

Canine and Feline Eosinophilic Skin Diseases

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EOSINOPHILIC DERMATOSIS

Eosinophilic dermatosis (ED) is a histologic diagnosis rather than a clinical diagnosis. It includes a heterogeneous group of diseases that are secondary to underlying antigenic stimulation (hypersensitivity reaction) in most cases. EDs all have one thing in common—the eosinophil. Eosinophils are phagocytic cells in the granulocyte lineage, as are neutrophils and basophils, that are produced in the bone marrow. Phagocytic cells contain granules that may or may not stain with dyes. Those cells with granules that take up acidic dyes, such as eosin, are called eosinophils. Eosinophils are involved in the inflammatory response to foreign material, especially parasites. They are one of the major sources of inflammatory mediators associated with type I hypersensitivity reactions. An eosinophil-derived cytokine, transforming growth factor- β_1 (TGF β_1) may also contribute to chronic inflammation.

A variety of molecules are involved in the activation and attraction of eosinophils [1–3], including the following:

1. Chemokines
 - a. Regulated on activation normal T-cell expressed and secreted (RANTES)
 - b. Monocyte chemoattractant protein (MCP)
 - c. Macrophage inflammatory protein-1 (MIP-1)
 - d. Eotaxin
2. Cytokines
 - a. Interleukin (IL) 1- β , IL-3, IL-4, and IL-5
 - b. Granulocyte macrophage colony-stimulating factor (GM-CSF)
 - c. Tumor necrosis factor- α (TNF α)
 - d. TGF β_1
3. Lipid mediators
 - a. Eicosanoids
 - i. Leukotriene (LT) B₄, LTC₄, LTD₄, and LTE₄

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- ii. Prostaglandin D₂ (PGD₂)
 - iii. Thromboxanes
- b. Platelet-activating factor
- 4. Complement fragments (C3a and C5a)
- 5. Adhesion molecules (expressed on eosinophil or vascular endothelium)
 - a. Selectins
 - i. L selectin/GlyCAM-1
 - ii. PSGL-1/P selectin
 - iii. ESL-1/E selectin
 - b. Integrins
 - i. LFA-1/ICAM-1
 - ii. Mac-1/ICAM-1
 - iii. VLA-4/VCAM-1
- 6. Mast cell degranulation products
 - a. Histamine and its metabolite, imidazoleacetic acid
 - b. Eosinophilic chemoattractant factor A
- 7. Immunoglobulins
 - a. IgG
 - b. IgA
- 8. Helminth-associated molecules

Little of an eosinophil's lifespan is spent in circulation; rather, it is primarily spent in the tissues. Once an eosinophil has arrived at its final destination, it begins the work of destroying the insult that attracted it to that site, such as a parasite, by phagocytosis or by releasing toxic compounds. Eosinophils can phagocytize small antigens; however, to kill large parasites, they extrude cellular contents via degranulation. Four major granules—secondary granules, small granules, lipid bodies, and primary granules—are found in the cytoplasm of eosinophils. These granules contain a wide variety of proteins, many with enzymatic activity. Major basic protein, eosinophilic cationic protein, eosinophilic peroxidase, and eosinophilic-derived neurotoxin reside within the secondary granule along with a number of cytokines, enzymes, and other proteins. Small granules contain a variety of enzymes, including arylsulfatase and acid phosphatase, whereas lipid bodies are responsible for eicosanoid formation. The function of the primary granule that contains Charcot-Leyden crystals is unknown at this time [1,2]. Taken together, these compounds are responsible for tissue destruction and inflammation. They have profound vasoactive and neurogenic properties that manifest clinically as erythema, wheals, and pruritus. Further details about the content and function of these cytoplasmic granules are beyond the scope of this article.

As mentioned previously, there are a variety of stimuli that can activate eosinophils, whereupon they can phagocytize foreign material or degranulate and release the contents of their granules. As previously mentioned, they can also synthesize the cytokines, including TNF α , IL-1, IL-3, IL-4, IL-5, IL-8, and GM-CSF, that are involved in an inflammatory response (type I hypersensitivity reaction) [2]. The degranulation of the eosinophils along with the production of cytokines evokes a profound inflammatory reaction in the tissue in which the

parasite resides. The parasite is then killed by this immunologic response. Unfortunately, this same immunologic response, whether uncontrolled or misdirected, can also respond inappropriately to other antigens, producing a hypersensitivity reaction.

There are a number of EDs that affect cats and dogs. In some of these diseases, the eosinophil is a major “player,” whereas in others, it is just part of the mixed inflammatory response. Causes of eosinophilic skin disorders in cats and dogs include hypersensitivity reactions (environmental allergens, insects [fleas and mosquitoes], food, intestinal parasites, and drugs), endogenous (free keratin and hair shafts) or exogenous (imbedded insect parts), infectious (bacterial or fungal infection [dermatophytosis]), viral (feline herpesvirus [FHV]-1 and retroviruses [feline leukemia virus [FeLV], feline immunodeficiency virus]), parasitic (*Cheyletiella*, *Otodectes*, *Sarcoptes*, *Notoedres*, and pediculosis), and idiopathic (unknown). In cats, ED should not be thought of as a disease but rather as a cutaneous reaction pattern to a variety of different stimuli. Regardless of the trigger, a number of different causes can cause similar immunologic, histologic, and clinical findings.

EDs described in cats or dogs include miliary dermatitis, “eosinophilic granuloma complex” (EGC, which includes feline indolent ulcer [IU], eosinophilic plaque [EP], and eosinophilic granuloma [EG]), feline mosquito bite hypersensitivity (MBH), canine eosinophilic folliculitis and furunculosis, and canine eosinophilic dermatitis and edema (Wells'-like syndrome).

