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Eosinophilic diseases of dogs

Caroline Mansfield BSc, BVMS, MACVSc, MVM, DipECVIM-CA
Department of Veterinary Clinical Sciences, Murdoch University, South Street, Murdoch 6150, Western Australia, Australia

Eosinophils are important components of the immune system, and are often involved in hypersensitivity disorders and parasitic infestation.[1] Eosinophilia is defined as an increase in the total eosinophil count in blood or tissue. Although the upper reference range for blood concentration of eosinophils in dogs is 0.75 x 10^9/L, significant circulating eosinophilia is considered to be present when the count exceeds 2.2-2.5 x 10^9/L.[2] This most commonly occurs as a leukaemoid response, or when eosinophil counts increase to a high levels in response to an underlying cause (see Table).[2] The most common underlying causes for an eosinophilic leukaemoid response in people are atopy and helminth infestation.[1] Dogs with *Angiostrongylus vasorum* (lungworm) or *Dirofilaria immitis* (heartworm) have been shown to have significant eosinophilia in a significant percentage of infected dogs.[2,3] However, in one survey performed by our centre of Perth metropolitan Rottweiler breeding kennels, it does not appear that the presence of low numbers of intestinal parasites predispose to higher eosinophil counts. A few dogs had intestinal parasites present (one or more of *Trichuris, Isospora, Giardia* and *Sarcocystis*), but none were considered clinically affected.

Common causes

Dogs are most commonly identified with eosinophilia secondary to dermatological diseases (such as sarcoptic mange), inflammatory bowel disease and pulmonary diseases, all of which may have a hypersensitivity component.[4-7] Interestingly, atopic dermatitis does not seem to cause a significant eosinophilia in dogs.[6,8] Paraneoplastic eosinophilia is commonly reported, as is eosinophilic CNS disease.[2,6,9-12] Dogs may also have significant organ infiltration with eosinophils (such as with eosinophilic bronchopneumopathy), but no circulating eosinophilia.[5] This may be due to the short circulating half-life of these cells.[7] Diurnal variation may also play a role, as circulating eosinophil numbers in healthy dogs have been shown to peak in late evening, and be at their lowest at noon.[13]

Breed prevalence

In both our local survey and in a large published analysis of eosinophilia, Rottweilers have been shown to be predisposed to eosinophilic disease.[6] A number of the Rottweilers that we surveyed had increased eosinophilic counts, but no identifiable parasitic, allergic or neoplastic disease, and there was no age or sex predisposition. However, certain kennels did seem to have increased incidence of eosinophilia, suggesting there may be a heritable component. German shepherds also appear to have an increased incidence of exaggerated eosinophil responses to normal stimuli.[6] Cavalier King Charles spaniels, Alaskan malamutes and Siberian huskies appear predisposed to eosinophilic stomatitis, intestinal and airway disease.[5,14-16]

Rottweilers are also over-represented in the published reports of hypereosinophilic syndrome (HES).[2,17] HES is a rare syndrome that has been described in people, cats and less commonly in dogs.[1,2,17-19] The criteria for the definition of idiopathic HES used in people are an eosinophil count persistently greater than 1.5x10^9/L, damage to end-organs such as the heart and lungs, no ascertainable cause for the eosinophilia and no evidence of clonality.[1] The prognosis for this condition is considered universally poor. However, there have been individual reports of good survival times with spontaneous resolution reported in one dog and resolution with hydroxyurea and prednisolone treatment in another.[17,18] Recently we have seen two related dogs (Rottweilers) that fulfilled the criteria for HES, but recovered with no, or very short-term, treatment. This suggests that there may be a similar disease to the 'benign HES' identified in people. Differentiation of HES from eosinophilic leukaemia (EL) is difficult, but generally demonstration of >5% blast cells in the bone marrow is necessary for diagnosis of EL.[1]

Mechanism

The exact mechanisms for eosinophilic production are unknown, but interleukin-5 (IL-5), IL-3 and GM-CSF all inhibit eosinophil apoptosis and have specific receptors on eosinophils and basophils.[1,2] Production of IL-5 by neoplastic lymphocytes has been implicated as one potential cause of paraneoplastic eosinophilia. Basophils are also primed by IL-3 and therefore basophilia often accompanies eosinophilia.[2] Eosinophilic bronchopneumopathy has been identified as being mediated by $CD4^+$ lymphocytes with a concurrent decrease in $CD8^+$ lymphocytes, suggesting a T helper (Th)-2 mediated response.[5] Further investigations of the molecular signalling mechanisms in affected animals is warranted, as this may allow for establishing simple tests to allow differentiation between allergic, infiltrative eosinophilic and neoplastic disease in dogs of all breeds.

Whatever the mechanism of initial production by the bone marrow, eosinophils are then attracted into tissues by local chemo-attractant molecules.[1] This is generally a Th-2 mediated response, and may be appropriate in cases of parasitism, as the cytotoxic components of eosinophils may destroy the parasite. Eosinophils contain many toxic inflammatory mediators.[1] Eosinophil cationic protein in particular appears to promote the activity of other toxic mediators in target tissue.[20] In addition, eosinophils produce compounds capable of increasing vascular permeability, stimulating mucus secretion and smooth muscle contraction.[17] If eosinophilia is inappropriately stimulated (i.e. in the absence of helminths), the accumulation of eosinophils has the potential to cause significant damage to the target organs.

References

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Parasitic	Ancylostomiasis Dirofilariasis Dipetalonemaiasis Ctenophalidiasis Angiostrongylosis Ascariasis Paragonimiasis Sarcoptes scabei Pneumomonyssoides caninum (?)
Hypersensitivity:	Flea allergy dermatitis Food allergy
Eosinophilic infiltrative disorders:	Eosinophilic bronchopneumopathy Eosinophilic gastroenteritis/colitis Hypereosinophilic syndrome
Infectious diseases	Suppurative processes (chronic upper respiratory disease, pneumonia, metritis, mastitis, lower urinary tract infection)
Neoplasia	Mast cell tumour Lymphomas Myeloproliferative disorders Solid tumours (myxosarcoma, basal cell tumour, squamous cell carcinoma, salivary gland adenocarcinoma, sweat gland adenocarcinoma) Haemangiosarcoma
Miscellaneous	Soft tissue trauma Cardiomyopathy Renal failure (?) Oestrus (?) Acute gastroenteritis (?) Pemphigus foliaceous (?) Snakebite (?) Hypoadrenocorticism (?) Immune mediated haemolytic anaemia (?) Hepatopathy (?) Chronic renal failure (?) Arthrosis (?) Hypocalcaemia (?) Pulmonary oedema (?) Constipation (?) Diabetes mellitus (?) Hypoparathyroidism (?) Juvenile nephropathy (?) Hydrothorax (?) Panosteitis (?)

Table: Potential causes of eosinophilia in dogs