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Characterization of Inflammatory Cell Infiltration in Feline Allergic Skin Disease

K. Taglinger[*], M. J. Day[†] and A. P. Foster[‡]

[*] *Buchenstr. 12, A-4861 Schoerfling, Austria,* [†] *School of Clinical Veterinary Science, University of Bristol, Langford House, Langford, Bristol BS40 5DU, and* [‡] *Veterinary Laboratories Agency, Shrewsbury, Kendal Road, Harlescott, Shrewsbury SY1 4HD, UK*

Summary

Sixteen cats with allergic dermatitis and six control cats with no skin disease were examined. Lymphoid and histiocytic cells in skin sections were examined immunohistochemically and mast cells were identified by toluidine blue staining. The 16 allergic cats showed one or more of several features (alopecia, eosinophilic plaques or granulomas, papulocrusting lesions), and histopathological findings were diverse. In control cats there were no cells that expressed IgM or MAC387, a few that were immunolabelled for IgG, IgA or CD3, and moderate numbers of mast cells. In allergic cats, positively labelled inflammatory cells were generally more numerous in lesional than in non-lesional skin sections, and were particularly associated with the superficial dermis and perifollicular areas. There were low numbers of plasma cells expressing cytoplasmic immunoglobulin; moderate numbers of MHC II-, MAC387- and CD3-positive cells; and moderate to numerous mast cells. MHC class II expression was associated with inflammatory cells morphologically consistent with dermal dendritic cells and macrophages, and epidermal Langerhans cells. Dendritic cells expressing MHC class II were usually associated with an infiltrate of CD3 lymphocytes, suggesting that these cells participate in maintenance of the local immune response by presenting antigen to T lymphocytes. These findings confirm that feline allergic skin disease is characterized by infiltration of activated antigen-presenting cells and T lymphocytes in addition to increased numbers of dermal mast cells. This pattern mimics the dermal inflammation that occurs in the chronic phase of both canine and human atopic dermatitis.

Keywords: allergy; cat; eosinophil; skin

Introduction

Atopic dermatitis, a chronic, inflammatory, pruritic skin disease affects both human beings and companion animals, especially dogs (Leung, 1995; Scott *et al.*, 2001). Many clinical and histopathological features of atopic dermatitis in dogs are similar to those found in man (Soter, 1989; Leung, 2000; Olivry and Hill, 2001; Marsella and Olivry, 2003). In cats, recurrent pruritic skin disease showing certain clinical similarities to human atopic dermatitis has been recognized for many years. As a consequence of pruritus, self-induced alopecia with or without primary lesions is a frequent presentation of feline atopic dermatitis. The feline disease is particularly diverse, however, and may present in various clinical forms, including symmetrical alopecia, "miliary" papulo-crusting dermatitis and eosinophilic granuloma complex lesions, which are distinct from the clinical features of atopic human patients and dogs (Marsella and Olivry, 2003; Foster and Roosje, 2005). This diversity of clinical presentation means that it is difficult to make an accurate clinical diagnosis of atopic dermatitis in cats. This problem is further complicated by the fact that the same cutaneous reaction patterns may accompany flea- or food-hypersensitivity. Indeed, cats may have environmental, flea and food allergies concurrently (Halliwell, 1997). It is also widely accepted that skin biopsy samples from cats with allergic skin disease are not diagnostic for the type of hypersensitivity, and that the pathological changes observed

Correspondence to: A.P. Foster (e-mail: a.foster@vla.defra.gsi.gov.uk).

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may vary depending on the clinical lesions sampled (Yager and Wilcock, 1994; Scott *et al.*, 2001; Gross *et al.*, 2005).