EOSINOPHILIC GRANULOMA COMPLEX

Background

In cats, the most common EDs are feline miliary dermatitis (FMD) and EGC. Regardless of which form of ED is present, the underlying cause is essentially the same. The most commonly identified underlying cause is a hypersensitivity reaction to insects (fleas and mosquitoes), environmental allergens (atopic dermatitis [AD]), or foods. Before condemning the cat to lifelong drug therapy, all attempts should be made to identify and, if possible, eliminate the underlying trigger(s).

In human beings, AD is a chronic inflammatory skin disease caused by cutaneous hyperreactivity to environmental triggers and is characterized by elevated serum IgE levels [4]. There are also human patients with severe AD who generate IgE antibodies directed against human proteins (self-antigens). The autoallergens identified to date have been intracellular proteins, perhaps released as the result of self-trauma from scratching. This suggests that although the IgE immune responses are initiated by environmental allergens, chronic allergic skin disease can be maintained by the release of human proteins derived from damaged skin [4]. A recent article [5] suggests that *Felis domesticus* allergen I (Feld I) could be an autoallergen responsible for chronic inflammatory reactions in cats with EGC.

EGC consists of the EP, EG, and IU. Clinically, these are distinct entities, but making a diagnosis based on histopathologic findings is potentially

confusing, because even though each of these clinical presentations has “typical” histologic changes, all forms can be observed on the same cat at the same time [6]. In fact, some lesions may have histologic features consistent with more than one of the reaction patterns [7]. It is best to think of the histopathologic changes associated with EGC as a reaction pattern rather than as a specific diagnosis.

Because EP, EG, and IU are most commonly a manifestation of a hypersensitivity reaction [7,8], differentiating among these, clinically or histologically, is not essential in establishing the underlying cause, nor is it helpful in choosing a treatment plan. Using histopathologic examination to rule in or rule out other similar-appearing diseases (eg, neoplasia, infection) is critical, because treatment and prognosis for these other diseases would be drastically different. Histopathologic examination should be performed in cases that clinically appear atypical or for those cases that fail to respond to prescribed treatment.

Because the diseases in the EGC have overlapping histopathologic findings, they are discussed as a group rather than individually. Histologic findings consistent with EGC are a variation on a theme. Findings vary depending on the stage (early versus late) and location of the lesion. Histologic findings may include epidermal hyperplasia with variable degrees of spongiosis and eosinophilic exocytosis, erosions, ulcerations, or epidermal coagulation necrosis. A luminal eosinophilic folliculitis and furunculosis may be present. There is a superficial to deep perivascular to interstitial to diffuse predominantly eosinophilic dermal infiltrate. A variable number of histiocytes, mast cells, and lymphocytes are present in the dermis. Mineralization of flame figures, which are distinct dermal deposits of collagen coated with amorphous to granular eosinophilic debris, may be present. A palisading granulomatous reaction containing epithelioid and multinucleated giant cells may form around flame figures as a result of proteins being released from degranulated eosinophils. In the past, these flame figures were described as collagenolysis or collagen degeneration. Subsequent studies have revealed that the collagen is normal (normal staining with Masson-Trichrome) and that the appearance of the collagen is attributable to its coating with substances from degranulated eosinophils [9].

EP may be singular, or there may be multiple lesions (Fig. 1). They are grossly alopecic and erosive to ulcerative erythematous patches or plaques most typically involving the ventral abdomen, perianal, and medial thigh regions. These highly pruritic lesions may also appear in the axillary regions, dorsal trunk, or flexor surface of the elbows. Although tissue and blood eosinophilia is a common finding, peripheral lymphadenopathy is only occasionally present. Direct impression smear cytology may show large numbers of eosinophils. As mentioned previously, it is important to identify and treat any underlying hypersensitivity. This is discussed further in the section on diagnosis and treatment.

FMD is closely related to EP. These two diseases are histologically similar but clinically distinct. FMD consists of pruritic, multifocal, erythematous papulocrusts that are frequently found on the trunk, neck, and face. Histologically,



Fig. 1. ED (plaque and/or patch form) in a 3-year-old neutered mixed-breed cat. This highly pruritic lesion was caused by environmental allergen-induced AD. Note the alopecic erosive plaque with crusting. The sutures that are present are from a skin biopsy.

FMD is characterized by multifocal spongiosis, eosinophilic and neutrophilic exocytosis with serocellular crusting, and areas of epidermal coagulation necrosis. There is superficial and middermal perivascular to interstitial dermatitis with eosinophils and mast cells, intraepidermal eosinophilic pustules, and sometimes eosinophilic folliculitis [10]. There is a group of cats with FMD that the owners report as not being pruritic. It is unclear whether these cats are “closet” itchers or whether the papulocrusts are truly a primary lesion of the disease and not a result of self-trauma. In this subgroup of cats, the lesions on the haired skin are discovered by the owners incidentally as they are petting their cat. The lesions also may be found during the physical examination as the hair coat and skin are palpated or when a fine-toothed comb is passed through the hair coat. It is easiest to think of EP as a coalescence of miliary dermatitis lesions. Diagnosis and treatment are discussed elsewhere in this article.

