Feline atopic dermatitis: Clinical signs and diagnosis

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SUMMARY

Although feline atopy was first decribed more than 25 years ago, the immunopathogenesis of this disease is still not entirely understood. It is thought to be similar to that of canine atopy .Cats can develop a variety of pruritic skin conditions including self-induced alopecia, cervico-facial pruritus and eosinophilic dermatosis (miliary dermatitis, eosinophilic plaques, eosinophilic granuloma and indolent ulcer). Feline atopy can also present as a respiratory disease similar to human atopic asthma. Establishing a diagnosis of atopy is difficult and requires exclusion of other cutaneous diseases such as flea bite allergy, food hypersensitivity, parasitic diseases and dermatophytosis. Evaluating the allergic status in cats with intradermal allergy testing or *in vitro* methods remains a challenge. Here is a diagnostic approach for identifying cats with atopic dermatitis.

Atopy is a genetic predisposition to develop IgE-mediated allergy to environmental allergens. In cats, atopy usually results in pruritic skin diseases, but there may also be a relationship between atopy and asthma. Feline atopy remains poorly understood, but its immunopathogenesis is thought to be similar to that of canine atopy. Characterization of inflammatory cell infiltration in feline allergic skin diseases showing one or more features (alopecia, eosinophilic plaques or granulomas, papulocrusting lesions) confirm infiltration of activated antigen-presenting cells and T lymphocytes in addition to increased numbers of dermal mast cells. This pattern mimics the dermal inflammation that occurs in the chronic phase of both canine and human atopic dermatitis [1]. In cats with recurrent "miliary" papulo-crusting dermatitis a significant total increase in dermal T-cells numbers was reported. Significantly more IL-4 positive cells were found in lesional and non lesional skin from allergic cats than from healthy controls [2]. Nevertheless, atopic cats do not have significantly higher concentrations of allergen-specific IgE than normal cats [3].

Estimates of the incidence of Feline Atopic Dermatitis (FAD) vary widely. Genetic predilection has not been proved. The strongest evidence to date in support of heritability is the presence of a disease closely resembling atopic dermatitis in three littermates [4].

Clinical signs

The age of onset is usually under 3 years of age. A unifying description of expected clinical features is not available for cats. The most consistent clinical feature is chronic recurrent pruritus manifested by scratching, biting and licking. Some cats hide to lick and tend to be secret groomers. Owners are often unable to distinguish pruritus from normal grooming behavior and may deny that the cat traumatizes itself. Pruritus may then need to be deduced clinically via indirect evidence such as trichograms revealing barbered hairs, tufts of hair in the cat's hiding places, vomiting of hair balls and excess hair in the feces.

Self-traumatized areas may be localized or generalized. The face, neck, pinnae, forelegs and ventrum may, as in dogs, be more severely affected. Nevertheless chronic skin changes such as lichenification and hyperpigmentation and secondary skin and ear infections due to bacteria or Malassezia yeasts are less common in atopic cats than in atopic dogs.

FAD is associated with several cutaneous reaction patterns. Lesions include self-induced alopecia, cervico-facial dermatoses, miliary dermatitis and feline eosinophilic skin diseases such as feline eosinophilic plaques, feline eosinophilic granuloma and feline indolent ulcer.

