Atopic Dermatitis: A New Approach to Diagnosis and Treatment

Charlie Pye BSc, DVM, DVSc, DACVD
Assistant Professor Dermatology, Atlantic Veterinary College

Atopic dermatitis is a genetically predisposed, inflammatory and pruritic allergic skin disease associated with IgE antibodies to environmental allergens.[1] Common allergens that pets can be reacting to are pollens, mould spores, indoor allergens such as dust mites and storage mites, dander and insects. Pruritus may be seasonal or non-seasonal depending on the allergens involved e.g. pollen versus dust mites. Pruritus is generally alesional at disease onset then lesions develop as the disease progresses and secondary skin changes or infection occur. Atopic dermatitis is a diagnosis of exclusion as no test exists that can be used to definitively diagnose this disease process. As many other diseases present similarly to atopic dermatitis, formulating differential diagnosis lists and using diagnostic testing to eliminate other differentials is recommended. Clients should be informed that no cure exists for atopic dermatitis and so the aim of treatment is to manage their pet's allergies life-long.

Pedigree analysis has demonstrated that atopic dermatitis is a heritable condition in the dog with certain breeds at an increased risk for developing canine atopic dermatitis (CAD) including the golden retriever, Labrador retriever, German shepherd, French bulldog and West Highland white terrier.[2,3] No definitive genetic markers have been identified but multiple studies including genome-wide association as well as genome-wide linkage studies have been performed to investigate the genetic basis of the disease.[4]

The prevalence of atopic dermatitis in both humans and other species has dramatically increased over the past decades. This increase has been attributed to changes within our environment as well as changes to our lifestyle. One possible explanation is the "hygiene hypothesis", a theory that states exposure to diverse microbes early in life helps modulate the immune system against development of allergic disease by stimulating T-helper-1 (Th1) and regulatory T cells (Treg) over T-helper-2 (Th2) cells.[5] Putting this theory basically; increased hygiene measures and levels of cleanliness decrease the diversity of infectious agents we are exposed to which then promotes the development of allergic disease through a hypersensitive immune response. In our canine companions, environmental factors associated with development of atopic dermatitis include living in an urban environment and living primarily indoors.[6] Other factors are found to be protective against the development of atopic dermatitis. These include being born and living in a rural environment, regular walks through woodlands/fields/beaches, living with a family with more than 2 children, having regular contact with other animals and living in a detached house.[6] As studies have numerous confounding variables, these associations do not prove cause and effect. It is highly possible that many environmental triggers exist that could influence disease development. There is still strong evidence to support the role of environmental factors in the pathogenesis of CAD due to fluctuating clinical signs (changing allergen levels), dogs developing IgE antibodies against allergens and allergen-specific immunotherapy benefiting 60-70% of dogs.[7] We know less about feline allergic skin disease. Currently the disease process is termed Feline atopic skin syndrome.

Many other non-environmental factors contribute to the development of atopic dermatitis in companion animals. Dysfunction of the skin barrier has been well documented and this dysfunction facilitates absorption of allergens that stimulate the immune system.[8] This induces a Th2 response that serves to downregulate structural proteins in the skin impacting barrier function.[8] Keratinocytes within the stratum corneum are imbedded within a lipid matrix consisting of free fatty acids, cholesterol and ceramides. Ceramides form the largest group of these lipids.[8] Non lesional skin of dogs with CAD has disorganized, abnormal and reduced numbers of lipid lamellae. Lesional skin also contains decreased numbers of ceramides and fatty acids.[8] For these reasons, restoring this barrier function during treatment is a highly important part of management of CAD.

