An Itchy Situation

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Introduction

Canine atopic dermatitis (CAD) is a genetically inherited hypersensitivity reaction causing inflammation and pruritus. It is most often associated with IgE antibodies to environmental allergens, and is a disease that must undergo life-long therapy as it can rarely be cured. Atopic dermatitis is one of the most common skin diseases of dogs ranging from 3-15% of the general dog population (15, 11). Dogs usually present between 6 months and 3 years of age with clinical signs such as pruritus and skin lesions of the mouth, periocular region, ears, flexor aspects of the elbows, digits, ventral abdomen, perineum and ventral aspect of the proximal tail. Clinical signs may be seasonal or non-seasonal with the majority presenting as non-seasonal. Diagnosis of atopic dermatitis includes identification of strongly associated clinical presentation along with the elimination of differential diagnoses (4,8).

History and Presentation

As CAD is a multifaceted disease, history and clinical presentation are key features in diagnosis. A general history should be documented to determine diet, genetic background, environment, recent exposure, contact with other pets, and presence of pruritus in other household pets (18,9,5). Typical clinical signs include gradual onset of pruritus of the face and extremities in the form of face rubbing, scratching the ears, foot licking and chewing, and scratching the ventrum. Other clinical presentations may include chronic otitis externa, conjunctivitis, uriticaria, respiratory disturbances and gastrointestinal disturbances. It has been found to occur most commonly in dogs 4 months to 7 years of age with both seasonal and non-seasonal manifestations. The most common hypersensitivity seen in dogs with CAD is to house dust mites making indoor dogs more predisposed and showing a non-seasonal dermatitis (9). If pollen or other seasonal plants are the cause of hypersensitivity, the clinical signs may present

seasonally. Corticosteroid therapy is generally effective in the beginning of treatment. Breeds found to be predisposed include the Chinese Shar-Pei, West Highland terrier, French bulldog, Bichon frise, Lhasa apsos, English springer spaniels, setters, boxers, German shepherd dog, Dalmatians, retrievers and Jack Russell terrier breeds (9, 18).

Pathophysiology

CAD is a multifactorial disorder with with genetic predisposition to inflammatory and pruritic allergic skin disease (11,15). "IgE antibodies, generated against environmental allergens, are demonstrable in ~80% of dogs affected with AD, and there is a temporal association between clinical signs of skin disease and the level of exposure to these allergens." (14,15) As the complete mechanism of CAD is still being researched, skin barrier defects and a hereditary dysfunction of the immune system are common in dogs with CAD with two definitive stages of pathogenesis being known. The first stage consists of sensitization when an allergen is absorbed percutaneously. The antigen is bound to Langerhan cells present in the suprabasilar layer of the epidermis. Langerhan cells engulf the antigen and further processes it. The allergen is then presented to the immune system and carried to a regional lymph node to T- helper 2 cells. As Langerhan cells migrate to the lymph nodes they mature and initiate proliferation and differentiation of memory and effector T-cells. The sensitization process continues as T-cells and B-cells interact creating clonal expansion, producing IgE antibodies, and producing memory and effector T-cells and B-cells. This leads to circulating and bound antigen-specific IgE (14,9,17).

Once the sensitization stage has occurred in an individual, a second stage called the elicitation stage can occur. In this stage an allergen is absorbed percutaneously and the Langerhan cells will already be primed with IgE. They present the allergen to the memory T-helper cells which propagates release of inflammatory mediators and cytokines such as IL-4, IL-

5, IL-10, IL-13, and IL-31. Cytokines activate eosinophils and inflammatory cells causing pruritus. Mast cells will also be activated by cross linking of allergen-specific IgE and degranulation occurs. Mast cell degranulation causes release of more inflammatory mediators such as histamine, serotonin, tryptase, chymase, leukotrienes, proteases, and heparin which contribute to further clinical signs. Histamine release allows the leakage of plasma from the vasculature by contributing to contraction of vascular endothelial cells. Thus the patient experiences clinical signs such as pruritus of varying intensity, inflammation of the skin, and potentially secondary skin infections (9,6,10,14).