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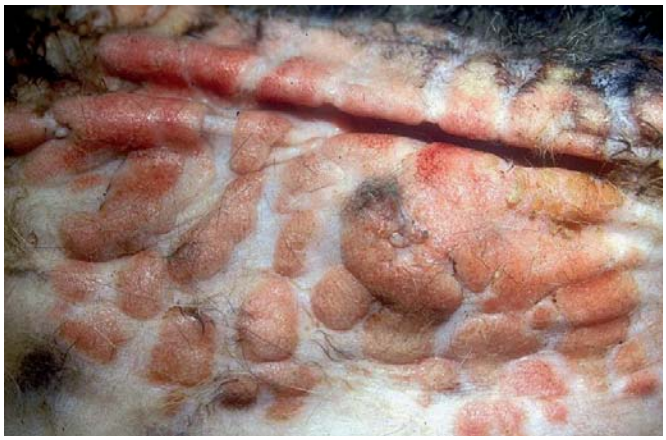
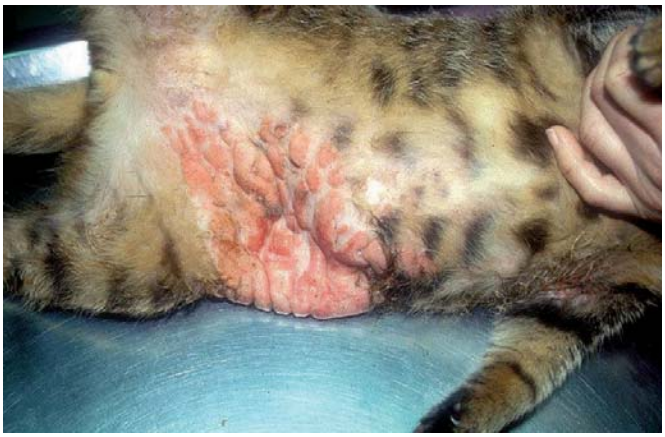
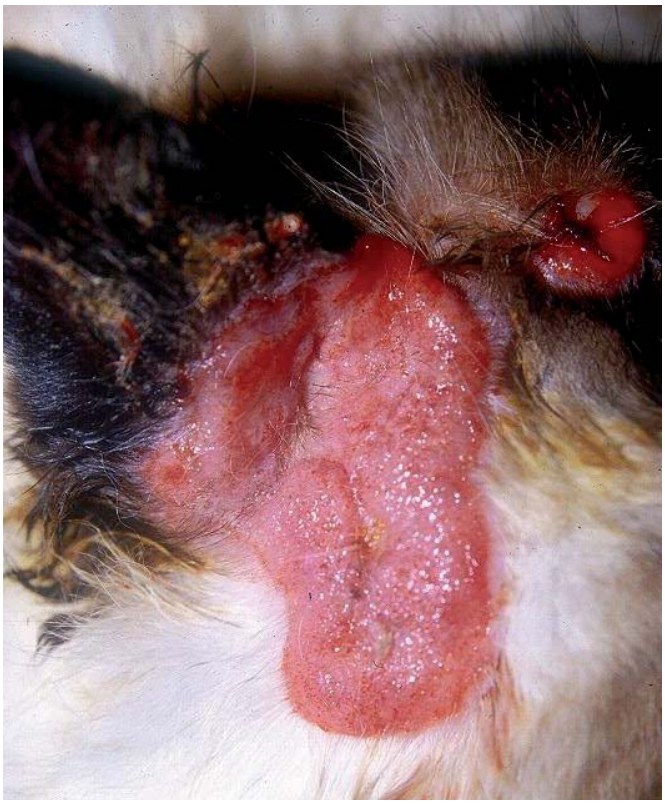




Eosinophilic plaques in atopic cat with intradermal positive reactions to pollens.

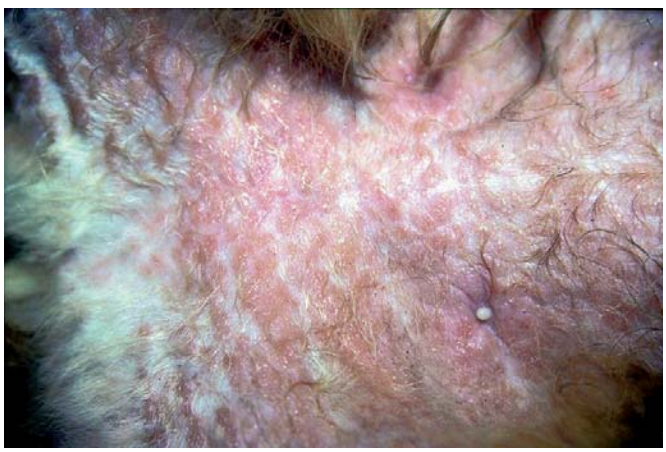
Eosinophilic plaques, eosinophilic granuloma, and eosinophilic ulcers are often grouped into what is called the 'eosinophilic granuloma complex". This term is not completely accurate, since the only condition histologically consistent with a granulomatous lesion is the eosinophilic granuloma and the etiology of these conditions is not always the same.
Eosinophilic dermatoses occur when there is an underlying pruritic condition irrespective of whether the cause is parasitic, allergic (atopy included), or fungal in nature. However, the ulcer and eosinophilic granuloma can be asymptomatic.