Immune dysfunction in atopic individuals has been well documented in studies. A polarized Th2 response and increased levels of Interleukin (IL)-4, IL-5 and IL-13 are found in serum of affected individuals. Increased numbers of Th2 cells promote humoral immunity and increase the production of allergen specific IgE antibodies.[9] These IgE bind to the surface of mast cells, are cross-linked by allergens and lead to mast cell degranulation. IL-4 and IL-13 are both pro-inflammatory interleukins and help induce pruritus by activating itch-sensing neurons in the skin.[9] IL-31 is also an

important pruritogenic cytokine which activates somatosensory neurons and upregulates the release of pro-inflammatory mediators.[10] IL-31 is increased in the serum of dogs with CAD and serum levels appear to positively correlate with disease severity.[11]

The microbiome of the skin in patients with atopic dermatitis has been compared to unaffected individuals. Non lesional skin of dogs with CAD harbours lower numbers of bacterial species indicating lower species richness.[12] The microbiota is also less diverse when dogs have superficial pyoderma secondary to atopic dermatitis.[12] Similar changes are noted with the fungal microbiota. Dogs with allergic skin disease are less rich in fungal species relative to unaffected dogs.[13] Dysbiosis of the cutaneous microbiome appears to be a feature of CAD but it is unknown what role this plays in CAD clinically. Additional research is needed to define the relationship between the cutaneous microbiome and the induction and exacerbation of CAD.

Clinical signs

Clinical signs of atopic dermatitis are numerous and include pruritus, alopecia, erythema, excoriations, papules, lichenification, hyperpigmentation, otitis and also secondary changes/lesions such as pustules, crusting, erosion etc.[1] The face, concave aspect of the ear pinnae, ventrum, axillae, inguinal area, perineal area and distal extremities are most commonly affected in canine CAD.[14] There are certain breed specific body sites that have been identified as often affected.[2] Clinical signs of CAD commonly present before 3 years of age and can be seasonal or non-seasonal. Clinical signs of CAD overlap with numerous other pruritic and inflammatory skin diseases. Cutaneous adverse food reaction and atopic dermatitis are clinically indistinguishable from each other so a diagnosis cannot be made on clinical presentation alone.

Differential Diagnoses

Differential diagnoses for atopic dermatitis include other pruritic diseases such as: Ectoparasites (fleas, *Sarcoptes*, demodicosis, *Cheyletiellosis*, Pediculosis, *Otodectes)*, secondary infection, flea allergy dermatitis, cutaneous adverse food reaction, contact dermatitis, cutaneous lymphoma and dermatophytosis. Many of these dermatologic diseases have similar clinical presentations so diagnostic testing is required to make a definitive diagnosis.

Work-up

With any pruritic individual a dermatologic minimum database should be performed to include cytology, flea combing and skin scrapings. Cytology will help identify any secondary infection present. One must remember that cutaneous infections in companion animals are secondary to the underlying skin disease. Once identified they must be treated but the diagnostic work up for the primary issue must be continued. Deep and superficial skin scrapings should be performed to identify any ectoparasites present such as *Demodex* and *Sarcoptes*. *Sarcoptes scabiei* can be challenging to find even on the best superficial skin scrapings. A positive pinnal pedal reflex has been associated with infestation and, if noted, would justify an ectoparasiticidal trial.[15] For other parasites such as Cheyletiella, unstained tape preparations can be used to visualize the mites. Ectoparasites should always be ruled out prior to allergy testing. Previous studies have found cross reactivity between house dust mites and *Sarcoptes* mites.[16] If ectoparasites are not ruled out, this can lead to false positive results on an intradermal allergy test. Pruritic individuals should also be assessed for fleas using flea combing and a wet paper towel. If debris is gained from the combing this can be placed between two sides of wet paper towel and the towel rubbed together gently. If the towel turns red this indicates that the debris is flea dirt and there is likely a flea infestation.

As cutaneous adverse food reactions (CAFR) and CAD can look so similar, a novel protein or hydrolyzed restricted diet trial should be recommended in a patient with non-seasonal pruritus to determine whether a patient's clinical signs are due to CAD or a CAFR. These "food trials" should last for 8 weeks and be fully restricted (within the realms of the ingredients of the diet). CAFR can have both an immune mediated and non-immune mediated basis, hence the numerous clinical signs one can see in a case of a patient with such a reaction. Gastrointestinal signs are seen more commonly with cutaneous adverse food reactions, such as vomiting, diarrhea, anal gland issues,

flatulence etc.[17] Individuals with CAFR may not respond as well to certain medications as those with CAD and pruritus may remain elevated despite medication usage. The most common food allergens in dogs are beef, dairy, and chicken and in cats are beef, fish, and chicken.[18]