Diagnostic approach/ Considerations

CAD is a diagnosis of exclusion in which three steps are crucial to ruling out other diseases in order to definitively diagnose the disease. The first step includes ruling out other diseases resembling CAD such as flea allergy dermatitis, parasitic dermatosis, infectious dermatitis, allergic contact dermatitis, and adverse food reactions. These diseases may have similar clinical presentations as CAD including pruritus, excoriations, papular eruption, scaling, macules, pyotraumatic dermatitis, erythema, hyperpigmentation, self-induced alopecia, lichenification and therefore must be ruled out. Next, interpretation of the the clinical features of the patients displaying signs of atopic dermatitis should be determined. Lastly allergy testing by intradermal or allergen specific IgE serum is required for confirmation of the allergy suspected and to gather allergens to place into allergy therapy. (9,7,5,4,8)

Flea Allergy Dermatitis (FAD) can produce pruritus and skin lesions in the lumbosacral area, tail base, and caudomedial thighs. The most common distribution consists of a papular eruption and crusting of the lower back and inner thighs. In order to exclude FAD or flea infestation, clinicians should consider the prevalence of fleas in a geographical area, consider

pruritus in areas such as the paws or ears that may not be affected by fleas, examine the pet for fleas using a flea comb, and place the pet and other household pets on monthly flea prevention. FAD and CAD can co-exist and can cause atopic dogs exposed to fleas to have intensified clinical signs (18,9,7,5).

Pruritic parasitic dermatoses can be caused by sarcoptic acariasis, cheyletiellosis, pediculosis, trombiculiasis, otoacariasis and demodicosis. Skin scrapes, ear swabs, hair combing, hair plucking, and tape impressions can be used to collect samples for microscopic identification of these parasites. *Sarcoptes scabiei var. canis* is most commonly identified via superficial skin scrapings but can also be identified by serology testing, skin biopsies, fecal flotation, or response to treatment. Demodex is identified through deep skin scapings, acetate tape impressions, and skin biopsies. Cheyletiella and Trombicula are identified microscopically via acetate tape impressions, superficial skin scaping, and coat brushings. Otodectes cynotis is identified microscopically through cytological examination of aural debris and on otic exam. Sarcoptes scabiei var. canis and Cheyletiella are not always identified through examination and may require an anti-parasitic trial treatment to completely rule out their presence (9,7,5).

Secondary bacterial and fungal skin infections are common in dogs with atopic dermatitis. The most common organisms associated with CAD are Staphylococcus pseudintermedius and *Malassezia pachydermatis*. Bacterial lesions appear as a papulopustular eruption and epidermal collarettes with clinical presentation offering a presumptive diagnosis. However, cytology with Diff-Quik staining allows identification of organisms to definitively diagnose the infection. Other forms of diagnosis include acetate tape prep and culture and sensitivity if other modes of diagnosis are non-diagnostic. *Malassezia* is also diagnosed through cytology of commonly affected areas including skin folds and areas holding moisture. In both

cases topical or systemic antifungals or antimicrobials can be used to rid the infection and therefore also determine the level of pruritus that is caused by the primary disease (9,5,7).

Canine Atopic Dermatitis (CAD) and Cutaneous Adverse Food Reaction (CAFR) are considered two separate diseases with similar clinical presentations. CAD is considered an immune-mediated hypersensitivity reaction to environmental allergens while CAFR can be considered an immune-mediated or non-immune mediated reaction to food (5,9). CAFR can be present separately from CAD or act as an amplifier of clinical signs when seen with CAD and thus must be differentiated with an elimination diet trial. CAFR usually presents as constant pruritus that may affect the face (lips, chin), axillary region, inguinal area, ears, and feet with age of onset varying from less than one year to over 7 years. It is typically refractory to corticosteroid therapy. Dogs may present with chronic otitis externa, licking and chewing of the feet, rubbing of the face, and secondary bacterial or fungal infections of the skin. Primary lesions include erythema and papular eruption with secondary lesions such as excoriations, crusts, lichenification, hyperpigmentation, and keratoseborrheic changes. Other signs not common in CAD but seen in CAFR may be gastrointestinal signs such as vomiting and diarrhea, urticaria, and rarely angioedema. Dogs with CAFR may have a history of diets that consist of commercial dog food, treats, supplements, human food, and chewable medications (5,9,7,4,14. An elimination food trial to rule out CAFR must consist of a novel protein or hydrolyzed protein, as the most common food reaction is to protein in the diet. The diet must be fed strictly for a minimum of 8-12 weeks. If no resolution of signs is seen, a home-cooked diet trial can be considered. During the elimination food trial, table food, treats, rawhides, toothpaste, pill-hiding treats, and flavored drugs should be prohibited as feeding small amounts of other foods can cause a relapse of clinical signs and alter diagnosis (11,9,5).

