

Feline Autoimmune Skin Diseases: Pathogenesis to Therapy

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Because of the rarity of most of the immune-mediated, and particularly, autoimmune skin diseases (AISD) in cats, such diseases represent a diagnostic and therapeutic challenge for general as well as specialty veterinarians. A correct diagnosis and understanding of the immunopathomechanism(s) of each of these specific diseases are often the key factors involved in making a rational choice among the available drugs.

AUTOIMMUNITY AND AUTOIMMUNE DISEASES

Autoimmunity is a multifactorial event resulting in the breach of self-tolerance and induction of an immune response against (a) self-antigen(s) in a susceptible animal. Although the traditional classification of autoimmune diseases as either B cell- or T cell-mediated is still used to simplify the complex nature of the processes, it is critical to realise that autoimmunity involves all, innate and adaptive, aspects of the immune response. Furthermore, genetics, environmental triggers like UV light, drugs and infectious agents are well-known factors that can play a role in the initiation or perpetuation of the autoimmune response.

For a disease to be called autoimmune, the tissue damage must be caused by an adaptive immune response to one or more self-tissue antigens. The most convincing proof that a particular disease is caused by an autoimmune response is the ability to replicate the disease in a recipient after passive transfer of the active immune components (antibodies and/or T cells). Such proof is currently lacking for all feline AISD, however.

AUTOIMMUNE SKIN DISEASES IN CATS: FROM IMMUNOPATHOGENESIS TO TREATMENT

Many feline autoimmune skin diseases recognised over the years represent clinical and/or histological homologues of those seen in humans and dogs. In general, these diseases are very rare, which represents the main impediment to understand the underlying pathomechanism. To overcome this lack of information, a translation of knowledge from human and canine disease equivalents is often undertaken. Similarly, well-established protocols for treatment of feline autoimmune skin diseases based on high-quality studies and large number of patients are currently unavailable. As a result, the treatment choice is often empirical, based on a single case report or is extrapolated from human and canine medicine. In general, clinicians prescribing an immunosuppressive treatment should always try to answer several main questions beforehand:

1. What kind of autoimmune skin disease am I dealing with?
2. Is this disease likely antibody mediated or T-cell mediated?
3. Are there published effective treatment protocols (in cats or other species)?
4. Are there any contradictions for usage of particular drugs in cats? (cats are not small dogs)

5. Are there any contradictions for usage of a particular drug in my patient? (concurrent disease, concurrent medications, etc.)
6. How am I going to monitor for efficacy and potential side effects?

Skin Diseases with a Dominant Antibody-Mediated Pathomechanism

In antibody-mediated diseases where autoantibodies drive the clinical phenotype of the disease, the breach in tolerance will result in the activation of self-reactive T cells that, in turn, will help B cells to produce autoantibodies. Secreted autoantibodies may target specific autoantigens and cause direct tissue damage (e.g., pemphigus, bullous pemphigoid), or they may form immune complexes and, thus, activate other immune cells and the complement cascade resulting in secondary tissue damage (e.g., SLE, bullous pemphigoid). Activated B cells, then, further add to the inflammation by producing a myriad of cytokines and, importantly, they internalise self-antigens from damaged tissues and present them back to cognate T cells, thus contributing to an amplification loop of the pathologic immune response.

Feline Pemphigus

The pemphigus group includes autoimmune blistering skin diseases in which autoantibody-targeted desmosomes undergo a variety of changes resulting in loss of adhesion and blister formation. Based on the depth of the blister formation, two pemphigus variants have been described in cats: a) superficial: pemphigus foliaceus (PF) and b) deep: pemphigus vulgaris (PV). Little is known about the pathogenesis of feline PF and PV and, at the time of this writing, the target antigen(s) remain(s) unknown. There is some evidence that cats with pemphigus produce antikeratinocyte autoantibodies. Indeed, keratinocyte-bound IgG were detected in a majority of feline PF and PV patients.¹⁻³ Detection of circulating autoantibodies by indirect immunofluorescence yielded only rare positive results in the past and this technique had been considered unreliable; this was likely due to the type of substrate used to perform the test and/or the quality of the secondary antibodies/reagents available in the past. The use of feline footpad and buccal mucosa increased the level of detection significantly. Indeed, seven out of 10 feline PF sera tested in our laboratory contained detectable antikeratinocyte IgG antibodies.

