Veterinary Dermatology
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Atopic dermatitis in humans and dogs

Martín A. Arcique, Jangi Bajwa

The term atopy was introduced by Coca and Cooke (1) in 1923, to describe a disease in humans with ongoing respiratory signs that affected subjects at a certain time of the year, mainly in spring. The condition, generally called "hay fever," was associated with a reaginic antibody, which was thermostable and could be transferred to normal individuals by the Prausnitz-Kustner test (1). In 1966, Ishizaka et al (2) determined that the reaginic antibody belonged to an undescribed class, which these authors called immunoglobulin E (IgE). By describing the unique immunoglobulin (IgE), further work in development of techniques for identification and research in related diseases was possible (2).

Dr. Arcique is a Specialist in Veterinary Internal Medicine, Clinical Practice limited to Veterinary Dermatology, Consultorio Veterinario de referencia en dermatologia e immunologia, Mexico; Dr. Bajwa is a Board-certified Veterinary Dermatologist, Veterinary Dermatology & Ear Referral Medical Clinic, Surrey, British Columbia.

Address all correspondence to Dr. Jangi Bajwa; e-mail: vet4derm@gmail.com

From an immunological standpoint, atopy in humans is defined by the European Task Force on Atopic Dermatitis as a familial (genetic) tendency to develop a response by cooperative T-lymphocytes (Th2) against common environmental antigens (3). Some of the characteristics encoded by genes in atopic individuals include abnormal expression of the gene encoding interleukin (IL)-4, mutations in the receptor for IL-12, polymorphism in the beta subunit of the high affinity receptor for IgE, and genetic variations in mast cell enzymes.

These examples can help us understand that all mutations described in humans converge at the point of improving polarization towards the presentation of allergens by dendritic cells, polarization towards the Th2 immune response, increase of IgE and its binding to mast cells, and an exaggeration of the inflammatory response mediated by type 1 hypersensitivity.

In 1941, the human allergist, F.W. Whittich (4), diagnosed and treated a dog suffering from hay fever. This was the first documentation of atopy in dogs. Interestingly, the dog exhibited a similarity with the presentation described in humans; however, dermatological signs were not mentioned in this first case. Initial identification and description of canine IgE was reported in 1973, with characteristics similar to those reported in humans (5).

Atopic dermatitis in humans and dogs

Atopic dermatitis (AD), atopic eczema, and eczema are synonyms in human medicine, referring to chronic inflammatory disease of the skin that presents intense itching, with patterns of distribution and configuration of characteristic lesions, which is genetically predisposed, and occurs frequently in families with atopic conditions such as atopic bronchial asthma, rhinitis, and/or atopic conjunctivitis (3).

In humans, the term inhalant allergic dermatitis was commonly used in the 1980s, implying that the path of allergen exposure in atopic patients is respiratory. It was similarly believed that in dogs with respiratory and dermatological manifestations compatible with AD, the same thing happened. However, with the advancement of knowledge in human AD patients with dermatological manifestations, it was found that they present damage to the skin barrier, which allows exogenous proteins to penetrate their epidermis. Evidence in favor of the percutaneous route as an allergen entry route in dogs was demonstrated in the skin of atopic dogs due to a focal proliferation of Langerhans cells, which were coated with IgE antibodies (6). More recently, Marsella et al (7) provided direct evidence that the primary route of allergen exposure in AD beagles is percutaneous. Although oral and respiratory exposures are also important, these routes mainly participate in exacerbating clinical signs (7). Thus, over time, the reason for the primarily dermatological presentation of the atopic dog was better understood, and involvement of the cutaneous immune system was studied.

Immunologic mechanisms in humans with atopic dermatitis

In humans, allergens suspended in air (mites, pollen, animal dander) can deposit on the skin of the AD patient, penetrate the epidermis and trigger the disease through 3 mechanisms:

1. Inherent proteolytic activity.
2. Activation of proteinase activated receptor-2 (PAR-2).
3. Binding to IgE antibodies.

These 3 mechanisms cause cutaneous inflammation in the AD patient (8).

Inherent proteolytic activity. Aerial allergens produced by dust mites and cockroaches have proteolytic activity on the skin that can contribute to delayed cutaneous recovery of AD patients. Dust mite proteins include serine cysteine proteases which alter epithelial junctions, degrade eosinophils, and activate keratinocytes, causing an increased production of IL-6, IL-8 and macrophage colony stimulating factor (GM-CSF). These exogenous proteases alter the natural balance of the skin between endogenous proteases and endogenous protease inhibitors, leading to delayed recovery of the stratum corneum. These effects contribute to alterations in the skin barrier and increased local inflammation. This allows aerial proteins, microbes, and other irritants to have easy access to the epidermis where they can interact with the cutaneous immune system and trigger type I and type II hypersensitivity reactions commonly seen in AD patients.

Activation of PAR-2. Aeroallergens exacerbate AD by direct activation of PAR-2, belonging to a subfamily of G protein-coupled 7-transmembrane domain receptors. PAR-2 receptor is located in epidermal keratinocytes and demyelinated nerve fibers of the dermis. It is crucial for neural transmission of the itch sensation, maintenance of calcium gradient ion, and recovery of the skin barrier, although the exact mechanism is not known.

Binding to IgE antibodies. In the classic IgE-mediated mechanism, allergens bind to specific IgE antibodies. These antibodies are deposited in Langerhans cells and mast cells, where they serve as receptors, and upon being stimulated by binding with allergens, they favor the inflammatory process in skin.

