Updates on Feline Atopic Dermatitis (or should we say CATopy?)
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INTRODUCTION
Despite the fact that feline allergic skin diseases are common conditions, our understanding of allergic skin diseases in cats have been growing very slowly compared to dogs. The most common allergic skin diseases in cats are flea allergy dermatitis, cutaneous adverse food reactions (food allergies) and atopic dermatitis. Others less common include mosquito bite hypersensitivity and contact dermatitis.

More recently, there has been much debate regarding the true occurrence of feline atopic dermatitis (FAD) and its correct terminology. Canine atopic dermatitis is defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features, associated most commonly with IgE antibodies to environmental allergens based on intradermal and/or IgE serology testing. What evidence exists for the occurrence of a similar feline condition, and could a similar definition be applied to cats? Evidence is still accumulating, however; similarities exist in cats compared to humans and canine atopic dermatitis.

The type of lesions and distribution pattern are quite variable, making it difficult to characterize and diagnose FAD. Treatment is usually lifelong and often a challenge, involving a multimodal approach.

TERMINOLOGY
This pruritic hypersensitivity condition in cats has been most commonly known as FAD, feline atopy or simply feline environmental allergies. Because the pathogenesis of this condition in cats has not been fully elucidated, the term atopy has been questioned, and other new names have been proposed to define this condition, including non-flea, non-food hypersensitivity dermatitis, atopic-like dermatitis or intrinsic atopic dermatitis (i.e., non-allergic form, without IgE involvement). More recently, the term recommended by the International Committee on Allergic Diseases of Animals (ICADA) is feline atopic syndrome (FAS). This includes, however, hypersensitivity caused by environmental and food allergens, or a combination of both. For ease of understanding, the author elected to refer to it in this text as FAD or feline atopy. Although, ironically, the term CATopy seems to be more appealing, considering the current knowledge.

SIGNALMENT AND GENETIC PREDISPOSITION
FAD appears to be more common in young cats, although it can affect any age. One recent study showed that it affected cats of 3 to 12 years of age, with 22% of the cats older than 7 years. Although previous studies indicated no sex predisposition, a recent study showed that females may be predisposed. Currently, there is no strong documented evidence for a genetic predisposition in cats to atopic disease. More recently published studies have suggested that pure bred cats including the Abyssinian and Devon Rex, and mixed breeds appear to be predisposed.
ETIOLOGY AND PATHOGENESIS

The Role of IgE antibodies: The development of IgE antibodies to environmental allergens is regarded as an important mechanism in the pathogenesis of atopic dermatitis in dogs. Several studies have demonstrated strong evidence that feline IgE exists. Attempts to measure the levels of feline IgE in serum have required the production of reagents able to detect feline IgE directly. This has been achieved in three ways, namely polyclonal antibodies, monoclonal antibodies and the human FcεR1 receptor that is used to measure IgE levels in dogs and humans. Unfortunately, studies using these reagents in cats have shown no difference in concentrations of house dust mite specific IgE in cats without skin disease and cats with presumed atopic skin disease. There are currently several laboratories that measure allergen-specific IgE in cats; however, there is variability in technique and interpretation. One study, however, demonstrated the development of clinical and histological cutaneous inflammation in 7 domestic non-allergic cats after cross-linking IgE intradermal administration. Intradermal testing is used in cats but often with unrewarding results and more difficult to interpret than in dogs, although obvious positive reactions are sometimes obtained. Therefore, although feline IgE exists, there is currently no strong evidence that IgE is involved in the skin disease that we label as FAD.

Cellular mechanisms: According to one study, the skin of atopic cats (lesional and non-lesional) seems to demonstrate similar changes compared to those observed in allergic humans and dogs, when compared with non-allergic cats, with larger numbers of mast cells and eosinophils, CD1a+ (Langerhans cells), MHC II cells, CD4+ and CD8+ lymphocytes and IL-4 producing lymphocytes, supporting a similar pathomechanism of atopic dermatitis in cats. Moreover, a small study using atopy patch test and aeroallergens in 6 cats with atopic dermatitis showed positive cutaneous erythematous reactions in 3/6 cats with histological evidence of inflammatory cells and cytokines seen in most of the cats, similar to what is seen in atopic disease, supporting the evidence of occurrence of atopic disease in cats.

The role of food allergens: The role of food allergens in FAD has not been investigated; however; concurrent food allergy and FAD has been documented. The clinical signs of food allergies and FAD appear to be indistinguishable.

Cutaneous barrier and transmission route of aeroallergens: Although an abnormal skin barrier and percutaneous, oral and respiratory transmission of aeroallergens have been shown to be very important in the pathogenesis of canine and human atopic dermatitis, the understanding and importance of these factors in atopic cats remain to be studied. One study showed that transepidermal water loss measurement may be a useful means for the evaluation of the epidermal barrier integrity in cats, with possible use in the monitoring of treatment of feline allergic skin diseases.