Miliary dermatitis of the cat is the eosinophilic dermatosis most specific to cats. It is characterized by small crusty papules, more or less erosive or ulcerated. They can be localized (along the back, face and neck) or generalized. Histologically, intercellular edema of the keratinocytes (spongiosis) is observed, with or without epidermal vesiculation ,and eosinophilic exocytosis. Dermal inflammation consists mostly of eosinophils and mast cells. In the most severe cases, marked spongiosis and secondary focal erosions or ulcerations make it difficult to distinguish the lesions of miliary dermatitis from those of eosinophilic plaques [6]. In fact, miliary dermatitis lesions are thought to be precursors of eosinophilic plaques, and both types of lesion can be found concurrently on the same animal. Miliary dermatitis is caused most frequently by allergic reactions, most notably associated with flea bite hypersensitivity but also allergy to environmental allergens.



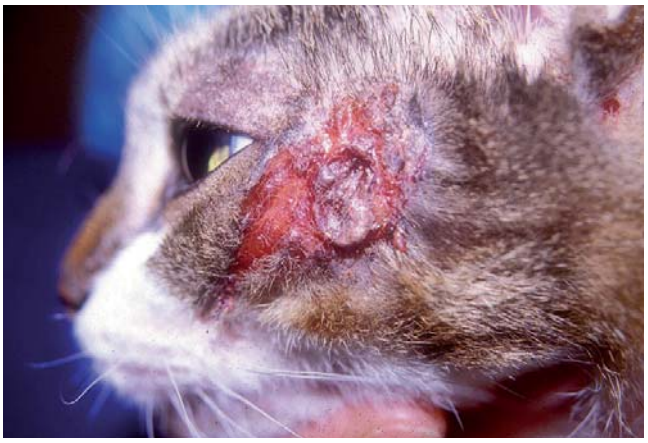
Eosinophilic granuloma presenting as nodules and plaques on the head.

Severely inflammed eosinophilic plaques in a cat allergic to house dust mites.



Eosinophilic plaques accompanied by severe pruritus are typically localized on the ventral abdomen, medial aspect of thighs, and peri-anal region. They are firm, raised, often ulcerated, and markedly inflamed. Chronic trauma due to constant licking contributes to the development of these plaques. Histologically, severe epidermal and follicular acanthosis, eosinophilic exocytosis , spongiosis , and epidermal and follicular mucinosis are frequently noted. The dermis is densely infiltrated with eosinophils associated with mast cells and a small degree of lympho- plasmacytic inflammation. An allergic reaction (e,g. to

Eosinophilic granuloma presenting as painful edema of the paws.



Severe facial pruritus with secondary crusts and ulcerations.

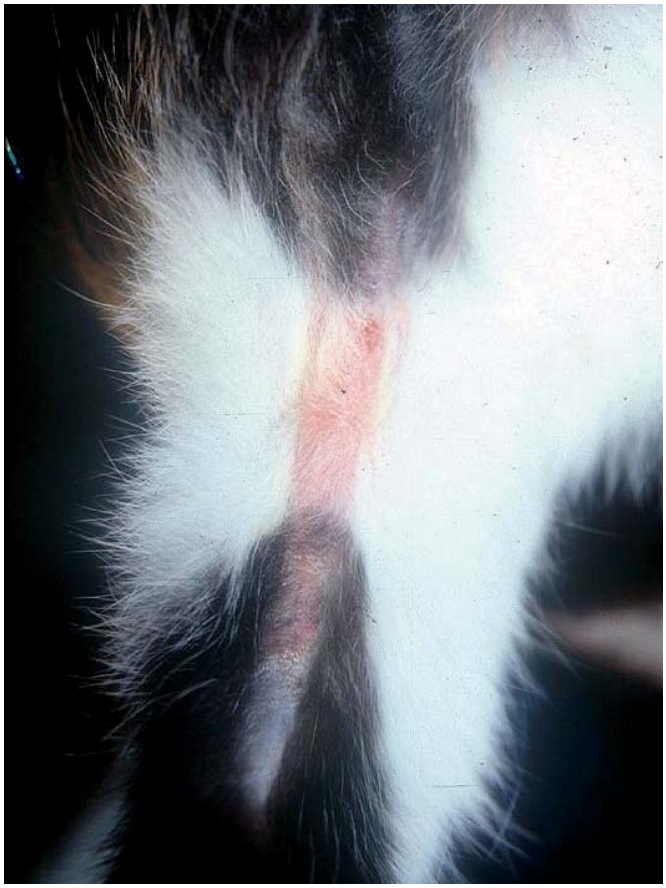
ectoparasites, food allergens or airborne allergens) is mostly to blame for this type of lesion.

