

CPD article

Pemphigus foliaceus in cats

Pemphigus foliaceus is the most common autoimmune skin disease in cats. Autoantibodies attack and destroy desmosomes, the structures connecting one keratinocyte to the other, causing what is clinically recognised as a pustular dermatitis. The target autoantigen within the desmosome is unknown in cats. The disease occurs more frequently in middle-aged cats and involves predominantly the pinnae, head and feet, including the claw folds. Clinical lesions include superficial erosions and honey-coloured crusts, alopecia, scaling and caseous material that can be expressed out of the claw folds, while pustules are rarely appreciated. Cats may be systemically ill. Diagnosis requires cytology and histopathology, as well as ruling out dermatophytosis and bacterial infections. Treatment is based on glucocorticoid monotherapy. Other immunomodulatory drugs, such as ciclosporin or chlorambucil, may be added to reduce the glucocorticoid requirement. The prognosis is good, but regular check-ups are mandatory because of potential relapse and possible adverse effects of the drugs used. <https://doi.org/10.12968/coan.2021.0072>

Silvia Colombo DrMedVet DipECVD, Private Practitioner, Servizi Dermatologici Veterinari, Legnano, 20025, Italy. colombo_silvia@yahoo.it

Key words: Cat | chlorambucil | ciclosporin | feline | glucocorticoids | pemphigus foliaceus

Autoimmune skin diseases are characterised by reactions of the immune system against 'self' antigens. The reaction can be mediated by antibodies or by cells belonging to the immune system (<https://pathology.jhu.edu/autoimmune/definitions>). In cats, autoimmune skin diseases are considered uncommon to extremely rare, with the exceptions of pemphigus foliaceus (pemphigus foliaceus) and vitiligo. Currently, the existence of some autoimmune skin disease, such as cutaneous lupus erythematosus, is questioned in the feline species. The autoimmune skin diseases reported in cats are summarised in *Table 1*. Pemphigus foliaceus is the most common autoimmune skin disease, although it represents only 1% of cases seen by veterinary dermatologists (Scott et al, 2013a).

Pathogenesis

Pemphigus foliaceus is an antibody-mediated autoimmune skin disease. Autoantibodies belonging to the IgG subclass attack and destroy the desmosomes, the special structures connecting one keratinocyte to another. The clinical result of the detachment of keratinocytes in the upper layers of the epidermis is a pustule, which is the primary pemphigus foliaceus lesion in all affected species (Bizikova, 2020). The target autoantigen within the desmosome has been identified in humans as desmoglein-1 and, more recently, in dogs as desmocollin-1, while it has not yet been identified in cats. A recent study showed that circulating anti-keratinocyte IgG antibodies were present in 77% of cats affected by pemphigus foliaceus. The authors postulated that the target autoantigen is likely to be different from the one identified in dogs and humans (Levy et al, 2020).

Pemphigus foliaceus in cats is spontaneous in the majority of cases, and may be uncommonly associated with drug administration, particularly with antibiotics and methimazole (Bizikova and Burrows, 2019; Jordan et al, 2019). Two cases

associated with thymoma (Biaggi et al, 2009; Coyner, 2011) and one case associated with feline leishmaniosis (Rufenacht et al, 2005) have also been reported. Two studies described development of pemphigus foliaceus in cats with a history of chronic allergic skin disease (Preziosi et al, 2003; Jordan et al, 2019). In the author's experience, it is not uncommon to diagnose pemphigus foliaceus in cases referred for the work-up of allergic pruritus.

Clinical features

There is no apparent breed predisposition, with over 60% of affected cats being domestic short- or long-haired cats. The median age of onset is 6 years and it is more common in females (female to male ratio: 1:5). The average time between onset of disease and diagnosis is 3 months (Preziosi et al, 2003; Bizikova and Burrows, 2019; Jordan et al, 2019).

