Canine and feline pemphigus foliaceus: Improving your chances of a successful outcome

A thoughtful diagnostic and therapeutic process is critical to managing dogs and cats suffering from this potentially fatal dermatologic disease.

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VETERINARY MEDICINE

Pemphigus foliaceus, the most common autoimmune skin condition in dogs and cats, is characterized by pustules, erosions, and crusts. In this article, we focus on the diagnosis and treatment of pemphigus foliaceus in dogs and cats.

PATHOGENESIS

Pemphigus foliaceus affects the epidermis, the outermost superficial skin layer. To help the epidermis act as a barrier to the outside world, the epidermis is composed primarily of tightly adherent keratinocytes. Two types of adhesion structures hold keratinocytes together. Desmosomes are responsible for cell-to-cell adhesion. Hemidesmosomes are responsible for cell-to-matrix adhesion. In the skin, hemidesmosomes bind the deep or basilar epidermal keratinocytes to the basement membrane.

The pemphigus variants occur when autoantibodies target the desmosomes between keratinocytes. Desmosome disruption results in separation of the keratinocytes, which is referred to as *acantholysis*. Keratinocytes that have lost their cell-to-cell adhesion are called *acantholytic keratinocytes*, not *acanthocytes* (*i.e.* crenated red blood cells).

In pemphigus foliaceus in people, the most common target of autoantibodies is the desmoglein 1 (DSG1) glycoprotein in the desmosome.[1,2] The autoantibody response primarily involves IgG (IgG4 subclass).[3] Initial studies in dogs with pemphigus foliaceus only rarely detected an IgG autoantibody response,[4,5] but more recent work using different substrates in indirect immunofluorescence testing confirms that IgG autoantibodies are important in canine pemphigus foliaceus.[6] However, DSG1 is not commonly targeted in pemphigus foliaceus in dogs[7] ; it is not yet known which part of the desmosome is targeted in most canine pemphigus foliaceus cases. Early immunoblotting studies revealed that the target was a 148 kDa or 160 kDa protein.[8,9] Immunoelectron microscopy shows that the site of autoantibody binding is in the extracellular region of the desmosome.[10]

The word *pemphigus* is used for the entire group of autoimmune blistering diseases in which intraepidermal separation occurs via acantholysis. Pemphigus foliaceus is a specific type of superficial pemphigus and is clinically distinct from deep pemphigus diseases. Another example of superficial pemphigus disease is pemphigus erythematosus. Examples of deep pemphigus diseases include paraneoplastic pemphigus, pemphigus vulgaris, and bullous pemphigoid.

The signs of an attack on keratinocyte adhesion structures are clinically evident. When the tight bonds between superficial keratinocytes are affected, it manifests as vesicles and pustules. When the tight bonds between basilar keratinocytes and the skin's basement membrane are affected, it manifests as bullae (large blisters) and ulcers.

More recently, *pemphigus foliaceus* has been proposed as the general term for all superficial pemphigus diseases, since there is an overlap in clinical, histologic, and immunologic characteristics among all the superficial pemphigus conditions.[11] Deep pemphigus conditions, though, still remain clinically and immunologically distinct from the superficial pemphigus conditions. Thus, the term *pemphigus* should not be used as a diagnosis by itself for any patient because it refers to a heterogeneous group of both superficial and deep pemphigus conditions.

SIGNALMENT AND CAUSES

Genetic factors can influence the development of pemphigus foliaceus. In dogs, it is more frequently diagnosed in two breeds with closely related genotypes,[12] Akitas and chows.[4] Pemphigus foliaceus has also been reported in littermates.[13] No breed disposition has been noted in feline pemphigus foliaceus.

Sex and age appear to be unrelated to the development of pemphigus foliaceus in dogs and cats. The age of onset is variable and ranges from 1 to 16 years in dogs[4,5,14] and less than 1 year of age[4] to up to 17 years of age[15] in cats.

Ultraviolet light

Ultraviolet exposure from the sun is a potential environmental trigger for pemphigus foliaceus. The skin lesions in dogs with pemphigus foliaceus can worsen in the summer and improve in the winter.[16,17] Exposing dogs with facial pemphigus foliaceus to ultraviolet B (UVB) results in increased epidermal acantholysis.[18] We think there is a lower prevalence of canine pemphigus foliaceus in cooler U.S. regions compared with warmer U.S. regions with more sun exposure.