An IU appears as an erosive to ulcerative lesion with slightly raised edges occurring most commonly on the midline of the upper lip or adjacent to the upper canine tooth. It may also involve the hard palate [6]. It is a reddish-brown to yellow lesion that is not painful or pruritic. Regional lymphadenopathy may be present [6,8]. An IU may be a precancerous lesion that progresses to SCC [8]. Blood eosinophilia and tissue eosinophilia are uncommon. A recent article expands our rule-out list for causes of IU [11]. In that article, it was reported that infection with *Microsporum canis* may be responsible for lip ulcers. This serves as additional proof on how a wide variety of antigens can stimulate a nonspecific reaction (ED) in cats. Diagnosis and treatment are discussed elsewhere in this article.

EG (linear granuloma or collagenolytic granuloma) is nonpruritic and appears as a mildly erythematous, alopecic, eroded, or ulcerated nodule or plaque. It is an off-white to yellow to pink lesion that may occasionally have

white granules in the middle of the nodule. The nodular form is most commonly found in the oral cavity (tongue, hard palate, or glossopharyngeal arches) or on the chin. It is speculated that the oral cavity lesion may be a local reaction to imbedded insect parts in some cats [8]. When EG involves the chin (“chin edema”), affected cats have a “pouty” appearance because of the swelling of the area. EG may also involve the footpad or the conjunctiva [8]. Lesions also frequently appear on the caudal thigh as a linear plaque that is nonpruritic. The linear plaque is frequently detected only by “accident” when the owner is petting the cat or during a physical examination. Peripheral eosinophilia may be present. Diagnosis and treatment are discussed elsewhere in this article.

EG and IU are unique in that there is a subset of cats with these lesions that have no detectable underlying cause. This was discovered in a study involving a closed breeding colony of interrelated specific pathogen-free cats that had a high incidence of EG and IU. Intradermal tests (IDTs) and food trials failed to identify an underlying hypersensitivity reaction. This led to the theory that there is a genetic heritable eosinophil dysregulation predisposing to the development of these lesions [7,8,12]. In this study, however, it was also reported that the lesions would wax and wane, with spring and summer exacerbations, suggesting the presence of an unidentified environmental trigger. By 2 to 3 years of age, these cats became asymptomatic. Thus, if EG or IU occurs in a young cat, there is a possibility (perhaps small) of a heritable basis and that the cat may “outgrow” the disease over time. Because there is no way to predict which cats are going to become asymptomatic and which are going to continue to have symptoms, it is best to approach each case as though the disease is going to continue to be a problem and there is an identifiable and treatable underlying hypersensitivity.

A new approach (and possibly less confusing) to EGC would be to group the diseases based on a clinical description of the lesions. These descriptions would replace EP, IU, and EG. Only two forms, the papular and/or plaque form and the ulcerative form, would need to be identified. The former would encompass the EP and EG lesions and would be firm flat-topped papules that may coalesce into plaques with alopecia or erythema and would have a variable amount of pruritus. These lesions may involve the ventral abdomen, inguinal regions, and inner thighs. The linear plaque that involves the caudal thighs would also be included in this form. The ulcerative form would replace the IU. It would appear as a nonpruritic painless ulceration on the midline of the upper lip or adjacent to the upper canine teeth. The ulcerative form may also involve the oral cavity.

Eosinophilic Granuloma Complex or Feline Miliary Dermatitis Diagnosis and Treatment

As is the case with most dermatologic diseases, a diagnosis is made by using a combination of signalment, history (including response to therapy), clinical findings, laboratory testing, and response to therapy.

Because ED lesions are fairly distinctive, it is tempting to forget that other diseases can appear similar to ED lesions. For IU, the differential diagnosis

would include SCC and infectious ulcers (herpes, calicivirus, FeLV infection, and *Cryptococcus*). For EP or EG rule outs, the differential diagnosis would include cutaneous epitheliotropic T-cell lymphoma, infectious granulomas (demodicosis, bacterial [including *Mycobacterium*], or fungal), mast cell tumor, and SCC [6,8].

The minimum database (MDB) for a cat presented with clinical signs consistent with ED depends on which form of ED is present but usually includes the following:

1. Skin scrapings (superficial and deep, because cats have superficial and deep forms of *Demodex* mites). Clear acetate tape preparations should be performed, as should combing the hair coat thoroughly with a fine-toothed comb to rule out other ectoparasites (eg, *Cheyletiella*, fleas).
2. Wood's lamp examination and dermatophyte culture. Because feline dermatophytosis is known as the "great imitator," all cats with skin disease should have a fungal culture performed. The use of the Wood's lamp examination alone is discouraged, because only 30% to 80% of the strains of *M canis* (the most common feline dermatophyte) fluoresce. Also, there are a variety of other causes of fluorescence, including scales, medication, and bacteria (eg, *Pseudomonas*) [13]. It is best to use the Wood's lamp as an aid in selecting which hairs to submit for fungal culture.
3. If the lesions appear atypical or do not respond to therapy, skin biopsy and histopathologic examination of the sample are appropriate. Other diagnostics that may be of value on an individual basis include macerated tissue cultures for bacteria or fungi. In the author's experience, complete blood cell counts (CBCs) and cytologic examination of lesions have been of little value.

Because EGC and FMD are most commonly associated with a hypersensitivity reaction, diagnostics for an allergic disease should be performed. In addition to the testing mentioned previously, all cats deserve an aggressive therapeutic trial for ectoparasites (especially directed toward fleas). This would include the administration of fipronil, imidacloprid, or selamectin biweekly for 30 days and then monthly for 2 more months (note that the administration of these products biweekly is an off-label use). The limitation of imidacloprid, which is an excellent insecticide, is that it is not an ascaricide; thus, it is not effective against mites. Depending on the region of the country, this factor may or may not be important.