Clinically and histologically, feline PF resembles its canine homologue. An excellent summary of the clinical and histological features of feline PF can be found in a recently published review.³ Conversely, little information is available for feline PV. Based on the published cases, cats with PV usually present with ulcerative lesions in the oral cavity, lips and nasal planum. Halitosis and salivation are associated symptoms and are likely related to the oral lesions and secondary infection.

Diagnosis of PV is based on thorough clinical assessment (type of lesions, mucosal involvement, positive marginal or direct Nikolsky's sign) and demonstration of the classical histological lesion of suprabasal acantholysis.¹ Further confirmation of diagnosis may include detection of tissue-bound and circulating antikeratinocyte antibodies by direct, as well as indirect immunofluorescence, using feline footpad and buccal mucosa substrates.

Because of the limited number of reported feline pemphigus cases, there are no established treatment guidelines for pemphigus management and, therefore, the choice of treatment is often based on the reported experience achieved with other immune-mediated diseases (immunosuppressive drugs used in feline medicine and their main side effects are listed in Table 1).

Traditionally, an immunosuppressive dose of prednisone or prednisolone at dosages 2–6 mg/kg per day was prescribed to treat both PF and PV. In most reported cases, a monotherapy with glucocorticoids was sufficient to control clinical signs.^{1,2} The wide range of the dosages and the observed "resistance" of some cats to glucocorticoids could have been due to the insufficient bioavailability of prednisone in cats. It is, therefore, recommended to use prednisolone instead of prednisone in this species.⁴

If additional immunosuppression is required, chlorambucil is often the drug of choice used in combination with glucocorticoids. Azathioprine had been used in feline PF and also other autoimmune and immune-mediated diseases.⁵ Unfortunately, reports of rapid and severe bone marrow suppression, even with every-other-day dosing, have been of concern, and this drug has been abandoned from a wide usage among clinicians. A possible explanation of such a high sensitivity of cats to azathioprine could be their low (genetic) activity of enzyme thiopurine methyltransferase responsible for degradation of toxic by-products in cats.⁶

New treatment options, whose efficacy for management of feline autoimmune diseases awaits to be investigated, include mycophenolate mofetil, leflunomide, methotrexate and cyclosporine. All these drugs have been already used to manage other immune-mediated feline diseases and, although not as a first choice drugs, they may present a therapeutic option in refractory cases, especially as glucocorticoid-sparing agents.⁷⁻¹⁰

Table 1. Immunosuppressive drugs used in feline medicine and their main side effects

Diseases Targeting the Basement Membrane Zone (with which subepidermal blistering disease am I dealing?)

In cats, only two autoimmune subepidermal blistering diseases have been characterised: bullous pemphigoid (BP) and mucous membrane pemphigoid (MMP).^{11,12} In both diseases, autoantibodies targeting basement membrane protein(s), specifically the NC16A segment of collagen XVII in BP, and the NC16A or laminin-5 (LM3A32) in MMP, were detected.

As only a very small number of feline cases has been described in the literature, diagnostic criteria for human and canine BP and MMP are the only ones that can be used to distinguish between these two entities. In general, BP presents usually as a skin-predominant disease with tense vesicles and ulcer (head, trunk,