Drugs

Drugs can influence the development of pemphigus foliaceus.[19] Some drugs directly induce acantholysis (drug-induced pemphigus foliaceus). Drugs can activate proteolytic enzymes in the skin that then disrupt desmosomes and result in biochemical acantholysis. Drugs can also stimulate the development of autoantibodies against desmosomes, resulting in immunologic acantholysis.[20] Drug-triggered pemphigus foliaceus occurs in patients predisposed to pemphigus foliaceus. The combination of the drug and other patient factors then triggers a flare-up of pemphigus foliaceus.[19]

Human drug-induced pemphigus foliaceus is usually associated with exposure to medications with chemical structures that can contribute to the activation of proteolytic enzymes in the skin. These drugs include thiol compounds containing –SH, or sulfhydryl, groups (*e.g.* penicillamine), medications that can undergo metabolic changes and form active –SH groups (*e.g.* penicillins, cephalosporins), or medications that contain active amide groups (*e.g.* enalapril).[20] In dogs and cats, pemphigus foliaceus has been suspected to be associated with a variety of medications such as cimetidine,[21] cephalexin,[22] amoxicillin and clavulanic acid,[23] ampicillin,[24] and trimethoprim-sulfonamide combinations.[25]

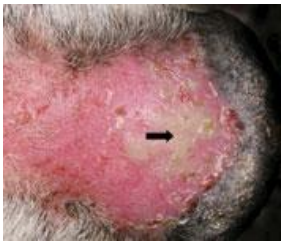
Many patients with newly diagnosed pemphigus foliaceus have a history of exposure to multiple medications. If a patient has either drug-induced or drug-triggered pemphigus foliaceus, discontinuing the medication could help manage the pemphigus foliaceus or cause the pemphigus foliaceus to go into remission. It is difficult, though, to prove an association between any drug and the pemphigus foliaceus. Drug rechallenge would definitively confirm drug-induced pemphigus foliaceus, but since this could harm the patient, we do not recommend drug rechallenge in cutaneous drug reactions. Observing apoptotic keratinocytes histologically cannot be used as a marker for a drug reaction since apoptotic keratinocytes may be seen in dogs with pemphigus foliaceus.[26]

If drug-related pemphigus foliaceus is suspected, review the patient's drug history carefully. Cutaneous drug reactions typically develop more than seven days after the first administration of a drug. If the patient has been previously exposed to the drug, reactions are quick and occur within 24 hours of drug re-exposure.[27]

More recently, we are aware of reports that administration of a topical spot-on product containing metaflumizone and amitraz (ProMeris—Fort Dodge Animal Health) has been associated with pemphigus foliaceus in dogs. The mechanism for this reaction is currently unknown but is an area of active research at one of our laboratories (T.O.).

Other causes

A variety of other factors are possible triggers for human pemphigus foliaceus. Fogo selvagem, a form of human pemphigus foliaceus endemic to some rural areas of Brazil, is likely due to a combination of environmental factors and possibly the patient's genetic susceptibility.[28,29] Nutrition (thiol-containing foods such as garlic and onions[30,31]) and infection[32] have also been associated with some cases of human pemphigus foliaceus. It is unknown if any of these factors, especially diet, are triggers in canine and feline pemphigus foliaceus.

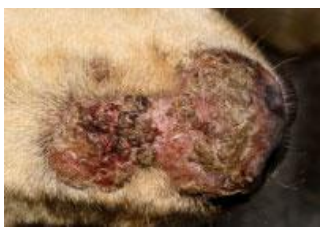


1. A pustule just caudal to the planum nasale of a dog; alopecia and erythema are also present in the dorsal nasal region.

Canine pemphigus foliaceus can be associated with a history of chronic skin disease such as allergies,[33] although no studies have definitively proved this link. Canine pemphigus foliaceus has also been reported in patients with other conditions such as hypothyroidism,[34] leishmaniasis,[35] thymoma,[36] and systemic lupus erythematosus.[37] Pemphigus foliaceus may be present in these patients through coincidence, or pemphigus foliaceus may be occurring in these patients through the induction of desmosome autoantibodies triggered by these systemic conditions.

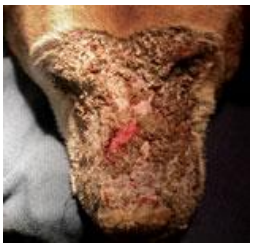
CLINICAL SIGNS

The earliest lesions of pemphigus foliaceus consist of erythematous macules that then progress rapidly to a pustular stage. Pustules tend to be large, irregular, and coalescing (*Figure 1*). Multiple hair shafts protruding from pustules are more consistent with pemphigus foliaceus and help differentiate pemphigus foliaceus from the more common cause of pustules, bacterial folliculitis.[38] Because pustules are fragile and easily ruptured, only crusts or the



2. Crusts from ruptured pustules on a

dried exudate from ruptured pustules may be noted (*Figure 2*). For this reason, crusts rather than pustules are the most commonly seen lesion in cases of pemphigus foliaceus.[4,5,14]



3. Ulceration from a deep pyoderma in a patient with pemphigus foliaceus. Ulcers should not be seen in pemphigus foliaceus patients unless another condition such as a pyoderma is present. Note the symmetrical appearance of the facial lesions.

Erosions can be noted, especially if a crust is removed. Ulcers are rare because pemphigus foliaceus is a superficial epidermal skin disease. Ulcers can be seen in cases of pemphigus foliaceus that have a concurrent condition that affects the deeper sections of skin such as a deep pyoderma (*Figure 3*). Rarely, erosions, crusts, and pustules can be grouped into an annular or polycyclic pattern. Pemphigus foliaceus lesions typically have a waxing and waning course. Lesions are usually bilateral and symmetrical.

