However, in more refractory cases, other immunosuppressive medications may need to be instituted. A recent case series also discussed the use of Apoquel as a long-term therapy in dogs with ischemic dermatopathy. (Levy B, Linder K, Olivry T.) Just like with vasculitis, it is important to try to determine the underlying cause and address it as best as possible.

Epitheliotropic Lymphoma

Epitheliotropic lymphoma is a rare cutaneous neoplasm usually of T-lymphocyte origin. In the dog, generally older animals are affected. Mycosis fungoides is the most common form to affect dogs. The disease presents in stages, starting with exfoliative erythroderma. Clinical signs include scaling, erosions / ulcerations, hypopigmentation, alopecia +/- pruritus. Epitheliotropic lymphoma is often misdiagnosed in this stage as it resembles several other dermatologic conditions. On average it takes 5-7 month to make a diagnosis.

Erythematous patches and plaques with associated scaling, alopecia, crusts, erosions / ulcerations then progress to nodules with the three forms often overlapping. This is the most common stage in which animals present due to the presence of the lesions.

The mucocutaneous form is common in dogs with lips, nose and eyelids frequently being affected – hypopigmentation and erythema can be seen with loss of architecture in the nasal planum. Ulcers can also occur in the mouth.

Footpads can be affected and can be hyperkeratotic, ulcerated, or depigmented.

In the disseminated form, dogs can develop signs of systemic illness, including Sézary syndrome and lymphadenopathy.

Diagnosis is suspected based on clinical signs and cytology. Biopsy is needed for definitive diagnosis.

Secondary infections can also occur and should be addressed using topical therapies +/- systemic antibiotics.

Cats can also develop epitheliotropic lymphoma, but this is even more rare. Due to the clinical signs of alopecia, erythema, scaling, they are oftentimes misdiagnosed as having dermatophytosis or parasites. Like dogs, cats can also develop non-healing erosions / ulcers or nodules which can mimic reactions such as eosinophilic granuloma complex. Cats can also develop a condition called feline cutaneous lymphocytosis which clinically and on histopathology can resemble epitheliotropic lymphoma. PARR testing and / or immunohistochemistry may be needed to differentiate between the two diseases.

The prognosis with epitheliotropic lymphoma is generally poor with certain exceptions, such as a solitary lesion which can be surgically excised. Treatment involves corticosteroids and chemotherapeutic agents. Retinoids and interferons have also been utilized in some treatment regimens. Pruritus can be addressed with treatment of secondary infections and Cytopoint.

Referral to a Veterinary Oncologist is highly recommended.

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