The eosinophilic granuloma is a clinical entity that occurs very frequently in the cat. The histological appearance of this lesion is pathognomonic for the condition. In the cat, lesions tend to have a cutaneous, muco-cutaneous, or oral location. They typically present in one of the following ways:

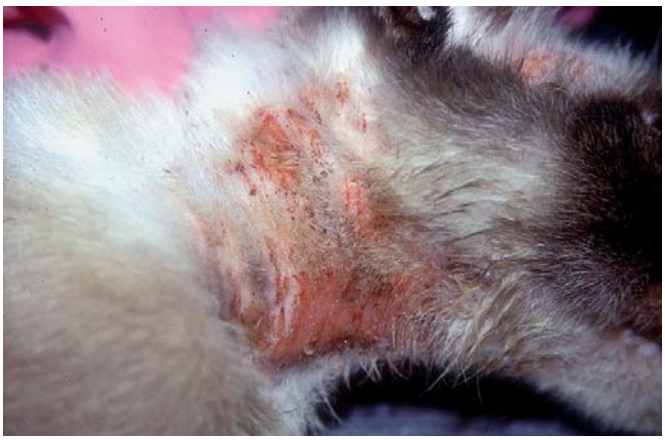
- As plaques or very firm papules, erythematous and occasionally yellowish, well circumscribed and with a linear distribution. They are located on the caudal thighs, or more rarely on the neck, thorax, or front legs.
- As plaques or nodules on the ears
- As pododermatitis with ulcerations of the toe pads, interdigital erythema, or edema of the toe pads.
- Edema of the lower lip or chin
- \Very firm nodules affecting the tongue and/or palate, sometimes ulcerated. Buccal lesions are sometimes accompanied by other signs including malodorous breath, anorexia, dysphagia, or hypersalivation.

These lesions do not initially seem pruritic. Eosinophilic degranulation may lead to the development of small, pinpoint, white or pink spots which cause pruritus and secondary erosion or ulceration due to chronic licking.

Linear eosinophilic granuloma.



Face and neck pruritus in an atopic cat.



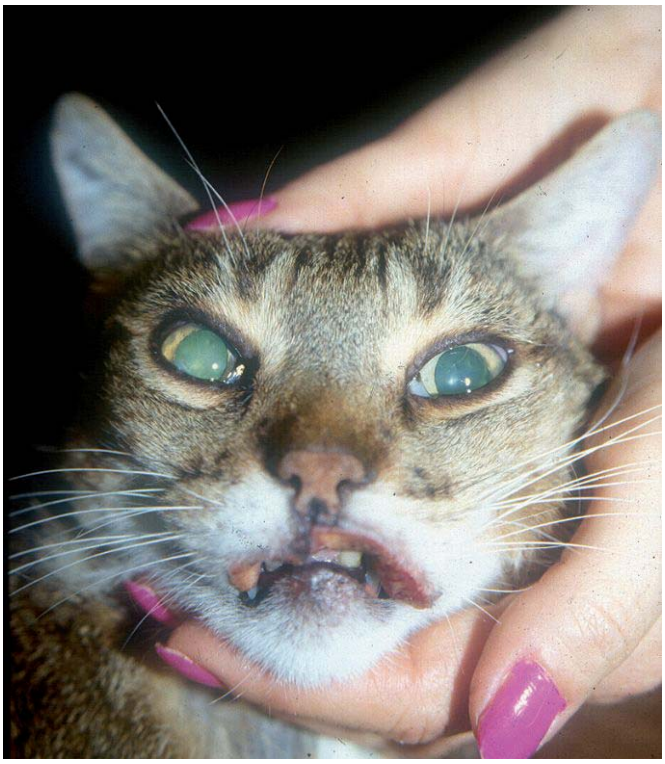
Seasonal bilateral indolent ulcer in a atopic cat.

The diverse clinical appearances of the eosinophilic granuloma make it difficult to diagnose, and cutaneous biopsies are often necessary to distinguish the nodular form of eosinophilic granuloma from neoplasia, mycosis, or abscess.

Histological H&E staining reveals irregular and granular collagen fibers that suggest a degenerative process. However, studies using special stains such as Gallego'trichrome and Masson'trichrome and electron microscopy have shown that the collagen fibers in eosinophilic granulomas are not degenerate, but covered by granules and products released during eosinophil degranulation that agglutinate around them (= flame figures). It is the poorly soluble proteins released by the eosinophilic granules that cause granulomatous reactions visible in their chronic form as zones surrounded by macrophages and giant cells, often is palisading array. [9].