Again, CAD should be a diagnosis of exclusion of other pruritic diseases due to similarities in clinical presentation.[19] This can be challenging when clients have limited financial means or tolerance for such a work-up. In such situations, Favrot's criteria can be used to assist in the diagnosis of CAD but cannot be used as the sole criteria for diagnosis.[20]

Treatment

Clinical consensus guidelines exist for the treatment of CAD.[21] Following are recommendations from these guidelines as well as other literature; these recommendations are broken down into categories. Atopic dermatitis is a disease generally requiring multi-modal treatment. The many treatments available for atopic dermatitis allow customization of your treatment protocol for each individual patient and their family.

Diet/supplementation

Supplementation with oral essential fatty acids (EFA) has previously been shown to regulate and normalize lipids in the stratum corneum of dogs with CAD. Benefits of supplementation will not be seen for months so this option is best suited for chronic management of the disease.[21] Several diets high in EFAs are on the market currently and may assist in decreasing pruritus or amounts of medications and therapies required. Alternatively, clients can provide separate supplementation of EFAs but should be made aware that the benefit might not be seen for 2 months after starting this supplement.[21] At this time, there is little evidence of superiority for any particular EFA combination, dosage, ratio or formulation (including enriched diets) to improve skin and coat quality in dogs with AD.

Topical therapy

Topical therapies for atopic dermatitis come in the form of shampoos, mousses, sprays, wipes, ointments and spot-on preparations. Topical therapy can be very beneficial for patients with atopic dermatitis as it directly treats the affected skin and may decrease or eliminate the requirement for systemic medications. Topicals can also decrease microbial load, improve barrier function and decrease inflammation and pruritus. Bathing with a non-irritating shampoo at least once weekly has been found to be beneficial in patients with CAD. The type of shampoo can be tailored to each patient pending their clinical signs. During active infection or flare ups of the allergic disease, bathing frequency can be increased to provide relief for patients. Bathing serves to mechanically remove allergens, debris and microorganisms from the skin surface as well as hydrates the skin.[21] Between bathing some of the other topical therapies can be used to manage infection or remove debris.

Topical barrier repair products available are formulated with topical lipids as well as ceramides, fatty acids and other ingredients. These products serve to replace the lipids lacking in the skin of individuals with CAD. These products are not recommended as monotherapy for CAD but can be useful as adjunct therapy in affected individuals. They are likely of less benefit in companion animals fed a diet enriched with EFAs.[21] Multiple barrier repair products are available. One such product, Allerderm (Virbac), has been shown to help restore the ultrastructural lipid abnormalities and significantly improve the severity of dermatitis in small numbers of dogs with CAD.[22]

Topical glucocorticoid therapy has been found to provide relief for both pruritus and inflammation in affected individuals. When prescribing, veterinarians should be aware of the potential risk of skin thinning with prolonged usage. Topical hydrocortisone aceponate spray (Cortavance, Virbac) has been studied for use during allergic flares and as a maintenance protocol for dogs with CAD. A greater then 50% reduction is pruritus has been noted in studies and when used at 5 x labelled dose for 14 days, no skin thinning was noted in a short period.[23] Twice-

weekly application of this spray has been shown to prolong the remission time in dogs with CAD between recurrence of disease, demonstrating a potential role in the long-term management of CAD.[24]

Systemic therapy

There are now multiple systemic treatments available for atopic dermatitis including anti pruritic agents as well as anti-inflammatory agents. These therapies are routinely used for management of patients with moderate to severe disease. Systemic corticosteroids continue to have a place in managing allergic skin disease, but long-term use should be avoided whenever possible as there are more safe, specific, and targeted therapies available, including cyclosporine (Atopica, Elanco), oclacitinib maleate (Apoquel, Zoetis), and lokivetmab (Cytopoint, Zoetis). It is important to recognize that each systemic medication is not equally efficacious in every patient with allergic disease. Some are mainly anti-pruritic agents whereas others are more potent anti-inflammatory agents.

