

STATE OF THE ART LECTURE

UPDATE ON INFLAMMATORY BOWEL DISEASE

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INTRODUCTION

Inflammatory bowel disease (IBD) is a collective term describing a group of disorders characterized by persistent or recurrent GI signs, with histological evidence of intestinal inflammation on biopsy material. Variations in the histologic appearance of the inflammation suggest that idiopathic IBD is not a single disease entity, and nomenclature reflects the predominant cell type present. Lymphocytic-plasmacytic enteritis (LPE) is the most common form reported, eosinophilic (gastro-) enteritis (EGE) is less common, and granulomatous enteritis is rare. Histiocytic ulcerative colitis (HUC) is a rare form, most commonly seen in boxer dogs.

It is a controversial, enigmatic, condition and much remains to be understood of its aetiopathogenesis, diagnosis and optimal treatment. Numerous studies have now been published on companion animal IBD, and our understanding is undoubtedly increasing. However, despite a growing knowledge base much remains to be determined and understood. This presentation will review the current understanding and current controversies in canine and feline IBD.

AETIOPATHOGENESIS OF IBD

The gastrointestinal associated lymphoid tissue (GALT) is the largest and most complex immunological organ of the body, and must be capable of mounting protective immune responses to pathogens, whilst maintaining tolerance to harmless environmental antigens such as commensal bacteria and food. A delicate balance exists at the level of the intestinal mucosa with the 'mucosal barrier' separating the cells of the GALT from the endogenous bacterial flora, which represents an enormous and potentially overwhelming antigenic challenge.

Whilst a number of recognized diseases are associated with chronic intestinal inflammation,

the cause of idiopathic IBD is, by definition, unknown. Rodent models of chronic intestinal inflammation have demonstrated that abnormalities in the mucosal barrier, the bacterial flora and/or the GALT itself can lead to the development of chronic mucosal inflammation. Firstly, disruption of the mucosal barrier allows increased passage of antigens across the mucosa and can lead to inflammation. Second, a dysregulated immune response, especially involving CD4⁺ T cells, could underlie the development of uncontrolled inflammation. Finally, in certain circumstances, the presence of certain luminal antigens (e.g. dietary components and more importantly the endogenous bacterial flora), can also influence the development and severity of mucosal inflammation. Studies of human IBD suggest that similar mechanisms may be involved in both Crohn's disease and ulcerative colitis. Whilst these mechanisms are also said to underlie IBD in companion animals, convincing data are limited. Most notably, a recent study of mucosal cytokine gene expression in dogs with chronic enteropathies, failed to demonstrate upregulation. Nonetheless, studies do suggest alterations in immune cell populations (although variable and inconsistent amongst studies) and a favourable response to anti-inflammatory and immunosuppressive medications. More work is, therefore, required to clarify the pathogenesis in both cats and dogs.

CLINICAL PRESENTATION

Idiopathic IBD is a common cause of chronic vomiting and diarrhoea in dogs and cats but its true incidence is unknown. IBD is most common in middle-age animals, and there is no apparent gender predisposition. Although IBD can potentially occur in any dog or cat breed, some breeds are predisposed e.g. GSDs, soft coated wheaten terriers, Shar peis and Siamese cats. In

cats, an association (termed 'triaditis') has been reported between IBD, lymphocytic cholangitis and pancreatitis.

Vomiting and diarrhoea are the most common clinical signs. The nature of signs approximately correlates with the region of the GI tract affected: gastric signs are more common if gastric or upper SI inflammation is present; LI-type diarrhoea may be the result of colonic inflammation, or may result from prolonged SI diarrhoea. The presence of blood in the vomit or diarrhoea is associated with more severe disease and, especially, eosinophilic inflammatory infiltrates. Severe disease is associated with weight loss and PLE, with consequent hypoproteinaemia and ascites.

