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ANAL FURUNCULOSIS: PROBLEM SOLVED?

Michael J. Day
School of Veterinary Sciences
University of Bristol, Langford, United Kingdom

INTRODUCTION AND PATHOGENESIS

Anal furunculosis (AF; sometimes incorrectly termed ‘perianal fistula’) presents as severe, chronic ulceration and sinus tract formation of the perianal skin of the dog. There is a unique breed predisposition for the German shepherd dog (GSD) and in most studies up to 90% of cases occur in dogs of this breed. The disease occurs in GSDs throughout the world.

Studies of the pathogenesis of AF have progressed through numerous phases over the years. A range of predisposing or trigger factors has been suggested, including low carriage of the tail base with poor ventilation of the perianal skin, underlying hypothyroidism, inflammation of perianal apocrine gland tissue and anal sacculitis. The latter factor has been widely debated, but recent studies have shown that the anal sacs of dogs with AF are most often either histologically normal, or focally affected by extension of a more superficial perianal inflammatory response into the sac tissue.

Affected GSDs may also have concurrent cutaneous furunculosis (or deep pyoderma), particularly of skin pressure points and caused by staphylococcal infection of hair follicles. Concurrent inflammatory bowel disease (IBD; specifically lymphoplasmacytic colitis) or ocular pannus is also sometimes documented in GSDs with AF.

The strong breed association, and the linkage of these multiple inflammatory/infectious disorders, has also given rise to the suggestion that there must be a genetic basis for AF in GSDs, and that this might involve defective mucocutaneous immunity. Certainly, immunological investigations of GSDs with deep pyoderma or IBD would tend to support this hypothesis. GSDs with deep pyoderma make strong serum IgG and IgA responses to *Staphylococcus*, have altered balance of blood lymphocytes by immunophenotype analysis, and have a relative deficiency of T lymphocyte infiltration into the dermal lesions in comparison with similarly affected dogs of other breed. Current studies of idiopathic IBD or antibiotic responsive diarrhoea (ARD) have focussed on a potential defect in mucosal production of IgA as permitting altered gut microbial colonisation and induction of enteropathy.
In the early 1990s, this author published several studies into the pathogenesis of this disease\textsuperscript{1,2}. The first of these was a retrospective study of the histopathology of surgically resected perianal tissue from 305 dogs with AF. In this population 84\% of patients were GSDs and these dogs had a mean overall age of 5.67 ± 2.43 years, but there was no clear gender predisposition. The study aimed to systematically evaluate the nature and intensity of the inflammatory response in defined areas of the perianal skin of these dogs. This study permitted the development of a proposed model of the pathogenesis of this disorder. The histopathological changes suggested that the disease starts as a bacterial infection (deep pyoderma) of the perianal hair follicles, with follicular rupture (furunculosis) and the extension of this inflammation into the deep perianal tissue as sinus tract formation. The rupture of perianal hair follicles, with release of keratin and bacterial superantigens into the perianal dermal microenvironment provides further stimulation of the host immune response. This results in massive infiltration of lymphocytes and plasma cells into the perianal skin and lining the deep sinus tracts.

The involvement of staphylococcal infection as an initiating and perpetuating factor in the disease was further suggested by serological studies confirming high serum IgG and IgA antibody responses to \textit{Staphylococcus}. The second phase of this investigation was an immunohistochemical study of selected of the perianal lesions previously reported. This confirmed that the infiltrating lymphoid population chiefly comprised T lymphocytes with plasma cells of the IgG and IgA class dominating.

These investigations were the first to suggest that canine AF might have an 'immune-mediated' pathogenesis. The disease might be initiated by bacterial infection that subsequently triggered an over-abundant lymphoplasmacytic immune response that perpetuated the tissue damage. There were some similarities in the histopathological and immunohistochemical presentation to the human idiopathic inflammatory enteropathy Crohn's disease (CD). CD patients often have similar perianal sinus tract/fistula formation to dogs with anal furunculosis. Recently, an inbred strain of laboratory mouse has been reported in which a clinical disease not dissimilar to AF/Crohn's perianal fistulation occurs.

These studies were extended by work showing the activation of cytokine genes within perianal lesions of dogs with AF. Elevation of mRNA encoding the cytokines IL-2, IFN-\textgamma, IL-1\beta, IL-6, TNF-\alpha, IL-8, IL-10 and TGF-\beta was reported in tissue from affected dogs and suggested to be consistent with a Th1-dominated immune response. Additionally, there was increased expression of genes encoding the tissue remodelling enzymes matrix metalloproteinase (MMP)-9 and MMP-13 that are likely derived from activated macrophages. The expression and responsiveness of macrophage Toll-like receptors (TLRs) has also been compared between normal dogs and dogs with AF. Blood monocytes from dogs with AF had reduced expression of the gene encoding TNF-\alpha following stimulation \textit{in vitro} with LD-MDP – a known activator of NOD2 (an intracellular TLR or pattern recognition receptor). This was interpreted to suggest NOD2 dysfunction in AF, but the study was very preliminary and the difference was found at the mRNA and not protein level.
TREATMENT

The approach to management of dogs with AF has been even more varied historically than ideas concerning the pathogenesis of the disease. The mainstay of therapy was traditionally surgical, involving complex and extensive removal of affected tissue (including the anal sacs) and reconstruction of the perianal area. The surgery is prolonged and difficult and there remains a risk of post-surgical faecal incontinence. Despite this, the surgical approach can be curative in a high proportion of patients and a recent study confirms the efficacy of surgical excision with concurrent dietary modification.