Lesions on the concave pinnae should increase your clinical suspicion of pemphigus foliaceus since few other pustular conditions affect the concave pinnae (*Figure 4*). Mucosal lesions are rare in pemphigus foliaceus.

4. Crusts and dried exudate on the concave pinna of a dog with pemphigus foliaceus. (Photo courtesy of Lauren Pinchbeck, DVM, DACVD.)

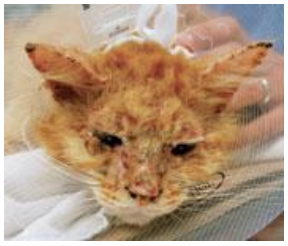
In most dogs, lesions initially appear on the face (the dorsal muzzle, planum nasale, periocular skin, and ears) and then regionalize or generalize over the course of months. Rarely, some dogs will either start with a generalized distribution or have only a localized form of the disease.

In dog and cats with generalized pemphigus foliaceus lesions, widespread erythema and exfoliation can be noted. Massive exfoliation, especially if extending beyond the borders of the original lesions, is more suggestive of bacterial infections than pemphigus foliaceus. Systemic signs such as fever, lethargy, anorexia, and lymphadenopathy can occur with pemphigus foliaceus.[15,33] Systemic signs seem more common in patients with generalized lesions. Pruritus, especially in patients with generalized disease, is variable in dogs and cats with pemphigus foliaceus.[5,14,15] Careful questioning of a pet owner can reveal whether the skin lesions developed before the pruritus. This timing of lesion development is in contrast to allergies, which usually start with pruritus.

5. Crusts on the footpads of a dog with pemphigus foliaceus.

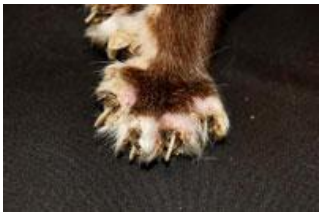
Canine pemphigus foliaceus can involve the footpads along with other sites on the body. Rarely, canine pemphigus foliaceus is localized only to the footpads. Pustules are only rarely seen on the footpads, probably because the pustules rupture while the patient walks. Clinically, pemphigus foliaceus on the footpads results in lameness and hyperkeratosis (*Figure 5*).[39,40] Canine pemphigus foliaceus can also rarely occur just around the claws.[41]

In most cats, pemphigus foliaceus is a mild and localized disease consisting of erosions and yellowish crusts. Pemphigus foliaceus can also spread and become generalized in cats.[15] Feline pemphigus foliaceus most commonly begins on the head (*Figure 6*). Lesions can also affect the pinnae. Cats can have marked suppuration and crusts on or around the footpads or ungual folds of the claws (caseous paronychia; *Figure 7*).[42,43] An onychodystrophy can also occur with these nailfold lesions.



6. Erosions and crusts on the face and ears of a cat with pemphigus foliaceus.

DIFFERENTIAL DIAGNOSES



7. Pedal pemphigus foliaceus in a cat.

Infectious causes of pustular dermatitis can mimic or complicate pemphigus foliaceus.

Superficial pustular dermatophytosis is a fungal infection involving *Trichophyton* species. The lesions can look clinically and histopathologically similar to those of pemphigus foliaceus.[44] While pustular dermatophytosis is uncommon,[45] we recommend evaluating each case of suspected pemphigus foliaceus for dermatophytosis because of the negative

consequences of immunosuppressive treatment in patients with a dermatophyte infection.

A dermatophyte culture can diagnose superficial pustular dermatophytosis, and cytologic examination of the macroconidia from the growth can identify the fungal species. The *Trichophyton* species that causes this form of dermatophytosis can be present both in the epidermis and in the hair follicle. Scale or crust along with hair should be sampled for the dermatophyte culture. A periodic acid-Schiff (PAS) stain is required to differentiate superficial pustular dermatophytosis from pemphigus foliaceus histologically.

Bacterial skin infections are another differential diagnosis for pemphigus foliaceus. Some staphylococci produce an exfoliative toxin that targets desmosomes, resulting in clinical signs similar to those of pemphigus foliaceus.[46] In these cases, large epidermal collarettes, often extending centrifugally, are present. Exfoliation tends to be more severe in bacterial skin infections than in pemphigus foliaceus. Patients with bacterial skin infections will also demonstrate bacteria cytologically. Cytologic examination often shows degenerative neutrophils with the bacteria. Culture of the exudate from within a pustule can identify the bacterial species.

DIAGNOSIS

Pemphigus foliaceus is diagnosed by evaluating the clinical history, physical examination findings, and results of diagnostic tests such as cytologic and histologic examinations (*Table 1*). Because of the potential for severe side effects, pemphigus foliaceus should be definitively diagnosed before systemic immunosuppressive therapy is started.