In addition to the affected cat, all four-legged haired pets are treated with one of these products monthly for 3 months. Lufenuron may be administered orally to all these pets for 3 months. Environmental treatment should include aggressive vacuuming and "spot" treating the areas where the pets spend most of their time. A spray containing a combination of a pyrethrin and an insect growth regulator should be used for the spot treatment. Initially, while awaiting the response to this insecticidal treatment, a 21-day course using a tapering dose of oral prednisolone may be used for symptomatic relief.

If there is a response to therapy, it may be that flea allergy is the trigger; alternately, it may be the case that the cat has seasonal environmental

allergen-induced disease and the seasons have changed or the problematic aeroallergens are no longer present. This may or may not present a diagnostic challenge depending on the historical information obtained. If the cat has a history of the lesions being present year round, it could be concluded that the seasonal change was not responsible for the improvement. If the lesions have not been present (or recurrent) for at least a year, the underlying disease may not be clarified until longer follow-up on the case occurs. During this time, continuation of the flea treatment should be maintained. (Please note that if a long-acting injectable glucocorticoid [GC], such as methylprednisone acetate, is administered simultaneously with flea control treatment, assessment of response is not possible until at least 4 months after the injection).

If the diagnostics performed were negative and the treatment for ectoparasites is unsuccessful in managing the skin disease, the next step depends on the severity of the disease and the frequency of its occurrence. If the symptoms occur once or twice a year, are fairly mild, and respond to a short course of oral prednisolone or an injection of a long-acting GC, symptomatic therapy is appropriate. If, conversely, the lesions are getting progressively more severe, more frequent, or require more than once- or twice-yearly GC therapy, investigation and treatment for cutaneous adverse food reactions (CAFRs) or environmental allergen-induced AD should occur.

It is critical to understand that environmental allergen-induced AD is a diagnosis of exclusion. Blood testing, or even an IDT, does not diagnose environmental allergen-induced AD. These tests are used to select antigen for allergen-specific immunotherapy (ASIT) once the diagnosis has been made. The diagnosis of environmental allergen-induced AD may be made historically (seasonal symptoms despite appropriate ectoparasite control) or may not be established until therapeutic trials and laboratory testing (as mentioned previously) have been performed.

When all the previously mentioned diagnostics and therapies have failed to diagnose and “cure” the problem and the symptoms are nonseasonal, a food trial should be performed. It is beyond the scope of this article to discuss the diagnosis of CAFRs in detail, but the author believes that the commercially available diets may rule in CAFR but cannot rule it out. The author is a firm believer that the only proper way to rule out a CAFR is by a home-prepared diet containing a novel protein and, in the case of dogs, a novel carbohydrate. Blood testing or an IDT is worthless. There are commercial diets that are novel protein based or contain hydrolyzed proteins. The limitation of these products is that a certain unknown percentage (it has not been established what percentage based on double-blind placebo-controlled trials) of dogs and cats respond to the novel protein or hydrolyzed diets. Thus, failure to respond to these diets does not rule out a CAFR.

Regardless of which method is used for the elimination diet trial, the new food should be fed for a minimum of 8 weeks in dogs and 12 weeks in cats. One possible explanation for the need for such a prolonged trial is because of the presence of histamine-releasing factors. Histamine-releasing factors are

a heterogeneous group of cytokines generated by chronic antigenic exposure and may cause histamine release in the absence of antigen. This release may continue for weeks after antigen is removed [14].

If the cat's symptoms recur in spite of the ectoparasiticide and food trials, the next step is to perform an IDT or serum "allergy" test to select an allergen for ASIT. The author prefers IDT over a blood test. The reader is encouraged to read elsewhere about the "pros and cons" of these testing methods.

If the owner declines ASIT, symptomatic treatment is needed while awaiting the response to a food trial or ASIT, the cat has failed to respond to ASIT, or the symptoms are infrequent, options for symptomatic relief include (please note that these therapies may be used concurrently with ASIT) the following:

1. Systemic antibiotics, such as amoxicillin-clavulanic acid (22 mg/kg administered every 12 hours), cefpodoxime proxetil (5 mg/kg administered every 24 hours; not approved for cats), cephalexin (22–30 mg/kg administered every 12 hours), cefadroxil (10–20 mg/kg administered every 12 hours), clindamycin (5–10 mg/kg administered every 12 hours; watch for esophageal irritation leading to esophageal stricture in cats). These may be useful in cats with mild IUs. Treatment should be for 4 to 6 weeks.
2. Systemic GCs, prednisolone (1–2 mg/kg every 12 hours and then tapering to every other day) rather than prednisone. Cats have unpredictable absorption or metabolism (to the active form) of prednisone; thus, only prednisolone should be used. As an alternative, methylprednisolone acetate (5 mg/kg) can be administered subcutaneously. For severe lesions, methylprednisolone acetate can be given two to three times 2 weeks apart. This is not a long-term therapy, nor should it be a standard therapy. Side effects associated with GCs in cats include diabetes mellitus, congestive heart failure, weight gain, demodicosis, dermatophytosis, and feline cutaneous fragility syndrome. Other oral steroids that may be useful in cases that fail to respond or become resistant to the effect of the previously mentioned GCs include oral triamcinolone (0.1–0.2 mg/kg administered every 24 hours) or dexamethasone (0.1–0.2 mg/kg administered every 24 hours). If these two GCs are used long term, it is best to administer them only every 3 days so that there is less suppression of the adrenal-pituitary axis. Intraleisional triamcinolone may be useful for a severe refractory IU or oral EG.
3. Antihistamines and ω -3 or ω -3/6 fatty acid combinations can be administered. The antihistamine is used concurrently with an ω -fatty acid supplement. The author has been underwhelmed with the response to these therapies in cats with EGC.
 - a. Hydroxyzine: 1.0–2.0 mg/kg administered two to three times daily for 14 days.
 - b. Chlorpheniramine: 0.4–0.5 mg/kg administered twice daily for 14 days. This pill is extremely bitter tasting.
 - c. Diphenhydramine: 1.0–2.0 mg/kg administered two to three times daily for 14 days. The liquid form has an alcohol base that cats strongly dislike.
 - d. Clemastine: 0.05–0.10 mg/kg administered twice daily for 14 days
 - e. Amitriptyline: 1.0–2.0 mg/kg administered once to twice daily for 21 days.