The main causes of eosinophilic granulomas are **allergic** or **parasitic**, sometimes complicated by secondary bacterial infection.

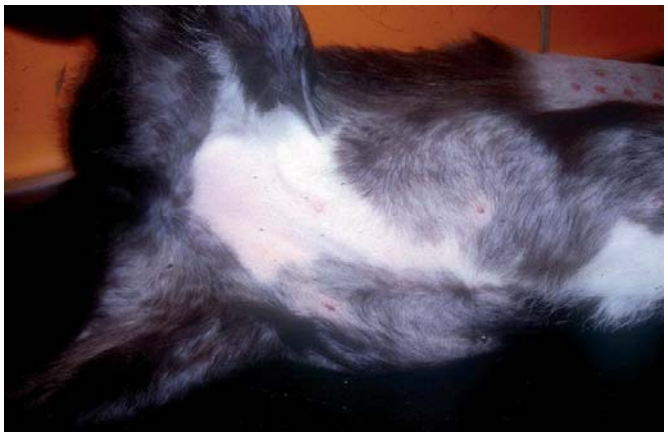
The **indolent ulcer** is a very common condition, although its pathogenesis is unknown. Lesions are well defined ulcers, with raised firm edges, varying from 2mm-5cm in size. The most common site is the junction of the skin and mucous membrane

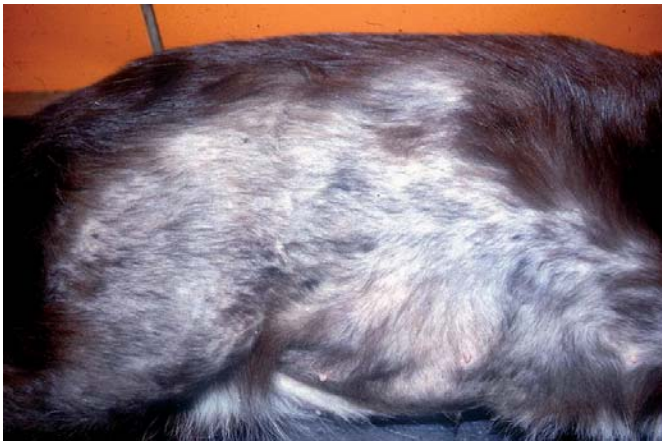


Seasonal keratitis concomitant with the lip ulcer.

of the upper lip apposing the lower canine tooth, just lateral to the philtrum. Lesions are usually solitary and unilateral, sometimes bilateral. They can create a somewhat monstrous appearance to the face. The lesion is bothersome to the affected cat especially as it makes eating difficult, but is not painful. An accompanying lymphadenopathy is sometimes described. The co-existence of an indolent ulcer with plaques or an eosinophilic granuloma suggests that an underlying allergy plays a role in its pathogenesis especially as the lesion often resolves with anti-parasitic therapy, an elimination diet, or immunotherapy. In one study, flea allergy dermatitis was induced in 10 cats both with intermittent and continual flea exposure. Five of the ten cats developed lip ulcers during this study period and all were exposed to fleas at the time of onset [10]. The POWER study identified hereditary transmission of the syndrome in a family of cats that developed lesions spontaneously without associated pathology. A genetic predisposition is therefore likely [11].

Extensive alopecia in an atopic cat.





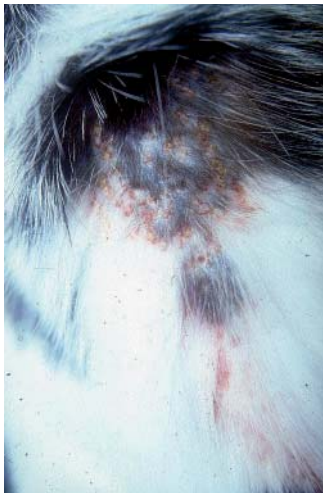
Differential diagnosis should include ulcers of infectious origin (bacterial, fungal, or secondary to FeLV), traumatic ulcers, and neoplasia (e.g.carcinoma, mast cell tumors and lymphoma).
The chronic indolent ulcer is characterized by a cellular infiltrate consisting of mononuclear cells and neutrophils, dermal fibrosis, and focal necrosis in the deepest areas of the dermis. If the lesion is biopsied in its acute phase, the cellular infiltrate consists mostly of eosinophils and mast cells, macrophages, and neutrophils. However, granulomatous changes are occasionally noted. In some cases, the interstitial and perivascular infiltrate consists of neutrophils and the ulcer is colonized by bacteriae. This is a dermatosis for which therapeutic failures are common and remission is often short lived.
All four forms of eosinophilic dermatoses may occur simultaneously or at different times in the same cat.