TABLE 1 VETERINARY MEDICINE

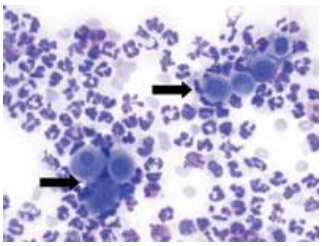
Diagnostic Criteria for Canine and Feline Pemphigus Foliaceus*

- Clinical examination identifies pustules rapidly evolving into shallow erosions and crusts, predominantly on the face and feet.
- Histologic examination shows superficial epidermal or follicular pustules rich in neutrophils and acantholytic keratinocytes.
- The results of a diagnostic work-up rule out other acantholytic neutrophilic diseases such as bacterial skin infections (impetigo, in particular) and pustular dermatophytosis.

*Source: Olivry T. A review of autoimmune skin diseases in animals I—superficial pemphigus. Vet Dermatol. 2016;27(2):79–100.

Table 1: Diagnostic Criteria for Canine and Feline Pemphigus Foliaceus*

Cytology


8. Cytologic examination of an intact pustule from a dog with pemphigus foliaceus showing rafts of acantholytic keratinocytes (arrows) and many nondegenerate neutrophils (Diff-Quik—Dade-Behring; 1000X).

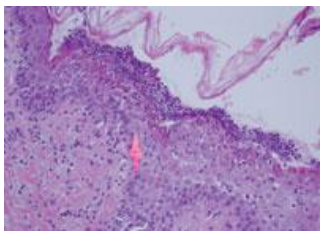
Cytologic examination of an intact pustule (Tzanck preparation) can be a useful in-clinic diagnostic test for tentatively diagnosing pemphigus foliaceus pending biopsy and histologic examination results. Cytologic examination of an intact pustule in pemphigus foliaceus shows nondegenerate neutrophils with acantholytic keratinocytes (*Figure 8*). The cytologic absence of bacteria makes bacterial skin infection a less likely cause of the clinical signs. Since some cases of superficial pustular drug reactions and dermatophytosis can have similar cytologic findings to those of pemphigus foliaceus, biopsy and histologic examination are still recommended before treatment of pemphigus foliaceus.

Blood tests

No hematologic changes are specific to pemphigus foliaceus. Dogs can have a mild to moderate leukocytosis with neutrophilia and a mild to moderate nonregenerative, normocytic, and normochromic anemia (anemia of chronic disease).[5] Cats can have similar changes in addition to basophilia, eosinophilia, lymphopenia, and monocytosis.[15] In cats, no association exists between feline leukemia virus or feline immunodeficiency virus and pemphigus foliaceus. While a complete blood count and serum chemistry profile cannot diagnose pemphigus foliaceus, they can help diagnose any concurrent systemic diseases that could be exacerbated by immunosuppressive therapy for pemphigus foliaceus. Blood work is also recommended to establish baseline values before starting immunosuppressive treatment. An antinuclear antibody test is not necessary in cases of suspected pemphigus foliaceus.

Histology

Biopsies should ideally be performed on pustules. Micropustules can be present under crusts and, thus, visible on histologic examination. For this reason, if an intact pustule cannot be found, biopsy of a crust is another option. To avoid disrupting pustules or crusts, do not scrub the biopsy site. Instead, gently clip the biopsy site while avoiding the removal of surface crusts. The biopsy site can then be gently blotted with alcohol.


9. Histologic examination of pustule obtained by skin biopsy from a cat with pemphigus foliaceus reveals

Biopsy results are more likely to be diagnostic if glucocorticoids, both topical and systemic, are discontinued before biopsy.[15] We recommend discontinuing glucocorticoids for at least one week before biopsy. Submit samples to a dermatopathologist along with a complete history and description of the clinical lesions. The distribution of the lesions is also important. A listing of dermatopathologists can be found online on the Veterinary Information Network (http://www.vin.com|~http://www.vin.com); search for "dermatopathologist registry") or by contacting your local dermatologist. Allow the

dermatopathologist to perform PAS stains so that the biopsy can be evaluated for pustular dermatophytosis.

subcorneal acantholytic keratinocytes and neutrophils (hematoxylin-eosin; 20X).

Histologic examination demonstrates predominantly superficial, eosinophilic, or neutrophilic pustules with acantholytic keratinocytes (*Figure 9*). Rarely, early cases of pemphigus foliaceus can show eosinophilic pustules with spongiosis (intercellular edema) in the epidermis or around hair follicles but no acantholysis.[47]

When bacterial skin infections (impetigo and exfoliative pyoderma) are present with pemphigus foliaceus, it can be difficult to determine which histologic changes are due to the pemphigus foliaceus and which changes are due to bacteria. In general, pemphigus foliaceus is more commonly associated with a greater density of acantholytic cells and large pustules that span across multiple hair follicles compared with bacterial skin infections.[38] Treat any concurrent bacterial infections with antimicrobials before biopsy to increase the chances of a clear diagnosis from histologic examination. If you receive a skin biopsy report that lists both bacterial skin infection and pemphigus foliaceus as possible diagnoses, a practical next step is to treat the possible bacterial skin infection with antimicrobial therapy. Bacterial culture of the skin may be necessary to select an appropriate antibiotic. Full resolution of lesions with only antimicrobial therapy is consistent with a bacterial skin infection rather than pemphigus foliaceus.