- f. Cyproheptadine: 0.5 to 1.0 mg/kg administered every 8 hours for 14 days. Warn owners about possible polyphagia. The author has also seen some anxiousness at the higher dose. This can be avoided by slowly increasing the dose over 5 to 7 days.
 - g. Fatty acids: if a ω -3/6 combination product is used, prescribe double the bottle dose. If the product contains only ω -3, use it so that the cat receives eicosapentaenoic acid at a dose of 40 mg/kg daily.
4. Chlorambucil is a nitrogen mustard derivative, cell cycle–nonspecific, alkylating antineoplastic and/or immunosuppressive agent. Its cytotoxic activity stems from cross-linking with cellular DNA. The reader should become familiar with this drug if he or she is going to use it for EGC. It should only be used in severe steroid-refractory cases of EGC. It is used in combination with GCs. The initial dose is 0.1–0.2 mg/kg administered every 24 hours (usually one half of the 2-mg tablet or 1 mg daily). Once the disease is in remission, tapering of the GC is begun, eventually going to an every other day dose of the GC. Chlorambucil effectiveness has a lag effect and may not be fully appreciated until 4 to 8 weeks on therapy. Once the cat is off the GC, or the minimum dose of the GC has been determined based on relapses, treatment every 48 hours with chlorambucil is attempted. If the disease flairs at any point, go back two to three dosage steps (doses of GC and chlorambucil used two to three steps previously) and then begin to taper again, stopping before the ineffective dose. Side effects associated with chlorambucil therapy are myelosuppression (anemia, leukopenia, and thrombocytopenia), gastrointestinal (anorexia, vomiting, and diarrhea), and, rarely, hepatotoxicity. CBCs, including platelet counts, in addition to measuring liver enzymes, should be performed every other week for the first 3 months, monthly for 3 months, and then every 3 months for as long as the cat is on the chlorambucil. In addition, urinalysis and urine cultures should be done every 6 months to evaluate for asymptomatic bacteriuria.
5. Cyclosporine (CSA), which is a calcineurin inhibitor, may be used in cases of EGC. By inhibiting calcineurin, an important enzyme responsible for T-cell activation, CSA prevents the transcription of proinflammatory genes. CSA also inhibits the activation of mast cells, eosinophils, lymphocytes, Langerhans cells, and keratinocytes. The dose the author uses in cats is 5–7 mg/kg of the microemulsified form (mCSA) administered every 24 hours. There have been mixed results with this drug [15,16]. The author has been pleased with the response to this drug and believes that it controls the disease adequately in 60% to 75% of the cats with EGC. Side effects in cats are limited and are primarily gastrointestinal, especially vomiting. Other side effects reported include cutaneous papillomatosis, hyperplastic gingivitis, hirsutism, papillomatosis, and activation of latent *Toxoplasma* infection. To minimize the most limiting factor of CSA (vomiting), the following protocol is used for a 10-lb cat: 10 mg of mCSA is administered once daily for 4 days, 20 mg administered once daily for 4 days, and then 30 mg administered once daily for 45 days. For the first 10 days, metoclopramide 2.5–5.0 mg is administered 30 minutes before mCSA. For the first 14 days, the mCSA is administered with a meal. After that, it is administered 2 hours before a meal. The product is available in a capsule form as well as in a liquid form. The liquid allows more flexible dosing but is extremely bitter tasting.

6. Comiconized palmidrol is an analogue of palmitoyl-ethanolamide. Palmitoyl-ethanolamide is produced in the area of mast cell degranulation by the surrounding tissue. It is an anti-inflammatory molecule that exerts its action by binding cannabinoid receptors (CB2) on mast cells. These receptors downregulate mast cell degranulation. In a preliminary study administering 10 mg/kg twice daily for 30 days to 15 cats with EG or EP, 10 (67%) of 15 cats showed clinical improvement of clinical signs and lesions [17].
7. Other treatment options, depending on the form of EGC, that have been reported to be effective include the following: doxycycline (25 mg administered every 12 hours; the medication must be followed with food or water to help prevent esophagitis and subsequent esophageal stricture), oral gold (auranofin, 0.1 mg/kg daily), surgical excision, cryotherapy, laser excision or ablation, α -interferon (3000 IU daily), and megestrol acetate (which should only be used as an absolute last resort because of serious side effects associated with its use, including adrenocortical suppression, transient diabetes mellitus, personality changes, increased weight, stump pyometra, mammary hypertrophy, neoplasias, and hepatotoxicity) at a dosage of 2.5 to 5.0 mg administered every 24 hours for 5 days and then at 2.5 to 5.0 mg administered semiweekly to weekly [18].