Cyclosporine (Atopica, Elanco) is a non-steroidal medication that inhibits intracellular calcineurin. This is an enzyme involved in the activation of T cells and transcription of pro-inflammatory cytokines. Cyclosporine comes as a capsule version or a liquid version and is libelled or use in both dogs and cats. Dosing begins once daily but then can be tapered pending the patient's response. Many individuals with atopic dermatitis are able to reduce the frequency of administration to every other day and some to twice weekly. Cyclosporine has a delayed onset of activity and has previously been shown to improve allergic symptoms in dogs with CAD after 4 weeks of daily administration.[25] One study looked at cyclosporine given daily in combination with prednisolone at 1 mg/kg daily for 7 days followed by alternate day dosing for 14 days. This led to a faster improvement of skin lesions and pruritus scores compared to when cyclosporine was given as the sole treatment.[26] Cyclosporine is metabolized by the cytochrome P450 3A4 enzyme (CYP3A4) in the liver. Drugs that inhibit CYP3A4 (ie, azole antifungals) or compete with P-glycoprotein (ie, ivermectin) can cause drug interactions with cyclosporine. Veterinarians must be cognisant of these interactions when prescribing these medications. The most common side effects of cyclosporine are gastrointestinal upset but gingival hyperplasia, papillomatosis and hirsutism may also occur.[25]

Corticosteroids are potent anti-itch and anti-inflammatory medications with a rapid onset of activity. Due to their plethora of adverse effects, these medications should be used judiciously for aggressive clinical presentations of atopic dermatitis. Once clinical signs have resolved glucocorticoids should be tapered to a much lower dose or substituted for a safer therapy longer term.

Oclacitinib (Apoquel, Zoetis) is a janus kinase (JAK) inhibitor approved for use in dogs at least 12 months of age. Oclacitinib is most effective at inhibiting JAK1, which mediates intracellular signaling of multiple interleukins but most specifically IL-31, a pruritogenic cytokine.[27] Oclacitinib is primarily an anti-pruritic medication with mild anti-inflammatory benefit. It is rapidly absorbed as demonstrated in studies looking at time to clinical effect and in some studies appears to decrease pruritus as well as or better than prednisolone.[28] The long-term administration of oclacinitib can be associated with the development of urinary tract infections, vomiting, otitis, pyoderma and diarrhea in approximately 5 to 10 % of dogs but more serious adverse drug reactions seem to be rare.[29] In younger puppies oclacitinib use has been associated with development of demodicosis and pneumonia when used at higher doses so it is not recommended to use this medication in individuals with a history of either disease. In initial safety studies some dogs were reported to develop cutaneous masses whilst receiving oclacitinib. A more recent study did not find a correlation between administration of oclacitinib and development of cutaneous masses.[30]

Lokivetmab (Cytopoint, Zoetis) is a caninized monoclonal antibody that binds IL-31, thereby preventing it from inducing pruritus. Lokivetmab should be administered every 4 weeks. In some individuals injection frequency can be decreased over time. Lokivetmab will decrease pruritus usually within 1 to 3 days. This author sometimes finds that dogs will not respond to the first injection but may respond on subsequent injections. No major side effects were noted in original studies and side effects were found to be similar to percentages noted in the placebo control group.[31]

Antihistamines may have a variable response between individuals so are not generally recommended for chronic cases of atopic dermatitis. Anecdotal evidence suggests they may provide some benefit for milder cases of the

disease. Oral fluoxetine and low-level laser therapy have been trialed as therapies for CAD. However, they appear to have little efficacy in the treatment of CAD.[32,33]

Allergen-Specific Immunotherapy

Allergen-specific therapy (ASIT) is a focused treatment for individuals with atopic dermatitis. Formulation of ASIT is based on results of allergy testing. Many different protocols for ASIT exist with different administration schedules and routes of administration but there is no proven superiority of one method over another.[21] Studies evaluating the efficacy of ASIT have shown that approximately 20% of dogs have an excellent response with complete remission and discontinuation of all other therapies. Another 40% to 50% have a satisfactory response with improvement in clinical signs and/or a decrease in need for concurrent therapies. The remaining 30% to 40% show insufficient response to ASIT.[34] ASIT must be continued for a minimum of 12 months to assess its benefit. During this time patients can continue to receive other anti-pruritic or anti-inflammatory therapies to maintain their comfort level and prevent flares and infections. Side effects are relatively uncommon but can include increased pruritus, irritation at the injection site and erythema at the injection site. Systemic side effects such as vomiting, diarrhea and anaphylaxis can occur but are rare. [34] ASIT is indicated in patients with severe clinical signs, insufficient management with symptomatic therapy, medication side effects, client wishes or duration of clinical signs for more than 3 months per year.