Systemic immunosuppression is not recommended without a firm diagnosis of pemphigus foliaceus. If a patient is suspected of having pemphigus foliaceus but diagnostic test results are inconclusive, additional biopsy of other lesions or, preferably, referral to a dermatologist is recommended.

Immunopathology

Immunofluorescence testing is used primarily for research purposes to characterize the immunologic response in pemphigus foliaceus. The identification of intercellular epidermal IgG via direct immunofluorescence is not specific to pemphigus foliaceus in dogs.[4,14] Indirect immunofluorescence identifies circulating autoantibodies but is highly dependent on the substrate. Immunofluorescence is not necessary to clinically diagnose and manage patients with pemphigus foliaceus.

INITIAL TREATMENT CONSIDERATIONS

Pemphigus foliaceus is often a chronic skin condition with a waxing and waning course. Clients should be aware of the possibility of disease recurrence after remission. Because of the potential side effects of medications, doses should be tapered in response to clinical signs.

It is important to educate clients about medication side effects so that they understand why medication doses need to be tapered. Remind clients that pemphigus foliaceus flares may occur after decreasing the medication dose. Without client education, it is easy for owners to become frustrated and perceive that the medications are not helping. The long-term costs of recheck examinations and tests to monitor pemphigus foliaceus patients receiving therapy can also be high. A client handout can help educate owners about pemphigus foliaceus (*to download a handout, go to* http://www.dvm360.com/pemphigus|~http://www.dvm360.com/pemphigus).

Once clients have been fully informed of the prognosis and medication side effects of treatment, initiate pemphigus foliaceus treatment. No set protocol exists for treating canine and feline pemphigus foliaceus. Instead, medications and their doses need to be selected for each individual patient based on the severity of clinical signs and the medications' efficacy and side effects.

Canine cases of pemphigus foliaceus with localized skin lesions may be managed with topical glucocorticoids. In mild cases, topical glucocorticoids can be used alone. In more severe cases, topical glucocorticoids can be used to minimize the dose of systemic immunosuppressive therapy. Topical glucocorticoids are less commonly used in cats because it can be more difficult to apply topical medications to cats. In most dogs and cats, systemic immunosuppression remains the initial treatment of choice for pemphigus foliaceus. Concurrent systemic antibiotic therapy should be considered if there is a bacterial skin infection.

MEDICATIONS USED FOR PEMPHIGUS FOLIACEUS

Glucocorticoids

Topical glucocorticoids can be used as monotherapy for mild cases of pemphigus foliaceus, especially in dogs with localized facial lesions. They can also be used in combination with other systemic medications in more refractory cases. A variety of glucocorticoids more potent than hydrocortisone have been used topically for pemphigus foliaceus such as betamethasone or triamcinolone, both of which are available in a variety of concentrations. Since glucocorticoids can cause skin atrophy, protect the area of glucocorticoid application from trauma. Mild skin atrophy can be managed by switching to a lower-potency topical glucocorticoid. More severe skin atrophy should be managed by stopping all topical glucocorticoids.

Systemic immunosuppression with glucocorticoids provides the most rapid clinical response in dogs and cats with pemphigus foliaceus. Prednisone is initially started at 2 mg/kg/day orally in dogs, and prednisolone is initially started at 2 to 4 mg/kg/day orally in cats. The dose of prednisone or prednisolone may then be increased if no improvement in clinical signs is evident within one or two weeks. Cats may respond better to glucocorticoids other than prednisone because of the lower bioavailability of prednisone compared with other glucocorticoids in cats.[48] If glucocorticoids of different

potencies are used, equivalent doses should be calculated. In cats, triamcinolone can be initially dosed at 2 to 4 mg/kg/day orally, and dexamethasone can be initially dosed at 0.3 to 0.6 mg/kg/day orally. The glucocorticoid dose should be selected based on the clinical signs. Dogs and cats with mild pemphigus foliaceus lesions may respond to lower doses of glucocorticoids.

Long-acting injectable glucocorticoids such as methylprednisolone acetate (Depo Medrol—Pfizer Animal Health) are not recommended for treating pemphigus foliaceus; the dose of any immunosuppressive medication should ideally be adjusted in response to the patient's clinical signs.

Dermatologists occasionally use high-dose pulse oral and intravenous glucocorticoid administration to treat pemphigus foliaceus in dogs. These high dosages (oral prednisone at 10 mg/kg/day[49] or intravenous methylprednisolone succinate at 11 mg/kg/day[50]) are typically given for three days followed by a much lower dose of oral prednisone (0.5 to 2 mg/kg/day). High-dose glucocorticoid administration is used primarily in severe pemphigus foliaceus cases in which quick remission of signs is required. Relapse is still possible once the glucocorticoid dose is decreased. At this time, high-dose pulse glucocorticoid therapy should be considered experimental; further studies are needed to demonstrate its benefit.