MOSQUITO BITE HYPERSENSITIVITY

Background

MBH is an uncommon ED of cats that was first described in 1988 [19]. Some authors consider it to be a member of the EGC, whereas others believe that it is a separate entity. Either way, it seems to be a hypersensitivity reaction to mosquito bites. There is significant geographic variability of this disease in the United States, correlating to the density of mosquitoes in a particular region. Also, because of the insect etiology, the disease is seasonal, correlating to the mosquito season in a particular area.

MBH only affects cats that are exposed to mosquitoes; therefore, the disease primarily affects indoor and outdoor or exclusively outdoor cats. There is no age, breed, or sex predilection. Affected areas include the poorly haired areas on the dorsal muzzle, the pinnae, preaural regions, periorbitally, skin around the nipples, and the footpads. Lesions progress from an erythematous papule or plaque to an erosion or ulcer that develops a crust. Alopecia and depigmentation of these areas may be present. Edema may develop on the muzzle or the footpads. Peripheral lymphadenopathy, fever, and eosinophilia are frequently present [6,20]. Histopathologic examination reveals a superficial and deep nodular to diffuse predominantly eosinophilic dermatitis, with eosinophilic luminal folliculitis and furunculosis and an occasional flame figure [10,21].

The differential diagnosis depends on the specific areas affected but could include pemphigus foliaceus or erythematosus, environmental allergen-induced AD, CAFR, flea bite hypersensitivity, dermatophytosis, demodicosis, neoplasia (eg, SCC, mast cell tumor), discoid lupus erythematosus, actinic dermatitis, *Cryptococcus* infection, and idiopathic EGC.

Mosquito Bite Hypersensitivity Diagnosis

As mentioned previously, the diagnosis of dermatologic disease is dependent on the combination of signalment, history, clinical findings, and response to therapy. In MBH, the history, symptoms occurring during mosquito season with known exposure to mosquitoes, clinical findings as described previously, and rapid and complete response to treatment consisting of avoidance of mosquito exposure or treatment with steroids support the diagnosis.

The MDB for a cat presented with signs consistent with MBH should include skin scrapings (superficial and deep), Wood's lamp examination, and fungal cultures to rule out demodicosis and dermatophytosis, respectively. Because of the seriousness of the rule-out diseases, it is advisable to biopsy the lesions and have histopathologic evaluation of tissue samples before instituting therapy. Remember that many of the differentials may be steroid-responsive diseases but that the long-term prognosis for control may be different than for MBH.

Mosquito Bite Hypersensitivity Treatment

Many cases need symptomatic treatment with systemic GCs (oral prednisolone or injectable methylprednisolone acetate using doses as previously discussed) in addition to minimizing or avoiding mosquito bites. Avoiding mosquito bites by restricting the cat to indoors (especially during and after dusk) is an effective treatment if the cat cooperates. An additional option includes applying insect repellents to the affected areas (use cautiously, because many are toxic in cats).

FELINE HERPESVIRUS DERMATITIS AND STOMATITIS

FHV is best known for its contribution to the upper respiratory syndrome (rhinotracheitis) of cats. Cats with this syndrome may present with oral or corneal ulcers along with sneezing and ocular and nasal discharge. The ulcers occur because herpesvirus is an epitheliotropic DNA virus capable of causing epithelial necrosis. A less common presentation is a syndrome of facial, truncal, oral cavity (stomatitis), or footpad ulceration associated with FHV infection. The face, especially the nasal planum, tends to have the most severe involvement.

Historically, affected cats have chronic ocular or respiratory disease or had an upper respiratory infection as a kitten. Eighty percent of all previously infected cats go on to become infected for life even though they may not be symptomatic (carrier state) [22]. Persistent infection with periodic or continuous shedding is common. Whenever a carrier cat undergoes stress or administration of GCs or another immunosuppressive therapy, there is a risk of a recrudescence of the virus, most commonly presenting with upper respiratory tract signs. Some cats develop a dermatitis or stomatitis in addition to or instead of the respiratory signs. The author has also seen the nasal planum affected in cats given intranasal vaccines containing FHV. In these cases, the disease is self-limiting and treatment is not necessary.

Clinical findings include vesicles, erosions, ulcers, and crusts that may involve the face (especially the nasal planum), footpads, trunk, or gums

(stomatitis). Signs of an upper respiratory infection (fever, anorexia, conjunctivitis, corneal or oral ulcers, nasal and ocular discharge, or sneezing) may be present. The differential diagnosis includes FeLV-associated dermatitis, cutaneous drug reaction, erythema multiforme, MBH, EGC, pemphigus vulgaris, and systemic lupus erythematosus [23–25].

Feline Herpesvirus Diagnosis

Historical clues would include a poor response or exacerbation of clinical signs when GCs are administered, a history of upper respiratory infection, the presence of concurrent immunosuppressive diseases (eg, FeLV, FIV) or neoplasia, or a history of refractory gingivitis and/or stomatitis. Diagnosis is confirmed by histopathologic examination in which there are intranuclear inclusion bodies present. Polymerase chain reaction (PCR) from conjunctival smears, fluorescent antibody from conjunctival smears, serology, and immunohistochemistry (IHC) for FHV antigen may help to support a diagnosis of FHV infection; however, because of the high incidence of FHV infection in the “normal” cat population, overinterpretation of a positive result is a concern. Recently, the IHC test was reported to be an accurate test for FHV infections [24].