Feline self-induced alopecia (= feline symmetrical alopecia) presents as hair loss due to constant excessive licking with no inflammatory lesions. The ventral abdomen is commonly affected but medial and lateral limbs, flanks and lumbosacral region may also be involved. Notable histopathological findings are superficial eosinophilic and mild lymphohistiocytic infiltrate. Differential diagnosis includes psychogenic alopecia. A recent study suggests that psychogenic alopecia is overdiagnosed in cats and that a medical cause (e.g. adverse food reaction or atopy) of pruritus is present in 76 % of feline patients with a presumptive diagnosis of behavior problem [12].

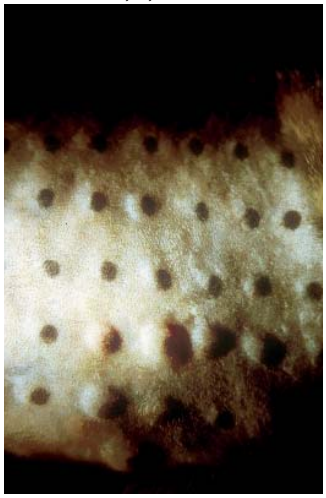
Cervicofacial pruritus leads to severe inflammatory self-induced lesions including erosions, ulcers and crusts. The location of the head may be due to the snooping behavior of cats and their tendency for hunting that expose the head to transmissible organisms or offending allergens, the sparseness of hair on the preauricular , dorsal muzzle and pinnae areas or anatomical particularities such as voluminous sebaceous glands on the chin . The lesions appear sometimes very impressive to owners. Atopy may be a cause of face and neck pruritus. Secondary bacterial infections occur more commonly than they are reported (probably underdiagnosed).

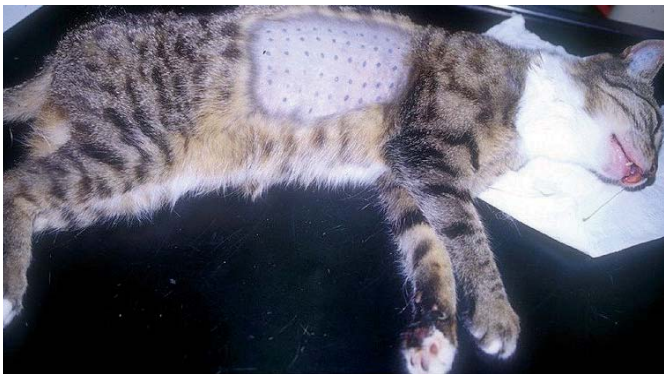
Feline asthma is very similar to human asthma. Feline asthma is

Miliary dermatitis in an allergic cat.



Positive skin tests in an atopic cat, distinct papules.





Intradermal skin testing in a cat. the cat is sedated, hair is clipped and skin is marked to visualize the injections dots.

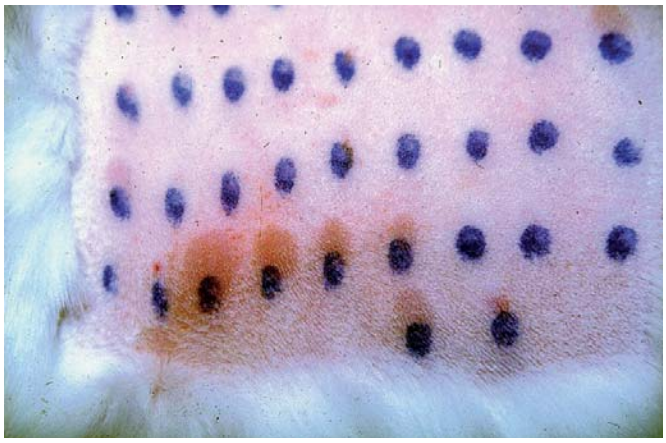
believed to involve a type I hypersensitivity to inhaled allergens. In a recent study, 20 cats presented with respiratory signs (recurrent bouts of coughing, wheezing, dyspnea) , radiographic images and bronchial cytology compatible with asthma showed positive reactions on intradermal allergy testing. Avoidance of dried food in 3 cats positive for storage mites or cockroach led a good and lasting remission of clinical signs. Specific immunotherapy was effective in controlling signs in12 cats [13].) It is likely than airborne allergens act as starting factors in feline asthma. Feline asthma is another clinical presentation of atopy in cats.