With this brief introduction to a small but important part of the causes for presentations and exacerbation of clinical signs in a human AD patient, it becomes apparent that control of this clinical picture should be multimodal and based on the knowledge of its various mechanisms.

Immunologic mechanisms in canine atopic dermatitis

In canine AD, various mechanisms for activation of clinical signs have also been reported. Recent studies in dogs indicate that activation of toll like receptors and PAR-2 in keratinocytes induces the production of cytokines and chemokines necessary for initiating and maintaining symptoms associated with AD (9). In acute lesions, allergic inflammation triggers the release of cytokines such as IL-4 and IL-13, which induce a T-helper 2 (T2) response (10).

In chronic skin lesions, CD8 cells predominate in the epidermis of an AD dog, while CD4 cells predominate in the dermis. Greater numbers of both cell types are present in lesional and non-lesional atopic epidermis as well as in lesional dermis compared to healthy skin. In contrast, non-lesional dermis exhibit an increase in CD8 cells only.

Interleukin-31 is a recently described cytokine thought to play an important role in AD and pruritus. Interleukin-31 was detected in more than 50% of serum samples from atopic dogs, but not in dogs with other inflammatory skin diseases or in healthy dogs (11).

Development of canine AD is associated with changes in both cutaneous and circulating lymphocyte populations. These lymphocyte responses are characterized by the production of a complex variety of cytokines, including not only T-helper 2 but also T-helper 1, T-helper 17, and regulatory T-cell responses. In addition, microarray gene expression analysis has enabled the identification of several non-cytokine factors that appear to be associated with atopic inflammation. These include the calcium-binding protein S100A8, serum amyloid A, and various protease inhibitors, as well as genes involved in epidermal barrier formation, innate immunity receptors, cell cycle proteins and apoptosis (12).

Such a variety of immunological mechanisms being at play in canine AD demonstrates the complex nature of the disease from an immunological point of view. Understanding the immunological complexity of the disease is valuable clinically as it helps in planning a multimodal treatment approach for canine AD patients. A single therapeutic strategy is usually inadequate in the long-term; thus the treatment goals should include long-term modification of the patient's immune response while minimizing therapy related long-term adverse effects.

Diagnosis of AD and allergen identification in humans and dogs

Diagnosis of AD in humans is clinical, since there is currently no test that can diagnose AD. There are standardized criteria based on clinical signs that an atopic patient may manifest; the major and minor criteria described by Hanifin and Rajka are the most utilized (13).

As in humans, the diagnosis of canine AD is also clinical, based on age of onset, breed, and clinical signs. No single test exists that can differentiate the atopic dog from a non-atopic dog. A sub-group of the International Committee for Allergic Diseases in Animals (ICADA) has developed a set of practical guidelines that can be used to assist in the diagnosis of canine AD. These guidelines include ruling out other skin conditions with clinical signs that can resemble or overlap with canine AD, detailed interpretation of the historical and clinical features of the condition. A new tool to assist with interpretation of these findings is the application of clinical criteria known as Favrot's criteria (14). It must be remembered that Favrot's criteria are not diagnostic tests, rather they are a tool that helps assess possible likelihood of AD in a patient, while taking into account other parameters.

Intra-dermal allergy testing and serum allergy testing are the 2 primary methods used for identification of offending environmental allergens. In humans, knowledge of the age of onset of AD is considered quite important, with food allergens inducing flares in some infants with moderate-to-severe AD, whereas environmental allergens such as house dust mite, pollen or animal fur seem to be more relevant triggers in older children and adults. The spectrum of relevant allergens may change with the course of disease. Clinical relevance of suspected offending allergens can be ascertained by the atopy patch test or allergen exposure in an environmental challenge chamber (a sealed chamber of aeroallergens). For suspected food allergy the current guidelines propose that the suspected food be administered in a blinded provocation test (3,15).

In dogs, it is not possible to distinguish clinical signs of atopic dermatitis caused by environmental allergens from those caused by food allergy. Elimination diet followed by a provocation challenge with the original diet should be performed in any dog with a suspicion of AD. Food allergies are considered more likely based on the presence of perennial pruritus, particularly in patients with a long history of pruritus and/or gastrointestinal signs. A dietary elimination length of 6 to 8 weeks is recommended, as 90% of dogs with food allergy show some improvement during this time period. Intra-dermal testing (IDT) to identify offending environmental allergens is considered the preferred diagnostic method among veterinary dermatologists (14). It is the only technique that can evaluate mast cell degranulation through binding of the specific allergen IgE to mast cells. Appropriate selection of allergens to test is fundamental in obtaining reliable IDT results. It is important to test for and identify the allergens present in the patient's environment.

Allergen-specific immunotherapy in humans and dogs

Allergen-specific immunotherapy (ASIT) has been used to treat allergic diseases in clinical practice for more than a hundred years, since Leonard Noon reported the effect of prophylactic inoculation of grass pollen in hay fever patients in 1911 (16). Administration of ASIT in human and canine AD patients can reduce symptoms and medication scores, alter the natural course of allergic diseases, prevent disease progression, and can help prevent new allergen sensitization (16). Allergen-specific immunotherapy is the only treatment that can reverse the immune response dominated by Th2 lymphocytes in atopic people exposed to aeroallergens. The 2 main routes for administering ASIT with scientific evidence of its effectiveness are subcutaneous and sublingual. While multimodal therapy is desirable in all canine AD patients due to the complicated immunological basis of the disease, modification of the patient's altered immune response by utilizing ASIT is encouraged in order to achieve long-term success, wherever available.

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