CLINICAL PRESENTATION

The large majority of cats (82%) with FAD has demonstrated severe non-seasonal pruritus, although pruritus can be variable. Cats often itch and overgroom secretly, making it more difficult to diagnose FAD.
Besides pruritus, cats with allergic skin disease have a wider variety of clinical presentations than dogs. This clinical variability has led to the concept of feline cutaneous reaction patterns. Four main patterns are currently recognized: 1. miliary dermatitis, 2. symmetrical non-inflammatory alopecia, 3. eosinophilic granuloma complex, 4. head and neck pruritus. Often cats show a combination of these patterns. The most affected areas include the abdomen, dorso-lumbosacral area, medial thighs, axillae, legs and paws. Other less commonly affected areas include head, neck and ears. These cutaneous reaction patterns are not pathognomonic for individual diseases, but are a common reaction of feline skin to a diverse range of diseases including other allergic skin disease, ectoparasites, bacterial and fungal infections, behavioural factors or idiopathic. FAD can occur concurrently with other dermatoses including food allergies, flea allergy dermatitis, malassezia dermatitis and superficial pyoderma, in addition to otitis externa, and rarely upper respiratory signs and lymphadenomegaly.

Unlike the dog, there is currently no defined phenotype for atopic cats. Without a characteristic clinical appearance, it is difficult to establish any useful clinical criteria that might point to a diagnosis of FAD. Cats with presumed atopic disease can present with any of the four described cutaneous reaction patterns. To date, there is no clear evidence that one pattern is more likely to represent feline atopic disease compared to another.

**DIAGNOSIS**

As reported for dogs and humans, there is no well-defined criteria to establish the diagnosis of FAD. A detailed history and a complete physical examination are important, however; the lack of specific immunological features of FAD and the variability of the clinical presentation make the diagnosis more difficult and challenging for the clinician.

Diagnostic tests that might assist with diagnosis and help rule out other similar skin conditions or concurrent problems such as secondary infections, include: skin scrapings, fecal test, skin and ear cytology, bacterial culture and susceptibility, trichogram, fungal culture, skin biopsy and allergy intradermal and/or serological testing. Skin biopsy does not provide specific information to differentiate the various allergic diseases, but might help in cases of more unusual clinical presentation or eosinophilic granuloma complex to rule out other conditions such as infectious diseases or neoplasia.

Basically, FAD should be considered a diagnosis of exclusion. It is important to rule out similar skin diseases such as parasites and food allergy. Every cat with non-seasonal allergic skin disease should undergo a strict elimination diet trial to rule out food allergies. Despite the uncertainty surrounding the role of IgE in feline atopic disease, dermatologists still perform allergy intradermal and/or serum testing once the clinical diagnosis has been established. Intradermal testing is often unrewarding in cats and more difficult to interpret than in dogs, although positive reactions may be obtained. Fluorescein may be injected prior to performing the test to allow reactions to fluoresce and be seen under UV light. A different form of allergy skin test typically used in humans, called prick test, has been investigated in 10 healthy cats and may be good to identify positive reactions in atopic cats, however; further larger and controlled studies are needed before its routine use. Although positive reactions are often seen with IgE serology test, the precise significance is not well known.

**TREATMENT**
Treatment may involve a combination of therapies and approach. As some cats with atopic dermatitis present concurrent flea allergy dermatitis, it is very important to make sure these cats receive monthly flea preventative. Likewise, cats with concurrent food allergy should have the diet controlled to avoid exposure to known or possible food allergens. When allergies to specific environmental allergens such as house dust and house dust mites are identified, allergen avoidance, elimination or minimization in the environment should be recommended. In most cats, anti-inflammatory and anti-pruritic medications are required to control the allergy signs.

**Allergen-specific immunotherapy (ASIT):** The use of ASIT as long term therapy, based on intradermal and/or serological allergy tests, can be successful in controlling the symptoms of FAD, although most studies have been open and not controlled. Therefore, to date, the best protocol and the efficacy of this treatment in cats have not been proven, and it may take up to a year to see a response, similar to dogs. The author usually recommends allergy testing and immunotherapy, particularly for young cats, and has seen variable therapeutic success (50-70%).

**Medicated baths:** Although apparently beneficial, most cats do not tolerate baths. The author does have a few allergic feline patients that are bathed weekly as they seem to like baths and the owners report amelioration of clinical signs in combination with other therapies.