limbs). Subepidermal clefting without cytolysis and with only mild eosinophilic and/or neutrophilic inflammation was seen on histology of the reported cat. On the other hand, MMP represents a chronic blistering disease affecting more commonly mucosae and mucocutaneous junctions and, on histology, none or only minimal inflammation accompanies the subepidermal clefting. Scarring may or may not be present. Additional diagnostic tests include the detection of basement membrane-bound immunoglobulins (most often IgG) and/or C3 in the patient's tissue (direct immunofluorescence) and the detection of circulating antibodies using salt-split buccal mucosa from a healthy cat (indirect immunofluorescence). In case of BP, the latter technique reveals the binding of immunoglobulins to the epidermal (roof) side of the cleft. Unfortunately, given that the reported cats with MMP were shown to be immunologically heterogeneous with either anti-NC16A or anti-laminin-5 antibody responses, the indirect immunofluorescence staining of a salt-split mucosal tissue cannot definitively distinguish feline MMP from BP. Indeed, the antibody deposits can be detected on either the epidermal (top) or dermal (bottom) side of the cleft of the salt-split mucosa in cats with anti-NC16A or anti-laminin-5 autoreactivity, respectively. Therefore, in general, the final diagnosis should always be the result of a combination of a thorough clinical, histological and, if available, immunofluorescence assessment.

A relevant treatment recommendation and prognosis cannot be made due to the small number of reported cases. An immunosuppressive dose of prednisolone was able to provide rapid remission of clinical signs in two cases, while only a partial remission was seen in the third. One possible explanation for the incomplete response in the second case could have been the choice of prednisone in which a lower bioavailability in cats has been suggested.⁴ Topical treatment with glucocorticoids could be of benefit in cats with localised lesions (e.g., on the ear pinnae).

Skin Diseases with a Dominant T-Cell-Mediated Pathomechanism

In some autoimmune diseases, self-reactive T cells that lost tolerance are the main effector mechanism responsible for the clinical signs. The tissue damage seen in such diseases is predominantly the result of a direct cytotoxicity of the autoreactive T cells and/or by their soluble products.

Erythema Multiforme (EM) and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN). (One disease with different severities or two different entities?)

In people, these three diseases had been, in the past, considered to be the same entity varying just in the severity and extent of the lesions. Today, it is believed that EM differs from the other two conditions not only clinically, but also etiologically (Table 2).¹³

Table 2. Comparison of different immune-mediated diseases

EMm	Typical or atypical raised targets < 10% of the body surface No mucosal involvement (or only oral mucosa)	Infectious triggers more likely
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EMM	Typical or atypical raised targets < 10% of the body surface Two or more mucosae involved	Infectious triggers more likely
SJS	Atypical flat targets and macules with or without blisters, more widespread < 10% of the body surface Mucosal involvement	Drug triggers more likely
SJS/TEN	Similar to SJS 10–30% of the body surface Mucosal involvement	Drug triggers more likely
TEN	Poorly defined erythematous macules and flat targets progressing to blisters > 30% of body surface Mucosal involvement	Drug triggers more likely

EMm: erythema multiforme minor; EMM: erythema multiforme major; SJS: Stevens-Johnson syndrome; TEN toxic epidermal necrolysis, SJS/TEN overlap syndrome (Modified from Al-Johani 2007)

The proposed pathogenesis in these three entities involves an alteration of keratinocyte antigenicity by virus or drugs, leading to a cell-mediated immune response and keratinocyte death. Only a small number of feline EM cases can be found in veterinary literature (published in English language)¹⁸⁻²⁴ and, therefore, it is not possible to draw conclusions about either breed or age predisposition.

In three out of the eight cases, the authors described maculopapular and target lesions on the ventral body with or without concurrent ulcerations affecting other parts of the body.^{18,22} More widespread crusts and/or ulceration with or without mucocutaneous or buccal mucosa involvement were described in other three cats,¹⁹⁻²¹ while thick crusts affecting > 50% of body area, including footpads and nail beds, were described in one case²³. Interestingly, the larger body area reported to be affected in some cases might suggest the diagnoses of SJS or TEN, rather than EM, if human criteria were to be applied.^{20,21,23} A drug trigger was possible in seven cases (a retrospective assessment using the Naranjo scale);²⁵ however, a preceding laryngotracheitis of unknown origin or a vaccination with feline rhinotracheitis-calicivirus-panleukopenia virus vaccine were reported in three cases^{19,21,23}. Finally, in the only case where drug association was not proposed by the author, feline herpes virus 1 (FHV1) DNA was isolated from skin biopsies of a cat presenting with widespread scaling and a history of an upper respiratory tract infection two weeks beforehand.²⁴

Although the histology of EM reveals the classical pattern with keratinocyte cell death at multiple levels of the epidermis, the clinical phenotype appears to be more variable than that of humans, ranging from target lesions to widespread scaling and ulceration. The inconsistency in the lesional phenotype could be due to the very small number of available cases, the high similarity in the histological lesions between EM, SJS and TEN or the lack of suitable classification system for such feline diseases.