The primary lesion of feline pemphigus foliaceus is a large subcorneal pustule, spanning multiple hair follicles. However, the lesion is easily ruptured and often cannot be appreciated. The most common lesions identified in felines are superficial erosions and honey-coloured crusts that are often coalescing, together with alopecia and scaling (*Figure 1*). The parts of the body most commonly involved are the pinnae (over 80% of the reported cases), the nasal planum, muzzle, eyelids and the footpads, although the disease may be generalised (*Figures 2 and 3*). The areas surrounding the nipples represent a peculiar location for pemphigus foliaceus in the cat, while the most distinctive localisation of pemphigus foliaceus is the claw fold. A thick, yellowish, caseous exudate can be expressed from the claw folds and, when present, this is a useful hint at the diagnosis (*Figure 4*). In the majority of cats, the disease involves two or more body sites, but localised lesions have been reported in 19% of cases. Lesions are usually symmetrical and pruritus is apparent in over 60% of

Table 1. Autoimmune diseases in cats

Antibody-mediated autoimmune skin disease	Prevalence	References
Pemphigus foliaceus	Uncommon	Bizikova, 2020; Bizikova and Burrows, 2019; Irwin et al, 2012; Preziosi, 2019; Preziosi et al, 2003
Pemphigus vulgaris	Extremely rare	Manning et al, 1982; Scott et al, 2013b
Mucous membrane pemphigoid	Two cases	Olivry et al, 2002
Bullous pemphigoid	One case	Olivry et al, 1999
Cell-mediated autoimmune skin disease		
Systemic lupus erythematosus	One case reported	Vitale et al, 1997
Cutaneous lupus erythematosus (nasal, discoid)	Five cases	Kalaher and Scott, 1991; Willemse and Koeman, 1989
Vitiligo	Uncommon	Tham et al, 2019
Antibody- and cell-mediated autoimmune skin disease		
Paraneoplastic pemphigus	One case	Hill et al, 2013



Figure 1. Honey-coloured crusts on the inner side of the pinna in a cat with pemphigus foliaceus.

cases (Preziosi et al, 2003; Bizikova and Burrows, 2019; Jordan et al, 2019).

Concurrent otitis externa, more often purulent and with secondary bacterial infection, may be diagnosed in approximately 30% of affected cats (Jordan et al, 2019). When pedal lesions are severe, cats are often systemically ill, having anorexia, lethargy, hyperthermia, enlarged lymph nodes and lameness. The most common clinicopathological abnormalities include leukocytosis and neutrophilia. Differential diagnoses include dermatophytosis, adverse drug reaction, (drugs are recognised triggers for



Figure 2. Severe crusting and small erosions on the nasal planum and bridge of the nose in a cat with pemphigus foliaceus.

pemphigus foliaceus), leishmaniosis (so far, only once reported with a clinical presentation similar to pemphigus foliaceus) and superficial pyoderma, which is uncommon in cats (Preziosi et al, 2003; Rufenacht et al, 2005; Bizikova and Burrows, 2019; Jordan et al, 2019).

Diagnosis

Despite the difficulty of identifying intact pustules in cats, useful samples for cytological examination can be obtained from the underneath of a crust or from the claw folds. Cytology shows large numbers of non-degenerate neutrophils and acantholytic cells, which may be in rafts. Acantholytic cells are round, nucleated and usually basophilic, as they come from the spinous layer of the epidermis (Preziosi et al, 2003; Bizikova and Burrows, 2019; Jordan et al, 2019). Bacterial infection as a complicating factor has been reported in 63% of cases, and *Malassezia* overgrowth in 19% of cases after cytological examination (Jordan et al, 2019).



Figure 3. Superficial skin layers peeling off the surface of a digital footpad in a cat with pemphigus foliaceus.

However, superficial pyoderma in cats does not usually present as a pustular dermatitis, and the role of the bacterial infection should be further investigated with culture and sensitivity testing. Secondary infections should be treated before taking biopsy samples for histopathological examination. Dermatophytosis should be ruled out by performing a fungal culture.

The confirmative diagnostic test is histopathology from skin biopsy samples and crusts. Microscopic examination of skin biopsies may show sub-corneal pustules containing neutrophils and acantholytic cells, sometimes admixed with eosinophils (Gross et al, 2005). Crusts are often multilayered with degenerating inflammatory cells, corneocytes and serum alternating. Including crusts in the samples can be extremely useful to the pathologist, because ghost acantholytic cells may be observed within the crust and intact pustules are very difficult to find in the feline patient. In the dermis, there is perivascular to interstitial inflammation, with neutrophils being the most common cell type, followed by mast cells, plasma cells, lymphocytes and eosinophils (Gross et al, 2005). In a series of cases, vascular changes with hyaline thrombi, hyalinised vascular walls, microhaemorrhage and leucocytoclasia were described in 17% of the cases (Jordan et al, 2019). Direct/indirect immunofluorescence testing kits are available only for use in research establishments.