Prior to ASIT, allergy testing must be pursued. This can be performed by intradermal skin testing or serologic allergy testing. These tests are not recommended as screening tests and should only be used to confirm the clinical diagnosis of canine AD. Results of these tests are used to formulate allergen specific immunotherapy. Allergens to be used for the test are selected based on geographical location as well as cross reaction between species and exposure. Intradermal allergy testing is widely considered the preferred diagnostic method amongst dermatologists but serologic allergy testing does have some advantages for certain patients such as no sedation required, medications can be continued up until the test date, no shaving required and less traumatic (no shaving or intradermal injections). Both intradermal allergy testing and serological testing are still lacking standardization so it is suspected that both false positive and false negative results may occur. A percentage of dogs with CAD may show negative reactions on an allergy test.[35] False negative reactions may occur due to improper technique, drug interference, testing performed during peak season, too low test concentrations of allergens or atopic-like dermatitis.[20,36] A study comparing IgE serological assays offered by four different laboratories showed substantial variation in both results and ASIT recommendations from the different laboratories.[37] This further highlights the need for standardization of these tests. With either test, results should be interpreted considering a patient's clinical signs, history and exposure to tested allergens. Even with these testing differences the success rate of ASIT based on intradermal allergy testing versus serologic allergy testing does not appear to be significantly different.[38]

Traditionally immunotherapy was delivered via subcutaneous injection. Over the last decade sublingual immunotherapy has also been found to be an effective means of administering allergy serum. A large, retrospective study of dogs receiving sublingual immunotherapy reported a good-to-excellent response in about 60 % of evaluable dogs, and in half of those who had failed previous subcutaneous ASIT.[39] Another large retrospective study of owners of dogs with CAD noted that two thirds of the dogs were rated as having a "satisfactory-to-excellent" response to immunotherapy after one year.[40]

Owner education

Realistic expectations surrounding atopic dermatitis treatment and management are paramount for treatment success. This disease is a life-long disease that cannot be cured and instead must be managed. Allergic individuals will continue to have flares of their allergic disease depending on allergen levels and environment. The aim of successful management is to try and minimize the number of flares and the severity of the flares and keep the patient comfortable. All companion animals "itch" so the aim of treatment is not to eliminate pruritus but to dramatically decrease it to a "normal" level.

If atopic individuals do have an allergy flare, they must be assessed for infection, ectoparasites or side effects or medications. If the flare is found to be due to CAD, it can be treated in many ways. Emollient topical formulations containing either lipids, complex sugars and antiseptics (Allermyl, Virbac) or ophytrium and lipids (Douxo Calm, Ceva) have been shown to provide a modest effect on skin lesions and pruritus in allergic dogs. The intensity and frequency of bathing may be the most important factor in relieving pruritus.[21] Topical glucocorticoid sprays are effective for the treatment of acute flares of canine AD. This treatment is especially suitable for localized skin lesions and for short durations. Application should continue until complete remission of signs and then tapered or discontinued. Prescribing a short course of oral glucocorticoids will generally improve signs of atopic dermatitis. Treatment with long-acting injectable steroids is not recommended for flares. Most pets with atopic dermatitis have pruritus that responds to oral glucocorticoids therefore failure of response to this treatment should prompt alternative diagnoses (for example, skin infections, ectoparasitism or other nonatopic food reactions).[21] Alternatively oclacitinib (Apoquel, Zoetis) or lokivetmab (Cytopoint, Zoetis) can be utilized to rapidly reduce pruritus in dogs with CAD during flares.[21]

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