Initial side effects of glucocorticoids include polyuria, polydipsia, and polyphagia. With longer-term use, a myriad of other side effects can develop such as gastric ulceration, hepatopathy (dogs), diabetes mellitus, calcinosis cutis, skin atrophy, and secondary infections. In a retrospective study, the use of gastroprotectants such as sucralfate or histamine receptor blockers (famotidine) had no effect on survival time in dogs with pemphigus foliaceus receiving glucocorticoids.[51]

In many dogs, glucocorticoids alone are insufficient to manage pemphigus foliaceus signs. In past studies, glucocorticoid monotherapy resulted in acceptable management of pemphigus foliaceus signs in only 35% to 39% of dogs.[5,52] Glucocorticoid monotherapy is more effective in cats. Complete remission with only glucocorticoids occurs in 62% to 100% of cats with pemphigus foliaceus receiving prednisone and triamcinolone, respectively.[15]

Table 2: Systemic Medications Used with Glucocorticoids in Dogs with Pemphigus Foliaceus

Any oral glucocorticoid should be tapered gradually once clinical remission of the pemphigus foliaceus is achieved (no new pustules or erosions). The exact glucocorticoid tapering protocol will vary in each patient, but, in general, glucocorticoids can be tapered by about 25% each time the dose is adjusted. Recheck the patient after each change in the oral glucocorticoid dose. If the pemphigus foliaceus recurs when the glucocorticoid is tapered, another immunosuppressive medication should be added. Likewise, when glucocorticoids alone cannot induce remission of pemphigus foliaceus, other immunosuppressive medications are then used as adjunctive therapy so that the glucocorticoid dose may initially be decreased and glucocorticoid administration can eventually be discontinued (*Tables 2 & 3*).

Azathioprine

Azathioprine is a purine analogue that interferes with cellular nucleic acid synthesis. Thus, its greatest cytotoxic effect is on proliferating cells such as lymphocytes. Azathioprine is more effective at suppressing humoral immunity than cell-mediated immunity.

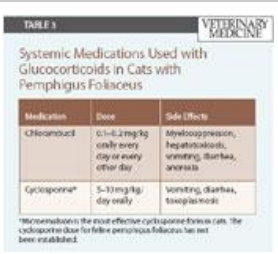


TABLE 3 VETERINARY MEDICINE

Systemic Medications Used with Glucocorticoids in Cats with Pemphigus Foliaceus

Medication	Dose	Side Effects
Chlorambucil	0.1–0.2 mg/kg orally every day or every other day	Myelosuppression, hepatotoxicosis, vomiting, diarrhea, anorexia
Cyclosporine*	5–13 mg/kg/day orally	Vomiting, diarrhea, toxoplasmosis

*Microemulsion is the most effective cyclosporine form in cats. The cyclosporine dose for feline pemphigus foliaceus has not been established.

Table 3: Systemic Medications Used with Glucocorticoids in Cats with Pemphigus Foliaceus

Azathioprine is the medication most commonly used to manage canine pemphigus foliaceus when lesions do not respond to glucocorticoid monotherapy. In these cases, lesions worsen or stay the same with glucocorticoids or signs relapse with lower dosages of glucocorticoids. Adding azathioprine in a dog with pemphigus foliaceus can then reduce the need for systemic glucocorticoids and potentially enable discontinuation of the glucocorticoid.

Azathioprine is commonly started at 2 to 2.5 mg/kg/day orally in dogs with pemphigus foliaceus. If azathioprine is being used with glucocorticoids to manage pemphigus foliaceus signs, do not reduce the dose or frequency of glucocorticoids immediately after starting azathioprine since azathioprine can take weeks to have an effect.

Side effects of azathioprine include bone marrow suppression resulting in leukopenia, anemia, and thrombocytopenia. Vomiting, diarrhea, hepatotoxicosis, and acute pancreatitis can also occur. In our experience, hepatotoxicosis is the most common side effect. Complete blood counts and serum chemistry profiles must be performed regularly while a patient is receiving azathioprine, usually every two to three weeks during initial therapy. When azathioprine and glucocorticoids are used together, it can be difficult to monitor for azathioprine-induced hepatotoxicosis because of the usual elevation of serum liver enzyme activities caused by glucocorticoid administration.

Azathioprine is metabolized by an enzyme called thiopurine methyltransferase (TPMT). Low TPMT concentrations increase the risk of myelosuppression. Variations in TPMT concentrations have been noted in dogs.[53] Cats have lower TPMT concentrations than dogs do,[54] and azathioprine is usually avoided in cats because of the high likelihood of severe myelosuppression.

Chlorambucil

Chlorambucil is an alkylating agent that causes cross-linking of cellular DNA. Doses range from 0.1 to 0.2 mg/kg orally every 24 to 48 hours. Side effects include vomiting, diarrhea, anorexia, and myelosuppression.[52] Chlorambucil is especially used in cats with pemphigus foliaceus that fail to respond to glucocorticoids since azathioprine is not a treatment option for cats. Complete blood counts and serum chemistry profiles must be performed regularly while a patient is receiving chlorambucil, usually every two to three weeks during initial therapy.