Figure 4. Thick, yellowish purulent exudate expressed from a claw fold in a cat with pemphigus foliaceus.

Treatment

In general, cats affected by pemphigus foliaceus respond to treatment better than dogs. The vast majority of cats achieves remission in 4 to 6 weeks on average. Spontaneous remission has been reported for drug-related cases (Bizikova and Burrows, 2019). Death as a result of the disease itself, adverse effects of treatment or concurrent diseases directly related to the drugs administered (for example, diabetes mellitus) is reported in 20% or less of cases (Preziosi et al, 2003; Bizikova and Burrows, 2019; Jordan et al, 2019).

Glucocorticoid monotherapy is the first treatment and the majority of cats do not require association with other immunosuppressive drugs to keep the disease in remission. Recommended induction doses are 2–3mg/kg/day when using prednisolone or methylprednisolone, 0.1–0.2mg/kg/day when using dexamethasone and 0.3–0.5mg/kg when using triamcinolone. In one review, a pulse therapy protocol with high-dose glucocorticoids was used in 39% of the cases, as an attempt

Table 2. Details of high-dose glucocorticoid pulse therapy in cats

Induction phase	Maintenance phase	
Triamcinolone 1 mg/kg orally once daily for 3 days	Prednisolone 10 mg/kg orally once daily for 3 days	Dexamethasone 1 mg/kg orally once daily for 3 days
Prednisolone 2–3 mg/kg orally once daily	Taper and repeat induction phase if needed	

Table 3. Adverse effects reported in cats treated for pemphigus foliaceus with systemic glucocorticoids

(Transient) diabetes mellitus	Polyuria	Lethargy
Upper respiratory tract infections	Polydipsia	Anorexia
Hepatopathy	Urinary tract infections	Skin atrophy/fragility
Polyphagia	Diarrhoea	Pancreatitis
Weight gain	Melena	Demodicosis

to gain quicker control of the disease. However, no advantages over traditional glucocorticoid therapy were observed (Bizikova and Burrows, 2019). Details of glucocorticoid pulse therapy are summarised in *Table 2*.

The dosage is gradually reduced when the disease is in remission and a slow reduction of 20–25% every 2–4 weeks is recommended (Preziosi et al, 2003; Bizikova and Burrows, 2019; Jordan et al, 2019; Preziosi, 2019). The ideal maintenance dose should be 0.5mg/kg orally once daily or on alternate days, when using prednisolone or methylprednisolone. A study of 37 cats explored the results obtained with glucocorticoid monotherapy. The authors reported complete remission within 8 weeks in 97% of cats, with a median induction dose of 2mg/kg of prednisolone administered once daily. The median maintenance dose in the study was 1.2mg/kg/week. Even with very slow dose reduction, relapses occur in over 50% of the cats on glucocorticoid monotherapy (Simpson and Burton, 2013). Another study evaluated the management of feline pemphigus foliaceus in general first-opinion practice, and some interesting observations were made. Firstly, remission was easily achieved in 90% of cats with glucocorticoid monotherapy, however more than 70% of cases relapsed when the dose was reduced. Second, severe adverse effects resulting from glucocorticoids were observed in 16% of cats, including two cats treated with long-acting injectable glucocorticoids, which should be avoided whenever possible (Coyner et al, 2018).

If glucocorticoids are not effective in maintaining remission when the dose is decreased, or severe adverse effects occur, discontinuation or a significant dose reduction may be required. Other immunosuppressive drugs should be added at this point, in order to decrease the dose and, if possible, ultimately discontinue glucocorticoids (Preziosi et al, 2003; Bizikova and Burrows, 2019; Jordan et al, 2019). The most commonly used immunomodulatory drugs in combination with glucocorticoids are ciclosporin (5–10mg/kg) and chlorambucil (0.1–0.2mg/kg/day). To achieve disease control, glucocorticoid dosage should be initially increased back to a higher dose or the initial dose when the second drug is added, and then gradually tapered again. Results with chlorambucil or ciclosporin as steroid-sparing drugs have been compared in a recent study, although the number of cats included was low (six cats per group of treatment). According to this study, the two drugs were equivalent in terms of response to treatment and time to obtain disease remission. However, all cats treated

with ciclosporin were eventually weaned off glucocorticoids, compared to one cat only in the chlorambucil group (Irwin et al, 2012). Further studies with more cases are necessary to confirm these findings.