DIAGNOSIS

Intestinal biopsy is necessary for a definitive diagnosis of IBD, although the clinical signs and physical findings may be suggestive. Further, a diagnosis of idiopathic IBD requires that all other aetiologies be excluded, including infectious, diet-responsive and antibacterial-responsive conditions. Therefore, a complete diagnostic work-up additionally involves preliminary laboratory evaluation (haematology, serum biochemistry and urinalysis, faecal analysis) and diagnostic imaging (radiography and ultrasonography). These tests eliminate the possibility of systemic disorders, anatomic intestinal disease (e.g. tumour, intussusception), extra-intestinal disease (e.g. pancreatitis) and known causes of intestinal inflammation. Further, by determining whether focal or diffuse intestinal disease is present, the most appropriate method of intestinal biopsy can be chosen.

Faecal examination is most important in eliminating other reasons for mucosal inflammation, e.g. nematodes (e.g. *Trichuris*, *Uncinaria*, *Ancylostoma*, *Strongyloides*), *Giardia* and bacterial infections (e.g. *Salmonella* or *Campylobacter*, *Clostridia*).

Other tests. An assay for canine α_1 -protease inhibitor has recently been developed and validated for use on faecal extracts. In preliminary studies it has proven to be a promising as a marker of early intestinal protein loss. Therefore, increased faecal α_1 -protease inhibitor concentrations would be expected in dogs with IBD.

Serum concentrations of folate and cobalamin are affected by intestinal absorption, and hence proximal, distal or diffuse inflammation can result in subnormal folate concentrations, cobalamin concentrations, or both, respectively. Although such alterations are not pathognomonic for IBD, they may provide supportive evidence and highlight the need for therapeutic supplementation. Anecdotal evidence suggests

that such deficiencies can be a reason for failure to respond optimally to immunosuppressive therapy.

Intestinal biopsy. Intestinal biopsy is necessary to document intestinal inflammation. Endoscopy is the less invasive, but is limited by the fact that samples are superficial and can only be collected from the proximal SI in most cases. Alternatively, full-thickness biopsies can be collected at exploratory coeliotomy, and such samples are superior for diagnosis. However, this technique is more invasive and can be problematic if severe hypoproteinaemia is present. Nevertheless, exploratory coeliotomy is, perhaps, most suitable for cats, given the tendency for multi-organ involvement (e.g. concurrent intestinal, hepatic and pancreatic inflammation).

Histopathological assessment of biopsy material remains the gold standard for IBD diagnosis, and the pattern of histopathological changes depends upon the type of IBD present. However, interpretation is subjective, and agreement between pathologists is often poor. Further, it can be difficult to differentiate severe IBD changes from those of alimentary lymphoma. An international working party is currently attempting to standardize diagnostic criteria for IBD.

TREATMENT OF IBD

Treatment usually involves a combination of dietary modification, antibacterials and immunosuppressive therapy. Unfortunately, objective information of efficacy is lacking and most recommendations are based upon individual experience. If possible, a staged approach to therapy should be used. Initially, anti-parasitides (e.g. fenbendazole, Panacur @ 50 mg/kg q24h for 3 days) should be administered to eliminate the possibility of occult endoparasite infestation such as *Giardia intestinalis*. Thereafter, sequential treatment trials with an exclusion diet and antibacterials are pursued, and immunosuppressive medication is used only as a last resort. If clinical signs are intermittent, the owners should be instructed to keep a diary; this will provide objective information as to whether an improvement as actually occurred.

Dietary modification. The first therapeutic trial usually involves the use of dietary modification. Use of an exclusion diet trial will eliminate the possibility of should an adverse food reaction, although cases with idiopathic IBD may also improve with dietary modification. This may either be because a secondary dietary allergy has developed, because other beneficial dietary characteristics (improved digestibility, reduced fat content, reduced fiber content, altered fatty acid composition etc), or because of a change in

feeding pattern (e.g. smaller volume per meal, increased frequency). An easily digestible diet decreases intestinal antigenic load, and thus decrease mucosal inflammation.

