Hypersensitivity in veterinary medicine has been recently redefined as “Objectively reproducible clinical signs initiated by exposure to a defined stimulus at a dose tolerated by normal dogs” [1]. A number of different types exist, broadly mediated by antibody or immunocompetent lymphoid cells. However this represents an oversimplification, and, as exemplified especially by atopic dermatitis (AD), a complex interplay between various arms of the innate and acquired immune systems is involved.

**SUMMARY**

Hypersensitivity in veterinary medicine has been recently redefined as “Objectively reproducible clinical signs initiated by exposure to a defined stimulus at a dose tolerated by normal dogs” [1]. A number of different types exist, broadly mediated by antibody or immunocompetent lymphoid cells. However this represents an oversimplification, and, as exemplified especially by atopic dermatitis (AD), a complex interplay between various arms of the innate and acquired immune systems is involved.

---

**Atopic dermatitis**

The currently accepted definition of canine atopic dermatitis (AD) is: “A genetically predisposed inflammatory and pruritic skin disease with characteristic clinical features associated with IgE antibodies most commonly directed against environmental allergens” [1]. There exists also a subset of canine AD in which IgE antibodies are not detectable. This is termed “atopic-like” dermatitis, and appears to be the equivalent of intrinsic AD in man.

The definition of classical canine AD implies a pivotal role for IgE in the pathogenesis which may well be the case. However in fact the pathogenesis of AD is exceedingly complex, and can be categorised under three headings, viz (i) defects in innate immunity, (ii) defects in barrier function, and (iii) defects in acquired immunity.

(i) **Defects in innate immunity**

The innate immune system is phylogenetically the oldest, and provides the first line of defence against invading microorganisms. In man, 80-100% of nonlesional skin of AD patients is colonised with *Staph aureus* as compared with 5-30% of normals. This, and many of the other abnormalities that accompany AD, are attributable to defects in the innate immune system, which has been extensively studied in man, and which has several components. There have been few studies in veterinary medicine, but the similarities in the disease between man and dog are such that similar abnormalities are likely. The description that follows draws heavily on studies undertaken in man [2], with veterinary studies specifically referred to when available.

(a). Pattern recognition receptors: These receptors recognize pathogens in the context of broad molecular patterns termed “pathogen-associated molecular patterns” (or PAMPS). Best characterised are the Toll-like receptors (TLRs). They are expressed by antigen-presenting cells, mast cells, neutrophils and keratinocytes. One of these, TLR2, has been shown to be deficient in some patients with AD thus rendering the skin more susceptible to infection.

(b). Neutrophils: Histopathology of both human and canine AD patients – even in the face of significant infection – are notable for the paucity of neutrophils. A number of studies in man have shown that upregulation of the leucocyte adhesion molecule CD11b is markedly decreased in human patients with AD as compared to normal individuals.

(c). Antimicrobial peptides (AMPs): These come from a number of sources, including keratinocytes, neutrophils, sebocytes and the cells of sweat gland ducts. They are generally present at low or undetectable levels, and at markedly increased levels in the...
face of injury. They have broad antimicrobial activity. A number have been shown to be deficient in human patients with AD, including LL-37. Vitamin D enhances LL-37 activity, and thus vitamin D, and particularly D3, may offer potential in treating infections. Canine studies on AMPs, however, have so far shown equivocal results [3].

Defects in barrier function
That barrier function is abnormal in both human and canine AD is well known. Barrier function is at two levels: (i) at the level of the Stratum corneum, composed of terminally differentiated corneocytes surrounded by a matrix of specialised lipids, and (ii) the tight junctions of the Stratum granulosum. In man, a mutation of filaggrin has been shown to be highly associated with AD, but is not present in all cases, and so other abnormalities must contribute [4]. In the dog, studies regarding filaggrin has been shown to be highly associated with AD, but it has been shown that the skin of dogs with AD contain lipids in globules, rather than dispersed to fill in all the intercellular spaces [5,6]. In man, abnormalities of the tight junctions have also been shown and are associated with reduction of claudin-1 in patients with AD [7].

Abnormalities in acquired immunity
Histopathology of the lesions
A study of the histopathology and immunohistochemistry of infiltrating cells gives valuable insights into disease pathogenesis. This has been studied in clinical cases, and also in atopy patch tests, were an antigen (usually house dust mite) is applied to the skin under occlusion. Biopsies of cases of canine AD, show evidence of epidermal Langerhans’ cell hyperplasia, and these often appear in clusters [8]. Armed with IgE antibody, these play a pivotal role in allergen capture and processing. Also noted are increased numbers of dermal dendritic cells that have similar functions [8,9]. Mast cell hyperplasia is frequently noted on histopathology reports, but careful studies have failed to demonstrate significant differences in the mast cell density in the dermis of atopic and normal dogs, [10]. Lymphocytes are frequent in the cellular infiltrate, with the vast majority being T cells, with only few B cells [9]. Both CD4+ and CD8+ cells are found in increased numbers, with a major increase in CD8+ cells in the epidermis. Finally, neutrophils and eosinophils are certainly seen in biopsies of affected skin, but in neither case are they a dominant feature.