Adverse effects occur in approximately 30% of cases (Bizikova and Burrows, 2019; Jordan et al, 2019) and are usually result from using glucocorticoids (*Table 3*). Chlorambucil may induce leucopenia, thrombocytopenia, anaemia and increased liver enzymes. Monitoring for adverse effects with haematology, biochemistry and urinalysis is recommended every 6 months if the cat is treated with glucocorticoid monotherapy or ciclosporin. When chlorambucil is administered, haematology should also be performed every 2–3 weeks over the first 3 months of therapy. Diarrhoea, hypertrichosis and disseminated mycobacteriosis have been observed in cats treated with ciclosporin.

Topical therapy with glucocorticoids or tacrolimus may be an option when the disease is localised (Bizikova and Burrows, 2019). Good results with oclacitinib have been described recently, although in a single case report (Carrasco et al, 2021). When secondary bacterial infection is identified on cytological examination, systemic antibiotics are recommended. Ideally, the antibiotic should be selected based on culture and sensitivity testing (Jordan et al, 2019). Other immunosuppressants suggested in older papers include doxycycline, gold salts, megestrol acetate and azathioprine, which is not recommended in cats because of the high risk of bone marrow suppression.

Prognosis

The prognosis for pemphigus foliaceus in cats is good, providing that patients are followed up with frequent checks and treatment modifications are introduced as soon as required. For example, in cats requiring high doses of glucocorticoids to maintain remission, a second immunomodulatory drug should be introduced in a timely fashion. Long-term remission with discontinuation of all drugs is not uncommon in cats (approximately 15% of cases). However, the majority of cats require long-term treatment with glucocorticoids, ciclosporin or chlorambucil either alone or in combinations.

Conflicts of interest

The author declares no conflict of interest.

References

- Biaggi AF, Erika U, Biaggi CP, Taboada P, Santos R. Pemphigus foliaceus in the cat: two case reports. Presented at the 34th World Small Animal Veterinary Association Congress, São Paulo, Brazil, 21–24 July 2009
- Bizikova P. Autoimmune diseases. In: Noli C, Colombo S (eds). *Feline dermatology*. Switzerland: Springer Nature; 2020:495–509
- Bizikova P, Burrows AK. Feline pemphigus foliaceus: original case series and comprehensive literature review. *BMC Vet Res*. 2019;15(1):22–37. <https://doi.org/10.1186/s12917-018-1739-y>
- Carrasco I, Martinez M, Albinyana G. Beneficial effect of oclacitinib in a case of feline pemphigus foliaceus. *Vet Dermatol*. 2021;32(3):299–301. <https://doi.org/10.1111/vde.12949>
- Coyner KS. Dermatology how would you handle this case. *Veterinary Medicine*. 2011;106(6):280–283
- Coyner K, Tater K, Rishniw M. Feline pemphigus foliaceus in non-specialist veterinary practice: a retrospective analysis. *J Small Anim Pract*. 2018;59(9):553–559. <https://doi.org/10.1111/jsap.12869>
- Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Pustular diseases of the epidermis. Skin diseases of the dog and cat*. 2nd edn. Oxford: Blackwell Science Ltd; 2005:4–26
- Hill PB, Brain P, Collins D, Fearnside S, Olivry T. Putative paraneoplastic pemphigus and myasthenia gravis in a cat with a lymphocytic thymoma. *Vet Dermatol*. 2013;24(6):646–649. <https://doi.org/10.1111/vde.12086>