Modifications of the surgical methodology including diathermy and cryosurgery were performed widely when these methods were first introduced into veterinary surgery. For a time, amputation of the tail was also widely performed in order to provide ventilation to the perianal area.

AF was therefore traditionally considered a surgical rather than medical disease. The role of faecal contaminant bacteria was recognized and covering antimicrobials and dietary modification was generally practised as an adjunct to surgery. The disease was not considered a candidate for immunosuppression due to the potential for bacterial infection of the tissue.

These long-standing tenets of management of this disease were radically reshaped with the introduction of ciclosporin treatment in the late 1990s. The basis for this was the studies described above defining AF as an 'immune-mediated' disease. As the disease was characterized by severe, chronic lymphoplasmacytic infiltration – inhibition of this might alleviate the extent of the tissue pathology.

Ciclosporin is a potent, and relatively selective, immunosuppressive drug that acts on specific intracellular pathways within T lymphocytes to inhibit their proliferation and cytokine production. Ciclosporin holds promise for the management of a range of companion animal immune-mediated diseases and is licensed for the treatment of canine atopic dermatitis (Atopica®, Novartis). In Australia, the drug also carries a license for the management of canine AF.

The down-side of ciclosporin is the expense of the drug, particularly for large breed dogs such as the GSD. Co-administration of ketoconazole (e.g. ketoconazole 10 mg/kg q24h plus ciclosporin 1 mg/kg q12h for 16 weeks) as an inhibitor of the cytochrome P450 pathway provides greater bioavailability and has been used to allow a reduced dose of ciclosporin to reduce the expense of therapy.

There are now numerous published studies of the application of ciclosporin to the management of canine AF. Most studies report dose rates of around 3 – 7.5mg/kg q12hr given orally (5 mg/kg q12h or q24h po for 4 weeks is often used). The drug does appear to have a dramatic and rapid effect on the severity of the perianal lesions, resulting in ‘medical healing’ of the disease, or shrinkage of the lesions to a size where surgery becomes much less complex. Therapy has been continued for up to 16 weeks. Another protocol is to continue therapy for two weeks after resolution of the lesions, or until there is no further improvement in lesions after a minimum of four weeks therapy. A second course of therapy has been given for recurrent lesions and some
dogs that were not surgical candidates have been maintained on longer term therapy (at around 2.5 – 3mg/kg q12 or q24 hr).

The use of ciclosporin is not always a miracle cure. A number of the published studies have monitored the progress of treated dogs for months to years after initial therapy. Although individual dogs may appear to undergo long-term remission from their disease, in other cases there is relapse or multiple relapse and some dogs do go on to require surgical management. In one study of 22 cases treated with ciclosporin, there was resolution of lesions after 4 weeks of therapy in 10 cases. Ten of the remaining 12 cases underwent surgical excision of remaining affected tissue. In this residual lesional tissue there was reduced expression of the IL-2 gene but no significant reduction of IFN-α mRNA compared with biopsies of lesional tissue taken at initial presentation.

A topical agent related to ciclosporin (0.1% Tacrolimus ointment) has also been applied to effect to the lesions of AF as either sole therapy or in combination with prednisolone and dietary modification.

Because of the expense of ciclosporin, other immunomodulatory agents have been evaluated. Combination azathioprine (50 mg per dog po q24h) and metronidazole (400 mg per dog po q24h) was used in a series of five GSDs with AF for between 5 – 24 weeks to reduce the lesional size before surgical excision. Most dogs showed visible improvement by 4 – 6 weeks after starting therapy, but this approach did not lead to complete resolution of the lesions as described for ciclosporin. Azathioprine (2 mg/kg po q24h to effect, then 2 mg/kg po 48h for 12 weeks, then 1 mg/kg po q48h for up to 12 months) plus prednisolone (2 mg/kg po q24h for 2 weeks then 1 mg/kg po q24h for 2 weeks and then withdraw) was also effective in some of a population of 14 affected dogs studied. In a study of GSDs with concurrent AF and histopathological evidence of colitis, management involved administration of oral prednisone (2 mg/kg po q24h for 2 weeks, then 1 mg/kg po q24h for 4 weeks) with concurrent dietary management (use of an alternative protein and carbohydrate diet). Five of six dogs with mild perianal lesions showed complete resolution of the lesions, but when lesions of all severity (mild to severe) were considered resolution was only observed in 33% of the 27 cases.

IS ANAL FURUNCULOSIS SOLVED?

The answer to this question is no. Although we now have a new treatment modality for this severe disease, it is not always an absolute cure and carries the risk of side effects and disease relapse. We still have many questions to answer about the pathogenesis of the disease, and investigations into these areas may help formulate new treatment options. It is not entirely surprising that a potent immunosuppressive agent will ameliorate the extent of a severe lymphoplasmacytic inflammatory lesion, but the use of ciclosporin does not address the initiating factors for the disease – merely the subsequent immune disturbance.

Of greater importance is the question of the distinct breed predisposition for the GSD. This is one of the strongest breed predispositions in veterinary medicine, for which there must be a genetic component to the pathogenesis. Our recent investigations have shown a marked association between disease and expression of a particular allele of a class II gene of the major histocompatibility complex (MHC). GSDs expressing DLA-DRB1 00101 develop AF with an odd’s
risk of 5.01 and those dogs that are homozygous for this allele have an earlier onset of disease. Particular alleles of the gene encoding the cytokine TNF- are also associated with AF, but this is because their expression is linked to that of DRB1*00101 rather than being independently associated. Current genome wide association studies (GWAS) are providing further insight into the disease pathogenesis. A number of associated genes have been identified, including the CTNND2 locus, which is also linked to human CD.

REFERENCES