Once these other diseases are ruled out, the clinical features of the animal displaying signs of atopic dermatitis should be interpreted. Clinical presentation of CAD commonly includes mild to intense pruritus beginning between 1 and 3 years of age with distribution on the face and ventrum and chewing of the feet commonly seen. CAD typically responds well to corticosteroid therapy at the start of the disease and can skew results of further testing. Otitis externa is seen in 80% of CAD cases and may be the only clinical sign on presentation (9,7, 5). Other criteria may include pododermatitis, specifically in the forelimbs, inflammation of the pinna, facial erythema, seasonal symptoms, lichenification of the flexural surface of the elbows and tarsus, conjunctivitis and or epiphora, failure of symptomatic therapy, and a chronic dermatitis. Once all other complicating or concurrent disease have been exhausted, the gold standard test is intradermal allergy testing (IDT). "IDT is an indirect measure of cutaneous mast cell reactivity due to the presence of IgE." (7,9,16). Allergens should be selected based on regional location as failure to select appropriate allergens can result in flawed findings. The allergens are injected intradermally following clipping and labeling sites for injection on the lateral thorax. The injection sites should be at least 2 cm apart and are filled with 0.05-0.1 mL of the diluted allergen. After 15-20 minutes, the sites are assessed for reactions which may consist of erythema, turgidity, and wheal diameter and formation. "By convention, an allergen reaction is positive when the wheal formed is at least equal or greater than halfway between the negative and the positive control reactions" (7). Varying degrees of positive exist with greater than or equal to 2/4 being a positive (7,15).

Allergen-specific IgE serology testing is also available for identification of allergens but only measures circulating allergen specific IgE. Allergen-specific IgE serology testing uses an

ELISA to detect specific IgE antibodies to allergens. Blood is drawn from the patient and therefore it is less traumatic to the patient with no sedation required (9,15).

Treatment and Management

Management of CAD consists of controlling the clinical signs of disease life-long, as a cure is not achievable. After identification of inciting allergens, more specific therapy can be implemented. Allergen avoidance is the most successful modality of treatment but in most cases this is not achievable and therefore other modalities of management must be implemented. Symptomatic treatment may be used to manage clinical signs initially if allergen specific immunotherapy is not warranted at that time due to short seasonal signs. Topical treatment may include shampoos, lotions, or topical corticosteroids that aim to eliminate allergens from the skin surface and provide temporary relief. Shampoos and lotions can help to remove the allergen from the skin surface, act against immune mechanisms, restore the epidermal barrier, and treat bacterial or fungal overgrowth. Topical corticosteroids can be used to reduce inflammation and cause less side effects if a focal dermatitis is present. If an ear infection is present, it should be treated with an antiseptic ear cleanser in addition to an antibiotic, anti-fungal, and anti-inflammatory otic solution topically (5,9,15).

Systemic treatments for symptomatic therapy may include oral corticosteroids, cyclosporine, antihistamines, essential fatty acids, Apoquel, Cytopoint, and antibiotics or antifungals when needed. Corticosteroids and cyclosporine can be used as treatment of pruritus by decreasing inflammation and reducing the inflammatory response of the immune system. Antihistamines antagonize allergic inflammation by interfering with effector reactions after histamine release and may prevent mast cell degranulation. Histamines are one of the mediators of pruritus and cutaneous inflammation and therefore antihistamines can be used in combination

with drugs to increase their efficacy. Essential fatty acids can be used in combination with antihistamines and corticosteroids as an additional anti-inflammatory and to restore the skin barrier (9, 15). Antibiotics should be implemented when a bacterial folliculitis or bacterial overgrowth of the skin is indicated. Antifungals should be used when *Malassezia* is found on cytology.