Diagnosis

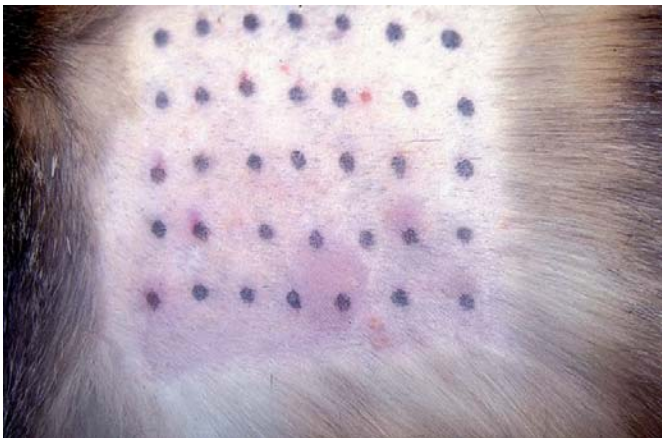
Considering so many diseases with similar signs, it is often difficult to make an accurate clinical diagnosis of atopic dermatitis in cats. The same cutaneous reaction patterns may accompany flea hypersensitivity, adverse food reaction and feline atopy. It is essential to perform a thorough physical examination and obtain a detailed history before proceeding to diagnostic tests and therapeutic trials to rule out differentials and confirm feline atopic dermatitis. The following diagnostic approach is proposed:

1. First and foremost it is critical to **identify the type of lesion present**. A biopsy may be necessary for atypical eosinophilic granuloma presentations and for nodular lesions. Cytological evaluation can also be very useful, and may reveal the presence of many eosinophils (confirming the diagnosis of eosinophilic dermatoses) or the presence of bacteria and granulocytes (suggesting pyoderma or even *Malassezia* dermatitis).

2. **Basic diagnostic tests and therapeutic trials** must always be carried out before specific allergy testing for environmental allergens.
   a. skin scrapings, direct examination of the cerumen and ear cytology are indicated particularly with facial lesions,
   b. use of Wood's lamp, direct examination of hair and scale, fungal cultures are systematically performed
   c. a **flea control trial** with topical flea products for 1-2 months in affected cats and in other pets living in the same environment should be conducted first. The best choice is an adulticide with effects on egg production and/or larva emergence or an adulticide associated with



Positive skin tests in a white atopic cat, see the erythematous wheals.



Positive skin tests with erythematous papules.

an insect growth regulator. The goal is to minimize the number of fleas or at least maintain it below the threshold which triggers an allergic reaction, and to provide long term control of parasitic infestation. Regular application of all products is critical to prevent recurrence. Bimonthly treatment is recommended for diagnostic purposes, and should be continued during the season in which fleas are most abundant. For the remainder of the year even in winter, monthly treatment can be administered. Products containing fipronil, imidacloprid, or selamectin can be used. In the cat, anti-parasitic therapy alone often leads to resolution of signs. However, lesions with a significant inflammatory component such as eosinophilic plaques may require a short course of corticosteroids. In these cases, absence of recurrence following cessation of corticosteroid therapy confirms the importance of anti parasitic therapy.

d. **elimination diet** of 8 weeks duration then. It can be a hydrolyzed protein diet or a home-cooked diet with a novel protein meat source (e.g. horse, lamb, rabbit, pork).A vegetable source is not required in the cat, although many cats seem to enjoy pumpkin. Beef, dairy, fish, eggs, and chicken have been implicated as the most commonly offending food allergens. Preservatives and other additives are also occasionally involved.
e. Search for **hypersensitivity to environmental allergens**

Allergy testing is reserved for those patients where environmental allergies are strongly suspected. The goal is to identify offending allergens for inclusion in specific immunotherapy.