- Irwin KE, Beale KM, Fadok VA. Use of modified ciclosporin in the management of feline pemphigus foliaceus: a retrospective analysis. *Vet Dermatol.* 2012;23(5):403–409. <https://doi.org/10.1111/j.1365-3164.2012.01069.x>
- Jordan TJM, Affolter VK, Outerbridge CA, Goodale EC, White SD. Clinicopathological findings and clinical outcomes in 49 cases of feline pemphigus foliaceus examined in Northern California, USA (1987–2017). *Vet Dermatol.* 2019;30(3):209–219. <https://doi.org/10.1111/vde.12731>
- Kalaher K, Scott D. Discoid lupus erythematosus in a cat. *Feline Pract.* 1991;17:7–11
- Levy BJ, Mamo LB, Bizikova P. Detection of circulating anti-keratinocyte autoantibodies in feline pemphigus foliaceus. *Vet Dermatol.* 2020;31(5):378–386. <https://doi.org/10.1111/vde.12861>
- Manning TO, Scott DW, Smith CA, Lewis RM. Pemphigus diseases in the feline: seven case reports and discussion. *J Am Anim Hosp Assoc.* 1982;18:433
- Olivry T, Chan LS, Xu L et al. Novel feline autoimmune blistering disease resembling bullous pemphigoid in humans: IgG autoantibodies target the NC16A ectodomain of type XVII collagen (BP180/BPAG2). *Vet Pathol.* 1999;36(4):328–335. <https://doi.org/10.1354/vp.36-4-328>
- Olivry T, Dunston SM, Zhang G, Ghohestani RF. Laminin-5 is targeted by autoantibodies in feline mucous membrane (cicatricial) pemphigoid. *Vet Immunol Immunopathol.* 2002;88(3–4):123–129. [https://doi.org/10.1016/S0165-2427\(02\)00166-6](https://doi.org/10.1016/S0165-2427(02)00166-6)
- Preziosi DE. Feline pemphigus foliaceus. *Vet Clin Small Anim.* 2019;49(1):95–104. <https://doi.org/10.1016/j.cvs.2018.08.009>
- Preziosi DE, Goldschmidt MH, Greek JS et al. Feline pemphigus foliaceus: a retrospective analysis of 57 cases. *Vet Dermatol.* 2003;14(6):313–321. <https://doi.org/10.1111/j.1365-3164.2003.00347.x>
- Rufenacht S, Sager H, Muller N et al. Two cases of feline leishmaniasis in Switzerland. *Vet Rec.* 2005;156(17):542–545. <https://doi.org/10.1136/vr.156.17.542>
- Scott DW, Miller WH, Erb HN. Feline dermatology at Cornell University: 1407 cases (1988–2003). *J Feline Med Surg.* 2013a;15(4):307–316. <https://doi.org/10.1177/1098612X12468922>
- Scott DW, Miller WH, Griffin CE, Campbell KL. Muller and Kirk's small animal dermatology. 7th edn. St Louis: Elsevier Mosby; 2013b:432–500
- Simpson DL, Burton GG. Use of prednisolone as monotherapy in the treatment of feline pemphigus foliaceus: a retrospective study of 37 cats. *Vet Dermatol.* 2013;24(6):598–601. <https://doi.org/10.1111/vde.12081>
- Tham HL, Linder KE, Olivry T. Autoimmune diseases affecting skin melanocytes in dogs, cats and horses: vitiligo and the uveodermatological syndrome: a

KEY POINTS

- Pemphigus foliaceus is the most common feline autoimmune skin disease, yet it only represents 1% of cases seen by veterinary dermatologists because other autoimmune skin diseases are even more rare.
- The clinical result of the detachment of keratinocytes in the upper layers of the epidermis is a pustule, which is the primary pemphigus foliaceus lesion in all affected species.
- The primary lesion is a pustule, although it is not often seen because it can be easily ruptured.
- The best diagnostic hint is a thick, yellowish, caseous exudate that can be expressed from the claw folds.
- When taking biopsy samples, always include crusts in the vial, because 'ghost' acantholytic cells may be present.
- Glucocorticoid monotherapy is the mainstay of treatment, but ciclosporin or chlorambucil may be added to discontinue or reduce the glucocorticoid dose.

comprehensive review. *BMC Vet Res.* 2019;15(1):251. <https://doi.org/10.1186/s12917-019-2003-9>

- Vitale C, Ihrke P, Gross TL, Werner L. Systemic lupus erythematosus in a cat: fulfillment of the American rheumatism association criteria with supportive skin histopathology. *Vet Dermatol.* 1997;8(2):133–138. <https://doi.org/10.1046/j.1365-3164.1997.d01-2.x>
- Willemsse T, Koeman JP. Discoid lupus erythematosus in cats. *Vet Dermatol.* 1989;1(1):19–24. <https://doi.org/10.1111/j.1365-3164.1990.tb00071.wv>