Histopathologic examination reveals necrotic, ulcerative, and crusting dermatitis with a primarily eosinophilic infiltrate and intranuclear viral inclusion bodies in the surface keratinocytes and follicular outer root sheath epithelial cells [10]. The nuclei of these cells exhibit margination of chromatin, and the cytoplasm has a foamy appearance. When viral inclusion bodies are present, the diagnosis is straightforward. Unfortunately, the viral inclusions are not always readily seen, and in those cases, differentiating FHV dermatitis from MBH or EGC is difficult.

No specific treatment is available. Symptomatic treatment for the upper respiratory signs should be administered. This may include ophthalmic medications and/or oral antibiotics for secondary infections and supportive care (eg, removing discharge from the eyes and nose, hand feeding if anorexic). Additional treatments that have not been evaluated with evidence-based medicine but have been anecdotally reported to be of value include the following:

1. α -Interferon, a cytokine with antiviral, antineoplastic, and immunomodulating properties, has been used to treat cats with FHV infections. Dose recommendations range from 1.5 to 2 million U/m² body surface area (BSA) administered subcutaneously three times a week (this is the dose used in human patients for herpes virus infections) to as low as 1000 IU/d administered orally. Side effects are uncommon, but malaise may be seen using the subcutaneous protocol. The author prefers to use the oral form at 3000 IU/d administered orally.
2. Concurrent lysine therapy at a dose of 250 to 500 mg administered twice daily. If a nonveterinary product is used, be certain that it does not contain propylene glycol, which is toxic in cats. Herpesvirus depends on exogenous arginine for replication. Lysine suppresses the incorporation of arginine into viral proteins; therefore, it has a virostatic effect. In a recent *in vitro* study [26], high concentrations of lysine did reduce the replication of FHV but

only if the media contained low concentrations of arginine. Placebo-controlled clinical studies need to be performed to determine whether lysine administration is useful in the management of FHV infections.

3. Systemic antiviral agents have not been investigated in cats and should be used with caution. The author has no experience with this family of drugs.

CANINE FACIAL EOSINOPHILIC FOLLICULITIS AND FURUNCULOSIS

Canine facial eosinophilic folliculitis and furunculosis is a peracute and rapidly progressive dermatitis of the muzzle. Lesions may also be found on the pinnae or lips, periorbitally, or in the sparsely haired areas of the ventral trunk. Initial lesions consist of erythematous or hemorrhagic papules, plaques, and nodules that rapidly become eroded, ulcerated and crusted (Figs. 2 and 3). These lesions tend to be painful. It has been suggested that the disease is associated with arthropod exposure and/or bites. Supporting this theory is the peracute onset, the frequent observation by the owner of an arthropod bite or exposure, and the rapid and complete response to systemic GCs. Refuting this theory is the observation that some cases occurred in the winter months with no known exposure to arthropods. An interesting yet unexplained observation is that this disease rarely recurs. It would be expected, whether the lesion was attributable to a direct arthropod insult or to a hypersensitivity and/or immune-mediated reaction, that there would be future exposure to arthropods, and thus recurrence of the reaction. What causes this disease and why it rarely recurs is an area for future research. Signalment obtained from a retrospective study revealed a 76% incidence in large-breed dogs, and of the incidence in dogs with a known age, 47% and 81% of the dogs were younger than 2 and 4 years of age, respectively [27].



Fig. 2. Eosinophilic folliculitis and furunculosis in a 4-year-old Samoyed. This dog was presented 2 days after the onset of the lesions. The owner reported the first lesion as a “pimple” and that it spread rapidly.



Fig. 3. A close-up view of the Samoyed. Note the nodules admixed with the extensive crusting and ulcerations.

Canine Facial Eosinophilic Folliculitis and Furunculosis Diagnosis

Diagnosis is based on signalment, history, and clinical findings. The differential diagnosis includes nasal bacterial folliculitis and furunculosis, dermatophytosis, demodicosis, pemphigus foliaceus, and pemphigus erythematosus.

Diagnostics should include deep skin scrapings, Wood's lamp examination, fungal culture, and biopsy. Cytology can be useful in this disease, in that numerous eosinophils are frequently seen. The author has also seen cases in which eosinophils were not seen on cytology yet were prominent on histopathologic examination, however. Neutrophils may also be present if there is a secondary surface pyoderma. Histopathologic examination is diagnostic for this disease. Findings include a mural eosinophilic folliculitis, luminal eosinophilic folliculitis, and furunculosis with a nodular to diffuse superficial and deep eosinophilic dermatitis. Erosions, ulcers, and serocellular crusts are also present. There may be marked dermal edema, dermal hemorrhage, and flame figures [27,28]. Interestingly, there are similarities in the histopathologic findings between this disease and MBH in the cat. These changes include the presence of diffuse eosinophilic dermatitis, foci of eosinophilic degranulation, and flame figures. Whether these similarities are attributable to a common pathogenesis or represent a nonspecific reaction attributable to different triggers is unclear. A CBC may reveal eosinophilia.

Canine Facial Eosinophilic Folliculitis and Furunculosis Treatment

Response to anti-inflammatory doses (1.0–2.0 mg/kg administered every 24 hours) of a systemic GC is rapid in most cases. Treatment with this dose is maintained until clinical remission (usually 7–14 days), and it is then tapered over an additional 14 days. Antibiotics are not usually needed unless bacterial infection is present (indicated by the presence of neutrophils and intracellular bacteria on cytology). The author has seen cases that were treated with antibiotics exclusively, with resolution of the lesions occurring but at a much slower

pace than those treated with GCs. Yet, in those cases treated with antibiotics versus GCs, clinical findings were identical on days 21 through 30.