Intra-dermal allergy testing was for a long time the only test available for cats. Skin testing is still considered the "gold standard" in feline allergy medicine. Selection of seasonal allergens to be included in the test is based on geographical location of the cat's home. Testing with allergen mixtures is not recommended unless strong cross-reactions have been proved (grasses). Intra-dermal skin testing is considered difficult to perform and to interpret in the cat.

Steroids should be stopped 2 months before skin testing is performed; anti-histamines should be stopped 2 weeks before. Stress induces a rise in serum cortisol, corticotropin, and α MSH (melanocyte stimulating hormone), which interferes with the reactivity of the test. As a result, cats should be anesthetized for intra-dermal skin testing in order to limit the stress response. The author recommends that the animal should not be hospitalized beforehand, and that the test should be performed as soon as the cat arrives at the clinic. Cats can be sedated with medetomidine, tiletamine/zolazepam, xylazine hydrochloride or ketamine hydrochloride.

Cat skin is finer and tougher than dog skin. Interpretation of intra-dermal testing requires some experience; there is currently a lack of consensus as how to interpret these tests in the cat. Interpretation should take place 15 minutes following injection, with the following signs to be evaluated: presence of erythema, swelling of the injection site, firmness of the swelling, diameter of the swelling, and to some degree the presence of pseudopods. Interpretation occurs 'with the eye and with the hands'. Subjective comparisons are inevitably made with positive and negative controls. Examination of the reaction sites is made in dim light with an oblique light source to examine the margins of the reaction sites, their size and volume. Erythema in cats with light colored skin is best visualized under normal lighting. When in doubt, reactions should be considered negative.

One study suggested the use of liquid fluorescein in 10% saline injected intravenously (5-10 mg/kg) after the last intra-dermal injection to facilitate interpretation of the cutaneous reactions. A Wood's lamp would then be used after 15-30 minutes to compare the diameter of each reaction to positive and negative controls, with a positive result being a diameter equal to or larger than the average of the positive and negative controls. The intensity of the fluorescence is not a necessary criterion for interpretation of the test. [14].

Diagnostic **blood testing** in the cat with hypersensitivity has not proved to be very useful. This is because of poor correlation with the results of skin testing, and because feline anti-IgE has questionable specificity in cats. All studies even the most recent ones have failed to demonstrate significant differences in allergen-specific IgE levels in sera from supposed atopic cats and that of normal cats. These studies have concluded that IgE

serology should not be used to diagnose feline atopy [15,16]. Direct cat basophil activation test or passive sensitization of human basophils by cat sera can be applied to allergy diagnosis in cats. Tests are based on the measurement of basophil activation or on the release of mediators such as histamine and LTC4 by flow cytometry. In a preliminary study, good clinico-biological correlation was obtained using a basophil activation model in a population of 40 allergic cats [17]. A more recent study adapted this method as a tool for the diagnosis of feline flea bite hypersensitivity on cats experimentally sensitized to fleas [18].

House dust mites are the most commonly incriminated allergens. In a study of 90 cats, *Dermatophagoides farinae* was positive in 80 % of cases and *Dermatophagoides pteronyssinus* in 46% of cases. 40 % of cats had one or more positive reactions to pollens [19]. In another study, house dust mites were reported to be common causes of positive intradermal test reactions [8].

In a study on 20 atopic cats with feline asthma, intradermal allergic tests were performed in 18 cats [13]. Three of these were negative even after when tested for a second time. 15 cats had positive reactions to *Dermatophagoides farinae* (8/15), *Acarus siro* (6/15), *Glyciphagus domesticus* (4/15), *Dermatophagoides pteronyssinus* (4/15), *Tyrophagus putrescentiae* (4/15), Cockroach (2/15), Ox-eye daisy, ragweed, false acacia (2/15), Hazel-tree, plane-tree (1/15), flea (3/15)
Specific immunotherapy was prescribed in 12 cats.

In conclusion, it is difficult to make an accurate clinical diagnosis of atopic dermatitis in cats as we lack the major and minor clinical criteria that we have in dogs. The diagnosis of feline atopic dermatitis is based on dermatological clinical signs specific to cats, exclusion of other skin diseases such as flea bite allergy, food hypersensitivity, ectoparasitic infestation and dermatophytosis, and skin test results. Evaluating the allergic status in cats with intradermal allergy testing or *in vitro* methods remains a challenge. Offending environmental allergens should be identified in order to initiate specific immunotherapy. Working on experimental models of allergic feline asthma might help to improve our understanding of the immunopathogenesis of feline atopy.

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