Histopathological features of feline AD are highly variable from case to case, although to an extent this may be reflective of a lack of defined criteria for the diagnosis [11]. There is generally an increase in the numbers of mast cells and eosinophils, with the latter being more prominent than in the dog [12]. Increases in CD4+ and CD8+ cells are noted as is an increase in dermal dendritic cells [13, 14].

Th1 vs Th2
It is well established that T cell responses in man and animals fall into one of two patterns – a Th1 response associated with IL-2, IL-12, γ-IFN and IL-18, which is expressed as cell-mediated immunity, and a Th2 response associated with IL-4, IL-5, IL-6 and IL-13 and facilitating antibody production, including IgE. Multiple studies undertaken in dogs and cats, including the high IgE-producing beagle model, have suggested that a Th2 response is associated with the acute phase of AD, whereas a Th1 response is associated with the chronic phase, were secondary infection is superimposed [15, 16, 17, 18, 19, 20]. The cytokines derived respectively from a Th2 and Th1 response promote that response via a positive feedback mechanism. Conversely, they are mutually inhibitory – i.e. γIFN inhibits the Th2 response, which has led to the use of γ-IFN as a treatment for CAD [21]. Similarly, successful immunotherapy in CAD is accompanied by a shift from Th2 to Th1 [22].

Mediators involved
The preformed, mast cell derived mediators are clearly of importance in canine and feline AD. They include histamine, proteases and serotonin, although there is little evidence that the latter is contributory. The limited efficacy of antihistamines as a sole treatment implies that other mediators are likely to have more pronounced pruritogenic and inflammatory effects. The membrane-derived mediators, especially the leukotrienes, and particularly LTB4 are implicated in a range of inflammatory dermatoses including AD and are promising targets for pharmacologic intervention [23]. In addition, the inflammatory cell milieu that characterizes AD offers the potential for the involvement of many other inflammatory mediators that are derived from keratinocytes and other epidermal and dermal sources. The spectrum of inflammatory mediators is thus multiple, which explains why drugs that target single mediators are generally only marginally effective.

Secondary features in the pathogenesis
Both bacterial overgrowth and overt pyoderma are common features of canine AD, although much less so in feline AD. A major reason for this is the enhanced ability of canine staphylococcal species to adhere to corneocytes of atopic dogs. This has been demonstrated by both in vitro and in vivo studies [24, 25]. The fact that IgE antibodies to antigens of the organism can develop makes this an important factor in the disease process [26].

Similarly, malassezia overgrowth is well documented [27], although precise quantitative studies comparing colonisation densities in atopic and normal dogs are lacking. As is the case with staphylococcal infection, an IgE response can compound the disease process [28]. Malassezia overgrowth has also been documented in allergic cats [29].

The likely sequence of events
The complexity of the immunopathogenesis of AD is such that any schematic representation of the chain of events involved must of necessity be speculative. Nonetheless, it is helpful to document the current views of the process – albeit in simplified form (see Fig 1).

1. Impaired barrier function facilitates the percutaneous absorption of allergen.
2. Allergen is captured by Langerhans’ cells armed with IgE antibody.
3. In the resultant immune response to the allergen, the genetic features of the atopic trait favour the development of an IgE response (Th2) – which is largely elaborated in the local lymph node.
4. Exposure of mast cells armed with IgE antibody initiates release of preformed and newly generated mediators, which aids the influx of inflammatory cells.
5. In turn, these release other pro-inflammatory mediators.
6. Particularly in the chronic phase, a concomitant Th1 response occurs with $\gamma$IFN prominent.
7. Secondary infection compounds the problem, leading to further Th1 responses.
8. A failure of immune regulation allows the continuation of the immune responses and resultant inflammation.

The pathogenesis of food hypersensitivity

Conventionally, adverse reactions to foods are divided into food hypersensitivity, where immune mechanisms are involved, and food intolerance where pharmacological factors are responsible (e.g. histamine and histamine-releasing factors). There is no data on the relative incidence of the two types. This discussion will dwell solely on the former.

Compared to the situation in man, there is a paucity of data on the pathogenesis of food hypersensitivity, and the veterinary literature contains a plethora of dogma based upon unreliable information. The first point to emphasize is that food hypersensitivity is not one disease – rather it is a spectrum of diseases that vary in their immunological mechanisms and in the organ that is affected (e.g. skin vs gastrointestinal tract).

That IgE-mediated food hypersensitivity exists in the dog is clear from (i) studies on experimental induction [30], (ii) on thorough immunological investigations of spontaneous cases [31], and (iii) on the characterization of an in-bred colony of beagle/Maltese crosses [32]. However it should be emphasized that although in the latter case IgE to incriminated allergens is readily demonstrable, dynamic changes in allergen-specific levels do not reliably follow withdrawal of the incriminated food and challenge – for which there are a number of possible explanations.