Cyclosporine

Cyclosporine is a calcineurin inhibitor that blocks the transcription of cytokine genes in activated T cells.[55] Cyclosporine is an approved treatment for canine atopic dermatitis (Atopica—Novartis Animal Health) and is used extralabel for a variety of other immune-mediated conditions in dogs and cats.[56] Cyclosporine's side effects in dogs and cats include inappetence, vomiting, diarrhea, gingival hyperplasia, hirsutism, papillomas, psoriasiform lichenoid-like dermatosis, and disseminated toxoplasmosis.[57,58] The microemulsion form of cyclosporine (Atopica; Neoral—Novartis) is more readily absorbed in dogs and cats and should be used instead of other forms of cyclosporine such as Sandimmune (Novartis). Complete blood counts and serum chemistry profiles must be performed regularly while a patient is receiving cyclosporine therapy. In cats receiving cyclosporine, elevated liver enzyme activities can be a sign of toxoplasmosis.[59]

In a small pilot study, cyclosporine monotherapy at 5 to 10 mg/kg/day was ineffective in managing pemphigus foliaceus signs in four out of five dogs.[60] Since the publication of that initial study, there have been anecdotal reports of using cyclosporine at 10 mg/kg/day or greater to manage pemphigus foliaceus in dogs, especially those with milder presentations.

Cyclosporine is more effective for pemphigus foliaceus when used in combination with other therapies. In three dogs with pemphigus foliaceus already receiving azathioprine and glucocorticoids, oral cyclosporine at 7.5 to 10 mg/kg/day was used with oral ketoconazole at 2.5 to 5 mg/kg/day to successfully induce remission.[61] The ketoconazole was used to increase cyclosporine concentrations. All dogs were then able to have glucocorticoids discontinued within three to 12 weeks of adding the cyclosporine and ketoconazole. Signs did not worsen when the glucocorticoids were discontinued. Cyclosporine was used successfully with prednisone to induce remission of pemphigus foliaceus signs in another study involving five dogs.[62] Initial doses ranged from 1 to 2.6 mg/kg/day and 5 to 18 mg/kg/day for the prednisone and cyclosporine, respectively. While the initial cyclosporine dose was maintained in each patient, the prednisone dose was then tapered to 0.5 mg/kg every other day with no relapse of signs. The cyclosporine was continued and eventually tapered to 3 to 4 mg/kg every other day. No studies exist on using cyclosporine to manage feline pemphigus foliaceus, but we have used cyclosporine to manage some patients.

In our experience, cyclosporine can take weeks to have a clinical effect on pemphigus foliaceus lesions. This delayed effect may be because of cyclosporine's action on T lymphocytes, the cells that drive the autoimmune reaction, without direct effect on autoantibodies that cause the skin lesions. Thus, if cyclosporine is used with glucocorticoids to manage pemphigus foliaceus signs, do not reduce the dose or frequency of glucocorticoids immediately after starting cyclosporine.

Tacrolimus

Tacrolimus, another calcineurin inhibitor, has been used topically for conditions such as localized atopy in dogs[63] and people. In dogs with a form of superficial pemphigus (pemphigus erythematosus), applying tacrolimus 0.1% as a thin film on facial lesions twice a day helped manage clinical signs.[64] In that study, tacrolimus was used as the sole therapy in one dog with superficial pemphigus, while the other dog was also managed with systemic immunosuppressive medications. Of note is that pemphigus erythematosus is suspected to be a crossover between discoid lupus and pemphigus foliaceus. It is possible that the nasal lesions of pemphigus erythematosus that responded to tacrolimus were the lupus-like lesions. In our opinion, in general, pemphigus foliaceus does not appear to respond to tacrolimus ointment.

Tacrolimus can cause a pruritic or burning sensation during the initial few days of application in people, and signs of pruritus and irritation have been observed in dogs with initial use.[63] These signs typically resolve despite continuation of therapy. In 2005, the tacrolimus label was changed to include a warning that some people have developed cancer while receiving this medication. Clients should wear gloves when applying this medication.

Niacinamide with tetracycline or doxycycline

Tetracycline is an antibiotic that also modulates the immune system by suppressing neutrophil chemotaxis and lymphocyte activation.[65] Tetracycline is used in combination with niacinamide for a variety of immune-mediated dermatologic conditions.

For dogs < 10 kg, 250 mg each of tetracycline and niacinamide are given orally every eight hours. For dogs > 10 kg, the dose is 500 mg of each every eight hours. Tetracycline and niacinamide are typically not used in cats because it is difficult to administer these larger-sized oral medications to most cats. Doxycycline has the advantage of needing less frequent dosing than tetracycline. It has been substituted for tetracycline and used at a dose of 5 to 10 mg/kg orally in dogs every 12 to 24

hours. However, there is no documentation of the benefit of doxycycline when it is substituted for tetracycline to treat canine pemphigus foliaceus.