**Antihistamines:** Oral antihistamines are variably effective in FAD. Antihistamines that may be tried include: Hydroxyzine (2 mg/kg q12h), Cetirizine (5 mg/cat or 1 mg/kg q24h - its efficacy has been controversial), Chlorpheniramine (2-4 mg/cat q12h), Diphenhydramine (2.2 mg/kg q12h), Amitriptyline (0.5-1 mg/kg q12h), Clemastine (0.68 mg/cat q12h) and Cyproheptadine (2 mg/cat q12h). The author most commonly uses hydroxyzine and chlorpheniramine. Sedation is the most common side effect and may actually be beneficial in some cats.

**Essential fatty acids (EFAs):** Oral EFAs (omega-3 and omega-6) may be helpful as adjunctive therapy or glucocorticoids and ciclosporin sparing agents. The right dose and ratio have not been established. The author uses the same dose as for dogs. Omega-3 (fish oil): 180 mg of EPA and 120 mg of DHA per 5 kg/day. Omega-6 (primrose oil, borage oil, flaxseed oil): 100-280 mg/kg/day. EFAs should be tried for at least 12 weeks to evaluate their full clinical benefit.

**Glucocorticoids:** Oral glucocorticoids are the most commonly used symptomatic treatment due to their efficacy and fast action. Most commonly prednisolone (2 mg/kg/day) is used, however; some cats may need more long acting glucocorticoids such as triamcinolone ( ) and dexamethasone (0.2 mg q24h). The dose is tapered gradually to the lowest efficacious and safest maintenance dose (usually q48-72 hours). They are usually well tolerated by cats, however; the main concerning adverse effect is diabetes. Topical glucocorticoids can also be used on localized cutaneous lesions for short periods of time (1-2 weeks) with precaution to avoid ingestion by the cat. The author avoids injectable glucocorticoids, only using it as a rescue therapy in fractious or cats that do not accept oral therapy, due to a higher potential for adverse effects.

**Ciclosporin:** Oral ciclosporin (5-7 mg/kg q24h, then tapered to the lowest effective dose, half of the daily dose, EOD or twice weekly) may be a good option for the management of feline atopic dermatitis. It is licensed for FAD and it is available in liquid oral formulation (Atopica®). In one controlled study in cats with presumed atopic dermatitis, ciclosporin was as effective as prednisolone. The author has had great clinical responses using ciclosporin in atopic cats. The most common adverse effects are gastrointestinal (vomiting, diarrhea and anorexia).
Recrudescence of latent toxoplasmosis is a concern, although the true risk and its relative risk compared to the use of glucocorticoids have not been established. The author usually recommends testing toxoplasmosis titers in outdoor cats prior to ciclosporin and recommends outdoor or rodent hunting cats to remain indoors during the initial treatment, if possible.

Ideally, baseline and annual physical examinations, hemograms and chemistry profiles should be performed in cats treated with systemic glucocorticoids or ciclosporin.

**How about Oclacitinib Maleate (Apoquel®)? Is that an option for FAD?** There is current evidence that, like its canine counterpart, IL-31 signals through JAK (janus kinase) pathway and induces pruritus in cats and that this is blocked by oclacitinib maleate. However, to date, there has been no controlled efficacy and safety studies investigating the use and the proper protocol of Apoquel® in cats with allergies. Apoquel® is not currently approved for cats. Apoquel® has been used in cats with allergies anecdotally and it appears that cats have had a mixed efficacy response. The doses used has varied from 0.6-1.0 mg/kg and frequency has varied from every 12-24 hours. It appears that higher doses may lead to higher clinical efficacy. There is only one small prospective non-controlled pilot study recently published investigating the efficacy, use of administration and tolerability of Apoquel® in 12 cats, of at least 12 months of age, with non-flea and non-food induced hypersensitivity dermatitis. Apoquel® was administered orally at 0.4-0.6 mg/kg q12 hours for 2 weeks, then tapered to q24 hours for 2 weeks (same protocol as labeled for dogs). There was good improvement in pruritus and clinical signs in 5/12 cats, while the other cats were unchanged, deteriorated or dropped out due to treatment failure. Owners scored ease of administration and tolerability as good to excellent in 10/12 cats. Adverse effects were not reported. Based on this study and anecdotal uses, Apoquel® may be an alternative treatment for cats with allergies, particularly in cats that do not tolerate or responds well to ASIT, glucocorticoids and ciclosporin, however; further studies in cats are needed to evaluate the optimal dose and protocol, the long-term safety and to determine which precautions are required.

**CONCLUSION**

FAD remains a very challenging condition to diagnose and treat. As we continue to struggle to help our feline allergic patients, we hope that more studies are conducted to improve our understanding of this condition, so we can better diagnose it and identify more specific, efficacious and safer ways to treat it.

**REFERENCES**