Oclacitinib (Apoquel) can be used for symptomatic treatment of CAD. It is a Janus kinase inhibitor that acts to inhibit pruritus and the inflammatory pathway. Janus kinase enzymes allow cytokines to transmit signals to the nucleus of cells to further activate an allergic response. The T-helper 2 cytokines include IL-4,IL-5, IL-10, IL-13, and IL-31 and T-helper 1 cytokines include IFN-y. These cytokines are dysregulated in dogs with pruritus caused by allergies. Apoquel functions by inhibiting JAK1, JAK2, JAK3 receptors, primarily JAK1 and JAK3, and the function of IL-2, IL-4, IL-6, IL-13, and IL-31 allowing for decreased cell signaling which would otherwise ignite the inflammatory and itch pathways. Oclacitinib can be used to treat acute or chronic cases of CAD but monitoring of the patient must be done as side effects can include exacerbation of pre-existing neoplastic disease and secondary ear and skin infections. It can be used long term or in cases with acute flare ups as it has a good safety profile (15,2,19).

Cytopoint is an injectable monoclonal antibody therapy that neutralizes IL-31, a main cytokine mediator of pruritus responsible in sending itch signals to the brain. It contains a high specificity for IL-31, and does not alter other immune system functions. It decreases clinical signs and enhances the skin's ability to heal. It has a duration of action for 4-8 weeks. It has a wide margin of safety and is commonly used in combination with other medications such as Apoquel, corticosteroids, cyclosporine and antihistamines with no known adverse reactions (20).

Allergen-Specific Immunotherapy (ASIT) is the cornerstone of the therapy in atopic dermatitis. (9) Allergen-specific immunotherapy is an individualized treatment protocol that uses the allergens identified from IDT or serological testing to create a solution for subcutaneous injections or oral allergy drops. The purpose of ASIT is to alter immune response to the allergens (12,2,3,8,12,15,16). Although ASIT is the cornerstone of therapy, CAD is considered a disease typically requiring combination therapy. ASIT has been shown to improve 50%-100% of canines with clinical signs with the mechanism of action not being fully understood (15). Response to immunotherapy ranges from 3-9 months with required lifelong management of clinical signs in the canine species. Some dogs have had much greater success with required ASIT for 2 years with succession of clinical signs. As ASIT is the only therapy that acts to compact the immune system's response to specific allergens, it is the only therapy to alter the outcome of disease with potential to achieve complete remission of CAD (2,3,8,12,15,16).

Conclusion

In conclusion, Canine Atopic Dermatitis is a common skin disease in canines that is incurable but can be managed with individualized treatment. There are no pathognomonic signs of CAD and therefore a thorough workup is required for diagnosis. Treatment should incorporate a combination of therapies that may need to be modified according to the patients recurring change in severity in order to completely control clinical signs (5, 18,9).

References

1. Chanthick, C., Anaman, S., & Buathet, K. (2008). The prevalence of positive intradermal allergy tests in 114 dogs with atopic dermatitis in the Bangkok metropolis, Thailand. Veterinary Immunology and Immunopathology, 126(3-4), 256-262. doi:10.1016/j.vetimm.2008.07.010

2. Cosgrove, Sallie B., Jody A. Wren, Dawn M. Cleaver, Kelly F. Walsh, Stacey I. Follis, Vickie I. King, Jezaniah-Kira S. Tena, and Michael R. Stegemann. "A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (Apoquel ®) in client-owned dogs with atopic dermatitis." Veterinary Dermatology 24.6 (2013): n. pag. Web.