Treatment of EM should be directed at eliminating the suspected offending cause. In severe or refractory cases, treatment with immunomodulatory/immunosuppressive drugs targeting T cells and/or their soluble products should be considered (Drug table). Indeed, both feline EM cases reported in literature that required other than a simple drug-withdrawal treatment were successfully managed with either glucocorticoids or intravenous immunoglobulins.^{22,23} Similarly, only very few cases of feline TEN cases could be found in the veterinary literature.^{18,26,27} Clinical signs seen in affected animals consisted of extensive erythematous macules and patches with variable degree of necrosis and ulceration. A positive Nikolsky sign was mentioned in one feline case. Additionally, systemic signs including malaise, lethargy, fever and pain and high percentage of mortality (3/7) were also reported. In all cases, a drug trigger was considered to be a possible etiological agent (organophosphate insecticide, d-limonene and beta-lactam antibiotics).

As early lesions of TEN (and SJS) often histologically resemble those of EM, a close assessment of the clinical signs and extent of the lesions are necessary for achieving a definitive diagnosis.

Feline SJS and TEN are dermatological emergencies and, as such, their treatment requires intensive supportive care to maintain the patient's hydration and prevent secondary infections and septicaemia. All preceding drugs should be withdrawn and immunomodulatory/immunosuppressive drugs targeting the T cells and/or their soluble products might be considered (IVIG, high-dose glucocorticoids), even though practice guidelines based on an evidence-based medicine approach are still missing in veterinary and human medicine.

Systemic Lupus Erythematosus (SLE). (Skin as a part of the clinical spectrum, the immunopathology behind the disease and alternative treatments)

Feline SLE is a multisystemic autoimmune disease caused by an immune system dysregulation, which results in autoantibody production and immune complex formation (type III hypersensitivity). Direct antibody-mediated cytotoxicity and T cell-mediated autoimmunity are also important contributors to the entire SLE clinical picture.

A definitive breed predisposition has not been established; yet, Siamese cats appear to be overrepresented in the published literature. Cats affected with SLE are usually systemically ill (fever, polyarthritis, renal disorder, haematological abnormalities, myositis, neuropathy, etc.) with or without skin manifestations. Skin involvement is present in approximately 60% of feline SLE cases, according to a recent internal medicine textbook (Ettinger 7th edition), and the lesions are usually described as erythema, erosions to shallow ulcers and crusting on the face, pinnae, nail beds, footpads or more generalised on the trunk. A bilateral symmetry is often observed.^{18,28,29}

Eleven criteria for diagnosis of SLE in animals have been adapted from human medicine and a fulfilment of three or more of these is required to make the diagnosis of SLE. Clinicians should bear in mind that skin biopsies are supportive of diagnosis, but not diagnostic by themselves. The classical histological finding in the skin biopsy is interface dermatitis with basal cell death, which may progress into a dermoepidermal separation and ulceration. Signs of concurrent vasculitis are rare, but may occur. Skin biopsies can also be used for demonstration of IgG and C3 deposition along the basement membrane using a direct immunofluorescence (positive lupus band test).

The treatment of SLE should include an avoidance of sunlight and should focus on targeting both T cell and B cell immune response. In the majority of reported cases, an immunosuppressive dose of glucocorticoids was found to be sufficient to control the disease.^{18,28,29} In more refractory cases, a combination therapy with chlorambucil can be used; although, because of potential side effects, it is recommended to taper down the chlorambucil before the steroids are reduced. Alternative treatments in refractory cases targeting predominantly T cells may include cyclosporine or mycophenolate mofetil (MMF); the latter had been successfully used in two feline IMHA cases poorly responding to steroids without adverse effects.⁸ Clearly, further studies evaluating the efficacy of MMF as a monotherapy or as a steroid-sparing agent is warranted to better determine the usefulness of this drug in the treatment of feline immune-mediated disorders.