Tetracycline and niacinamide appear to be more helpful as a sole therapy in mild cases of pemphigus foliaceus, especially those cases with lesions localized to the face. It can also be used in combination with glucocorticoids or azathioprine.[66] It can take several weeks for tetracycline and niacinamide to have a clinical effect. Once remission occurs with tetracycline and niacinamide, the frequency of administration can be decreased to once or twice a day.

Side effects include lethargy, anorexia, diarrhea, and increased risk of seizures. Lethargy and anorexia are especially associated with niacinamide. If the niacinamide needs to be discontinued, the tetracycline (or doxycycline) alone can continue to have immunomodulatory activity.

Other medications

A variety of other therapies have been used for pemphigus foliaceus, including cyclophosphamide, injectable gold salts, intravenous immunoglobulins, mycophenolate mofetil, and dapsone. Referral to a veterinary dermatologist is recommended before using these therapies. Referral is also recommended if treatment failure occurs with any of the medications discussed in this article.

MONITORING

No matter which medications are chosen to manage pemphigus foliaceus, frequent recheck examinations are important to assess clinical response and to determine when to taper medications. We recommend rechecking all pemphigus foliaceus patients within one or two weeks of starting medical management. A substantial improvement in clinical signs within 10 days of starting glucocorticoid therapy in dogs is a positive prognostic factor in the successful management of pemphigus foliaceus.[5]

Glucocorticoids are often used for pemphigus foliaceus treatment induction because of their rapid onset. If marked clinical improvement is noted, the glucocorticoid dose or frequency of administration should be tapered by about 25%. If clinical signs have stayed the same or worsened despite glucocorticoid therapy, the glucocorticoid dose should be increased or combination therapy should be started. Combination therapy should also be started if remission of the pemphigus foliaceus cannot be maintained when the glucocorticoid dose is tapered. We recommend rechecking patients before and after each change in medication type or dose to help monitor clinical signs.

Cutaneous side effects of immunosuppression such as a bacterial skin infection, demodicosis, or dermatophytosis can look clinically similar to a pemphigus foliaceus flare. It is important to rule out these conditions instead of assuming that any new dermatologic lesions are due to pemphigus foliaceus, otherwise lesions may worsen from immunosuppression, and refractory pemphigus foliaceus may be erroneously diagnosed. Skin scrapes and hair plucks should be performed on new areas of alopecia, and cytologic examination should be used to evaluate lesions for secondary skin infections.

Table 4: Principles of Treating Pemphigus Foliaceus in Dogs and Cats

Depending on the medication being used to manage the pemphigus foliaceus, blood work may be necessary to monitor for medication side effects. Regular urine bacterial cultures are recommended for dogs and cats receiving systemic immunosuppressive therapy to monitor for occult urinary tract infections.[5] Urinalysis to identify an active sediment (white blood cells in the urine) is not an effective way to screen for urinary tract infections in most patients with pemphigus foliaceus because systemic immunosuppression may suppress the number of white blood cells in the urine even when a urinary tract infection is present. The principles of treating canine and feline pemphigus foliaceus are summarized in *Table 4*.

The outcome of treating pemphigus foliaceus in dogs and cats is variable; 40%[51] to 88%[4] of dogs with pemphigus foliaceus have their condition managed successfully. Neither a younger age of onset nor a localized disease pattern correlate with improved survival times.[51] The only factor that has influenced long-term survival time in dogs with pemphigus foliaceus is the concurrent use of antimicrobials with immunosuppressive medications, likely because the antimicrobials minimize the development of secondary bacterial skin infections and urinary tract infections. Prolonged remission after immunosuppressive therapy can occur in dogs and cats with pemphigus foliaceus.[15,67]

Mortality from pemphigus foliaceus can occur because of disease progression, medication side effects, or client-requested euthanasia. Severe cases of pemphigus foliaceus can result in marked cachexia or sepsis secondary to infections. Adverse effects are common with most of the medications used for pemphigus foliaceus. Euthanasia accounted for almost 70% of deaths in pemphigus foliaceus dogs in one retrospective study.[51] Reasons for client-requested euthanasia included not being able to control the pemphigus foliaceus, a perceived poor quality of life, and the development of adverse effects from medications. For all these reasons, pemphigus foliaceus should be considered a potentially fatal dermatologic condition. Consultation with a specialist or referral can be helpful when managing pemphigus foliaceus cases.

SUMMARY

Pemphigus foliaceus is a pustular and crusting autoimmune dermatologic condition. The prognosis for pemphigus foliaceus in dogs and cats is variable, and signs can wax

and wane. A diagnosis is based on the patient's clinical history, a histologic examination of skin samples, and a diagnostic work-up that rules out other neutrophilic and pustular skin conditions. A variety of immunomodulatory medications can be used to manage pemphigus foliaceus. Frequent recheck examinations and client communication are important for managing pemphigus foliaceus. Because of the potential for severe medication side effects, medications should be selected and tapered based on the severity of clinical signs.

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