However IgE-mediated food hypersensitivity is likely to be involved only in cases that relapse within 24-48 hrs of challenge – which accounts for only a small proportion of the confirmed cases [33].

If one extrapolates from the situation in man, the majority of cases are likely to result from a combination of IgE-mediated reactions, with cell-mediated hypersensitivity and/or IgG antibody. In people with atopic dermatitis where food hypersensitivity is involved, the best diagnostic results are achieved when IgE is measured and patch testing with food antigens is also undertaken, and this is probably reflective of the dual nature of the immunopathogenesis [34].
The relevance of IgG antibody measurements, and hence of the involvement of this isotype in the pathogenesis is controversial. In a study which measured food-specific IgE and IgG in 22 cases of confirmed adverse food reactions, the difference in antibody levels between normal dogs and those with confirmed adverse food reactions was actually greater in the case of IgG than it was for IgE [35]. However, association is not causation. Similarly, in a recent study of irritable bowel syndrome in man, a placebo-controlled diet trial was undertaken based upon the measurement of food antigen-specific IgG. Those patients who were fed a diet that excluded antigens to which an IgG response was shown exhibited significantly superior outcomes than did those fed a diet including such antigens [36]. Again, this does not, of course, necessarily indicate that the IgG was implicated in the disease process – it could well be an epiphenomenon.

In summary, there is good data on the role of IgE in a small proportion of cases. Whether cell-mediated hypersensitivity or IgG antibody is responsible for the majority of cases, perhaps in conjunction with IgE, must await results of further studies.

The pathogenesis of flea allergy dermatitis

The immunopathogenesis of flea allergy dermatitis (FAD) has been the subject of much study over the past 3 decades. Initially, it was assumed that the work done on guinea pigs in the 1960s was directly applicable to the dog and cat, but it was established that this was not the case.

The flea allergen

It is generally held that salivary allergens injected when the flea sucks blood are responsible for the immune response. Early work suggested that the allergen was a hapten which became a complete allergen on union with dermal collagen [37], but more recent studies have shown that there are a number of protein allergens involved [38], and the major allergen which is recognised by some 90% of flea allergic dogs has been cloned and produced in recombinant form [39].
The immunopathogenesis of allergic skin diseases in dogs and cats - R.E.W. Halliwell

Immunological mechanisms involved

Observation of the sites of flea feeding in allergic dogs show that in the majority of dogs, an immediate reaction occurs which is papular or urticarial. This may wane to be replaced by a papular eruption which is maintained for up to 4-5 days. Histopathology of these reaction sites at varying times has revealed features of both immediate (IgE-mediated) hypersensitivity evidenced by oedema between the collagen bundles, and an egress of eosinophils from dermal blood vessels and of delayed (cell-mediated) hypersensitivity with a perivascular predominantly mononuclear cell infiltrate (Fig 2 a, b, c) [40]. In some 10-20% of patients, delayed reactions only are noted, and assays for flea allergen-specific IgE will be negative. If biopsies are taken between 4 and 18hrs after a flea bite, special processing and staining will reveal an influx of basophils which may account for up to 20% of the cellular infiltrate (Fig 2 d) [41]. The pathogenesis is thus quite complex, and it is also possible that IgG antibodies may be involved, as they are readily detectable in the sera of patients with FAD [42]. Interestingly, animals who are continually exposed and who suffer no obvious clinical signs have an absence of IgE antibodies, and low or undetectable levels of IgG [42, 43].

The development of hypersensitivity

Studies on the experimental induction of FAD have shown that all dogs can become sensitized, although atopic dogs are predisposed [44]. Early antigenic exposure and continual exposure tend to be protective, whereas intermittent exposure favours the development of hypersensitivity. Once hypersensitive, dogs often maintain this state indefinitely, although with time the incidence of hypersensitivity tends to decline [38, 43]. It does not appear, however, that the same features are applicable to feline FAD [45].

The pathogenesis of allergic contact dermatitis

It is generally believed that uncommon condition results from a delayed, cell-mediated hypersensitivity [46, 47]. However the characteristic epidermal spongiosis that is seen in man is infrequently observed in clinical cases and in biopsies of positive patch test sites, and whilst the dermal infiltrate does contain mononuclear cells, a significant neutrophilic influx suggests that the immunopathogenesis, and hence the cytokine milieu may differ from that in man (Fig 3) [48]. The infrequency with which this condition is observed in veterinary medicine makes in depth investigations difficult.

Conclusions

The current state of knowledge of the pathogenesis of allergic skin diseases in the dog and cat has been reviewed. Although much progress has been made over the past three decades, much remains to be done. The realization that canine AD in particular is a good model for the study of human AD, will likely facilitate further studies in this area.

References