3. Deboer, D. J. (2017). The future of immunotherapy for canine atopic dermatitis: a review. Veterinary Dermatology, 28(1). doi:10.1111/vde.12416

4. Deboer, D., & Hillier, A. (2001). The ACVD task force on canine atopic dermatitis (XV): fundamental concepts in clinical diagnosis. Veterinary Immunology and Immunopathology, 81(3-4), 271-276. doi:10.1016/s0165-2427(01)00312-9

5. Favrot, C., Steffan, J., Seewald, W., & Picco, F. (2010). A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. Veterinary Dermatology, 21(1), 23-31. doi:10.1111/j.1365-3164.2009.00758.x

6. Halliwell, R., & Deboer, D. (2001). The ACVD task force on canine atopic dermatitis (III): the role of antibodies in canine atopic dermatitis. Veterinary Immunology and Immunopathology, 81(3-4), 159-167. doi:10.1016/s0165-2427(01)00309-9

7. Hensel, Patrick, Domenico Santoro, Claude Favrot, Peter Hill, and Craig Griffin. "Canine atopic dermatitis: detailed guidelines for diagnosis and allergen identification." BMC Veterinary Research 11.1 (2015): n. pag. Web.

8. Hillier, A., & Deboer, D. J. (2001). The ACVD task force on canine atopic dermatitis (XVII): intradermal testing. Veterinary Immunology and Immunopathology, 81(3-4), 289-304. doi:10.1016/s0165-2427(01)00313-0

9. Jasmin, Pierre. Clinical handbook on canine dermatology third edition. Carros: Virbac, 2011. Print.

10. Nuttall, T., Knight, P., Mcaleese, S., Lamb, J., & Hill, P. (2002). T-helper 1, T-helper 2 and immunosuppressive cytokines in canine atopic dermatitis. Veterinary Immunology and Immunopathology, 87(3-4), 379-384. doi:10.1016/s0165-2427(02)00076-4

11. Olivry, T., Mueller, R. S., & Prélaud, P. (2015). Critically appraised topic on adverse food reactions of companion animals (1): duration of elimination diets. BMC Veterinary Research, 11(1). doi:10.1186/s12917-015-0541-3

12. Plant, J. D., & Neradilek, M. B. (2016). Effectiveness of regionally-specific immunotherapy for the management of canine atopic dermatitis. BMC Veterinary Research, 13(1). doi:10.1186/s12917-016-0917-z

13. Pucheu-Haston, Cherie M., Petra Bizikova, Melissa N. C. Eisenschenk, Domenico Santoro, Tim Nuttall, and Rosanna Marsella. "Review: The role of antibodies, autoantigens and food allergens in canine atopic dermatitis." Veterinary Dermatology 26.2 (2015): n. pag. Web.

14. Santoro, D., Marsella, R., Pucheu-Haston, C. M., Eisenschenk, M. N., Nuttall, T., & Bizikova, P. (2015). Review: Pathogenesis of canine atopic dermatitis: skin barrier and host-micro-organism interaction. Veterinary Dermatology, 26(2). doi:10.1111/vde.12197

15. Saridomichelakis, M. N., & Olivry, T. (2016). An update on the treatment of canine atopic dermatitis. The Veterinary Journal, 207, 29-37. doi:10.1016/j.tvjl.2015.09.016

16. Schnabl, B., Bettenay, S. V., Dow, K., & Mueller, R. S. (2006). Results of allergen-specific immunotherapy in 117 dogs with atopic dermatitis. Veterinary Record, 158(3), 81-85. doi:10.1136/vr.158.3.81

17. Shida, M., Kadoya, M., Park, S., Nishifuji, K., Momoi, Y., & Iwasaki, T. (2004). Allergen-specific immunotherapy induces Th1 shift in dogs with atopic dermatitis. Veterinary Immunology and Immunopathology, 102(1-2), 19-31. doi:10.1016/j.vetimm.2004.06.003

18. Wilhem, Sylvia, Marcel Kovalik, and Claude Favrot. "Breed-associated phenotypes in canine atopic dermatitis." Veterinary Dermatology 22.2 (2010): 143-49. Web.

19. Gonzales, A. J., Bowman, J. W., Fici, G. J., Zhang, M., Mann, D. W., Mitton-Fry, M. Oclacitinib (APOQUEL®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. J. vet. Pharmacol. Therap. 37, 317–324.

20. "Cytopoint." Zoetis. Zoetis Services LLC, n.d. Web. 03 Apr. 2017.