A variety of commercially available antigen-limited diets are available which combine single protein and carbohydrate sources. Recently, hydrolyzed protein diets have also been introduced, and initial experience of their use is promising. Supplementation with oral folate and parenteral cobalamin is indicated if serum concentrations are subnormal.

Antibacterial therapy. Treatment with antimicrobials can be justified in IBD, in part to treat secondary SIBO, and partly due to the importance of bacterial antigens in IBD pathogenesis. Ciprofloxacin and metronidazole are most commonly used in human IBD, but metronidazole is the preferred drug for small animals. The efficacy of metronidazole may not just be related to its antibacterial activity, since there may be immunomodulatory effects on cell-mediated immunity. Further, other antibacterials such as tylosin may also have immunomodulatory effects, and empirically this drug has proved useful in many cases. In fact, a recent study in a rodent model of intestinal inflammation has shown that both metronidazole and tylosin are effective in decreasing inflammation. Finally, cases of HUC have recently been shown to respond to antibacterials such as enrofloxacin, suggesting a possible infectious agent underlies this condition. In fact, a recent study has confirmed the presence of invasive *E. coli* in HUC lesions.

Immunosuppressive drugs. If cases do not respond adequately to dietary modification, with or without antibacterials, immunosuppressive therapy is indicated. In dogs and cats glucocorticoids are used most frequently, and prednisone or prednisolone are the drugs of first choice. In severe IBD, prednisolone can be administered parenterally, since oral absorption may be poor. Budesonide, an enteric-coated, locally active steroid that is destroyed 90% first-pass through the liver, has been successful in maintaining remission in human IBD with minimal hypothalamo-pituitary-adrenal suppression. A preliminary study showed apparent efficacy in dogs, but limited information on the use of this drug is available.

In dogs azathioprine is commonly used in combination with glucocorticoids, when initial response is poor or steroid side effects are marked. However, its activity may be delayed in onset (up to 3 weeks) and, given its myelosuppressive potential, regular haematological monitoring is necessary. Azathioprine is not recommended for cats and chlorambucil (2-6 mg/m² PO q24h until remission, then tapering) is a suitable alternative. Other immunosuppressive drugs include

methotrexate and ciclosporin. Methotrexate is effective in the treatment of human Crohn's disease, and a recent case report has suggested efficacy in canine IBD. Ciclosporin has recently been adopted by many as a treatment for refractory IBD and a recent study has confirmed its effectiveness in such cases. The main limitation to its use is its cost.

Novel therapies for IBD. Novel therapies are increasingly used for human IBD, attempting to target more accurately the underlying pathogenetic mechanisms. They include new immunosuppressive drugs, monoclonal antibody therapy, cytokines and transcription factors and dietary manipulation. In the future such therapies may be adopted for small animal IBD. Finally, modulation of the enteric flora, with probiotics or prebiotics, may have benefits in targeting the pathogenesis of IBD.

PROGNOSIS AND PROGNOSTIC INDICATORS

A recent study examining prognosis in canine IBD has suggested that success of therapy is variable. Although many cases reportedly respond only a quarter achieve complete remission; a further half still have intermittent signs, whilst response is poor in the remaining cases and many are euthanased.

In humans, activity indices are used to quantify IBD disease severity, aiding the assessment of the response to treatment and the prognosis. An activity index has recently been suggested for clinical signs of GI disease in dogs (the canine IBD activity index; CIBDAI) and response to treatment has been shown to correlate with improvement in CIBDAI score. Its use in future studies of canine IBD is recommended since severity and response can be compared. In fact, many of the most recent studies have incorporated the scheme.

Other potential markers for IBD prognosis include serum acute phase proteins, such as C-reactive protein, which has been shown to be increased in canine IBD and decline upon successful therapy. Mucosal pANCA expression has recently been shown to be increased (prior to therapy) in cases that ultimately respond to dietary management, and expression of this marker increases post-therapy in steroid-responsive cases. Finally, low pre-treatment mucosal lymphocyte P-glycoprotein expression has recently been shown to predict a favourable response to therapy, suggesting that it.

REFERENCES

References are available on request.