CANINE EOSINOPHILIC DERMATITIS WITH EDEMA (WELLS' SYNDROME)

Wells' Syndrome Background in Human Beings

Wells' syndrome is an eosinophilic cellulosic disease of human beings. Clinically, people with Wells' syndrome present with a history of sudden onset of annular erythematous or edematous patches that rapidly evolve into plaques. These plaques may be single or multiple and may occur anywhere on the body. The patient may report mild pruritus, and there may be pain associated with the lesions. Papules, vesicles, bullae, erosions, ulcerations, or nodules may also be present. The disease may be recurrent [29,30].

The cause is unknown, but cases have been associated with an arthropod bite or sting, cutaneous viral infections, cutaneous parasitic infestations (eg, toxocariasis, ascariasis, onchocerciasis), leukemia, myeloproliferative disorders, AD, fungal infections, and cutaneous drug reactions [31–34]. Because of the many causes of this disease, it is best to think of Wells' syndrome as a reaction pattern rather than as a specific diagnosis.

The pathogenesis is unclear; however, there has been a study in which an increase in the IL-5 level was identified [29]. In this study, the increase in the circulating IL-5 level was associated with a relative increase in circulating CD3+CD4+ T cells. This increase in IL-5 could explain the increase in blood and tissue eosinophilia that is present in this disease. Degranulation of the eosinophils then occurs, leading to the clinical signs of edema and inflammation.

Wells' Syndrome Diagnosis

Diagnosis is made by histologic examination of a skin biopsy. Histopathologic findings on biopsies include a dermal infiltrate of eosinophils and histiocytes. In older lesions, the dermal infiltrate changes from eosinophilic to histiocytic with giant cells that surround some of the collagen fibers (flame figures). Flame figures represent eosinophilic debris coating collagen bundles [35–37].

Wells' Syndrome Treatment

Treatment for Wells' syndrome depends on the triggering event. This may include antifungal therapy, antihistamines, topical or systemic GCs, CSA, and dapsone [29].

Canine Wells'-Like Syndrome

ED with edema (Wells'-like syndrome) is a rarely reported disease in dogs. A case report of a dog that had urticaria with ED was not identified as Wells'-like syndrome, but it may have been this disease [38]. In that report, the authors believed that the disease was triggered by a heartworm preventative, diethyl-carbamazine. The first report of dogs with Wells'-like syndrome was published in 1999 [39]. In that study of nine dogs with this disease, all dogs presented with "target" lesions, erythematous patches with a central pallor, on the pinnae

and ventrum. In some areas, these lesions progressed to erythematous serpiginous plaques. In four of nine dogs, there was also involvement on the extremities. Some of these lesions were purpuric and failed to blanch with diascopy, which is most consistent with hemorrhage from damaged and/or dysfunctional blood vessels. Edema, ranging from facial to generalized, was present in six of nine dogs. Fever (six of nine dogs) and lymphadenopathy (four of nine dogs) were also reported in this study. Urinalysis, tick titers for Rocky Mountain spotted fever, *Ehrlichia canis*, *Borrelia burgdorferi*, and antinuclear antibody (ANA) were all within normal limits or negative. CBCs revealed mild stress leukograms (neutrophilia with lymphopenia). Hypoalbuminemia was also reported. Histopathologic abnormalities reported from skin biopsies included superficial to deep perivascular to interstitial eosinophilic dermatitis with dermal edema and vascular dilatation. Four of nine dogs had flame figures, although, surprisingly, dermal hemorrhage, as suggested by the clinical findings, was not present.

Seven of the dogs were treated with anti-inflammatory doses of GCs for up to 4 weeks. Five of these seven dogs had the disease resolve within 4 weeks. In the other two dogs, the disease waxed and waned. The final two dogs were treated with antihistamines or received no therapy. Both of these dogs had resolution of their disease. The authors speculated that cutaneous drug reactions were the cause in seven of nine dogs and that an arthropod bite was causative in one case. Historically, five of the nine dogs had a history of allergic skin disease, perhaps suggesting that they were “prone” to hypersensitivity reactions. The other possibility is that because most cases were seen in the late summer or early fall months, environmental allergens may have triggered the disease. This author has seen a case in a 6-year-old intact female Labrador Retriever with



Fig. 4. This 6-year-old intact female Labrador Retriever was presented for fever, lethargy, and these extensive lesions on the ventral abdomen that occurred within a week of receiving vaccination and a long-acting heartworm injection (moxidectin). Over the next year, these symptoms and lesions recurred two more times without any known precipitating trigger. Note the erythematous patches involving the ventral abdomen



Fig. 5. A closer view of the dog in Fig. 4. These lesions failed to blanch with diascopy, consistent with vascular damage.

a history of seasonal atopy that was diagnosed with ED with edema (Figs. 4–6). The disease began shortly after administration of a long-lasting injectable form of heartworm preventative. The disease continued to wax and wane, regardless of the therapy (including immunosuppressive doses of GCs).

SUMMARY

EDs include a heterogeneous group of diseases that are secondary to underlying antigenic stimulation (hypersensitivity reactions) in most cases. Treatment options may include GCs, antifungal agents, antibiotics, food trials, ASIT, or



Fig. 6. The dog in Fig. 4 also had extensive involvement of the pinnae and temporal regions. Like many of the dogs reported with Wells'-like syndrome, this dog had a history of allergic skin disease but had never before had any involvement of the these areas.

CSA. To avoid the indiscriminate administration of chronic GCs or random therapeutic trials, a systematic approach to the diagnosis of these diseases should be performed.

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