Recently, two papers reported a successful treatment of two canine lupus variants with hydroxychloroquine, an antimalarial drug also used in human lupus therapy.^{30,31} In people, this drug was reported to have limited side effects, the main one being retinopathy. No adverse events were reported in the dogs from the two studies.

Thymoma and Autoimmunity

Thymus plays multiple roles in the development and regulation of the adaptive immune system: a) development of immunocompetent T cells; b) differentiation of T cell into subsets; c) establishment of immune tolerance; d) regulation of production of mature T cells in the thymus and at the periphery via hormones. Therefore and not surprisingly, a neoplasia affecting the thymus could disturb this finely tuned process and lead to an immune dysregulation.

In cats, thymomas are uncommon (3 per 1060 cats diagnosed with neoplasia,³² or 2 per 3200 hospital-admitted cats³³). Although the most common clinical signs are dyspnoea and pleural effusion, numerous reports of autoimmune/immune-mediated conditions associated with thymomas can be found in the literature. The most commonly reported entities are myasthenia gravis and thymoma-associated exfoliative dermatitis (TAED), but a case of immune-mediated granulocytopenia and a case of erythema multiforme have been also described in cats with a thymoma.^{19,34-37} Similarly, dogs and up to 45% of people with thymomas will be diagnosed with a concurrent autoimmune disease.^{36,38}

It is not fully understood how a thymoma leads to an immune dysregulation, but several hypotheses have been proposed: a) an escape of thymoma-driven thymocytes into the periphery without critical selection and maturation; b) an increased proliferation of thymocytes leading to the expression of aberrant (autoreactive)

T cell receptors (TCR); or c) genetic mutations resulting in an impaired expression of HLA class II molecules by epithelial cells in the thymus responsible for T cell education.

As seen in Table 3 below, thymoma in cat can be associated with several autoimmune processes, which usually involve both antibody-mediated and cell-mediated cytotoxicity. Treatment should be aimed at removing the thymoma. In some cases, however, the already started autoimmune response requires an additional immunosuppressive treatment (IVIg in cases like TEN or PNP as an initial treatment could be of benefit, immunosuppressive dose of glucocorticoids with or without concurrent cytotoxic drugs like chlorambucil). In case of complete tumour removal, the immunosuppressive treatment is usually needed only temporarily.

Table 3. Dermatological presentations observed in cats with thymoma

Thymoma-associated syndrome	Clinical presentation	Histology
Exfoliative dermatitis	Erythema, exfoliation and secondary alopecia (generalised, often starting at the head and progressing caudally)	Epidermal hyperkeratosis, interface dermatitis and mural folliculitis; milder transepidermal apoptosis than EM
Exfoliative dermatitis/Erythema multiforme combination [^]	Erythema and exfoliation on the head and pinnae, ulceration at the site of imidaclopride application and erythematous papules and "bull's eye" lesions in the groin and axillae	Keratinocyte apoptosis at all levels, lymphocyte satellitosis and interface dermatitis
TEN-like*	Large macules progressing into ulcers affecting > 70% of the body, oral and mucocutaneous ulceration	Diffuse devitalisation of the epidermis, lymphocytic exocytosis and apoptosis at all levels at the periphery, same process affects the hair follicle epithelium
Paraneoplastic pemphigus*	Maculopapular rash progressing into deep erosions and/or ulcers (abdomen, ear canals)	Subepidermal clefting with scattered apoptotic keratinocyte throughout the epidermis and interface dermatitis present

[^] one published case (Godfrey 1999) and one unpublished; * unpublished cases [one case each; P. Bizikova; P. Hill (the latter is currently in press)]

CONFLICT OF INTEREST STATEMENT

The author discloses no conflicts of interest.

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