Skin biopsy samples from lesional skin of human patients with atopic dermatitis have increased numbers of Langerhans cells (LCs) and dermal dendritic cells. These cells act as potent antigen-capturing and -presenting cells and play a major role in the pathogenesis of the disease (Leung *et al.*, 1987; Allam and Novak, 2006). Moreover, reports implicating the importance of dendritic cells in canine atopy have also been published (Day, 1996; Olivry *et al.*, 1997). The quantitative distribution of epidermal LCs has been evaluated in normal cats (Saint-Andre Marchal *et al.*, 1997b) and these cells have been phenotypically characterized as expressing CD18, MHC class II, CD1a and CD4 (Saint-Andre Marchal *et al.*, 1997a). Roosje *et al.* (1997) reported significantly greater numbers of CD1a-positive and MHC class II-positive dendritic cells in lesional skin from atopic cats than in the skin of healthy control cats; however, the authors did not describe the clinical features or the types of lesion sampled. In cats with recurrent "miliary" papulo-crusting dermatitis a significant total increase in dermal T-cell numbers was reported (Roosje *et al.*, 1998). Subsequently, significantly more IL-4-positive cells were found in lesional and non-lesional skin from allergic cats than in healthy controls (Roosje *et al.*, 2002). These results are consistent with studies of immune-cell infiltrates in human and canine atopic skin (Van der Heijden *et al.*, 1991; Sinke *et al.*, 1997).

Mast cell numbers in normal feline skin may vary depending on location (Foster, 1994; Beadleston *et al.*, 1997). Toluidine blue staining revealed no significant differences in median mast cell density between skin from control dogs and skin (lesional or non-lesional) from atopic dogs. However, a double-enzyme labelling technique (labelling of the mast cell-specific proteases tryptase and chymase) demonstrated that the median mast cell density was significantly lower in lesional and non-lesional skin from atopic dogs than in the skin of controls (Welle *et al.*, 1999). Similarly, differences in mast cell numbers were found in feline allergic skin, depending on the staining method used (Roosje *et al.*, 2004a), but the biopsy site did not appear to affect the number of mast cells (and eosinophils). This was in contrast to earlier reports of these parameters in normal feline skin (Foster, 1994; Beadleston *et al.*, 1997).

The aim of the present study was to throw further light on the nature and distribution of the immune cell populations that infiltrate the skin of cats suffering from allergic dermatitis. To this end, the distribution of T lymphocytes, IgG-, IgA- and IgM-producing plasma cells, macrophages/monocytes, mast cells and MHC class II antigen was analysed in skin biopsy samples from normal cats and cats with allergic skin disease.

Materials and Methods

Biopsy Material From Normal Control Cats

Skin tissue samples from six cats used as normal controls in a previous study (Foster, 1994) were examined. These samples, obtained from the lateral thorax, were formalin-fixed and paraffin wax-embedded. The cats from which they were obtained had a variety of diseases that did not affect the skin, either macroscopically or histopathologically; the clinical details are described in Table 1. The mean age of the control cats was 5.5 years (range 2–14 years).

Biopsy Material From Cats with Allergic Skin Disease

Skin samples were taken from 16 cats presented at the School of Clinical Veterinary Science, University of Bristol. All of the following procedures formed part of the routine diagnostic investigation of suspected allergic skin disease. This group consisted of 14 domestic shorthairs, one Bengal and one Ocicat, and there were seven neutered males, eight neutered females and one entire female. The mean age was 4 years (range 1–8 years). Details of these animals, together with the location of the skin lesions and the type of the lesions sampled, are given in Table 2. Cats were included in the study if they showed chronic or recurrent pruritus or dermatitis, or both. Pruritus due to ectoparasite infestation was ruled out by investigation of the coat, hair plucks and skin scrapings, in addition to appropriate ectoparasiticidal treatment. Dermatophyte infection was excluded by negative fungal culture. To rule out dietary hypersensitivity as a cause of pruritus, owners were requested to feed their cats a home-prepared diet for 6–8 weeks. Unfortunately, due to lack of compliance, only four cats finished this dietary trial, but none of these showed any clinical improvement. For the other 12 cats, an elimination diet was recommended at the time of consultation, but as owner and animal

Table 1
Six control (C) cats

Cat	*Age (years)*	*Sex*	*Breed*	*Disease status*
1	3	FN	Siamese	Lymphadenopathy
2	7	FN	Burmese	Hyperadrenocorticism
3	1.5	FE	DSH	FIV-positive
4	2	MN	DSH	FIV-positive+*Chlamydia*
5	6	MN	DSH	Hyperadrenocorticism
6	14	MN	DSH	Hyperthyroidism

DSH, domestic short hair; MN, neutered male; FN, neutered female; FE, entire female; FIV, feline immunodeficiency virus.