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Review Article

TECHNICAL REVIEW ON INFLAMMATORY BOWEL DISEASE IN DOGS AND CATS

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Introduction

Inflammatory bowel disease (IBD) is an idiopathic gastrointestinal disorder which is characterized by persistent or recurrent GI signs. It is thought to be the most common cause of chronic intestinal disease in dogs and cats (Willard *et al.* 2008). The cellular infiltrate in IBD is composed of variable populations of lymphocytes, plasma cells, eosinophils, macrophages, neutrophils, or combinations of these cells (Fogle et. al., 2007). As the definition of IBD requires there to be no underlying cause of intestinal inflammation, so to call it idiopathic IBD. However, Day *et. al.,* (2008) stated that the indiscriminate use of the term IBD is unhelpful as a number of other diseases are associated with chronic intestinal inflammation and should be ruled out before true IBD can be diagnose. As per Kiselow *et. al.,* (2008), extensive diagnostic investigations must be performed to exclude the known causes of intestinal inflammation before IBD can be diagnosed. Lymphocytic-plasmacytic enteritis (LPE) is considered to be the most common histological form of IBD in dogs and particularly in cats; esinophilic gastric-enteritis (EGE) is the next most common form. Neutrophilic inflammation is sometimes seen, especially in cats but idiopathic granulomatous enteritis is considered uncommon.

Etiology and Pathogenesis

The aetiology of IBD in dogs and cats is unknown, but comparisons have been made with human IBD where the breakdown of immunological tolerance to luminal bacterial antigens is thought to be critical. Breakdown may result from disruption of the mucosal barrier,

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dysregulation of the gut associated lymphoid tissue (GALT), or disturbances in the microbial flora, or any combination of these factors.

Recognition of bacteria by the intestinal mucosa Toll-like receptors (TLRs) are found on the baso lateral surface of enterocytes. The receptors recognise pathogen-associated molecular patterns (PAMPs) on invading bacteria. Via intracellular signalling, TLRs stimulate the nuclear transcription factor NF-κB, which activates the transcription of the mRNA encoding pro-inflammatory cytokines such as tumor necrosis factor (TNFα) and various interleukins (IL), thereby triggering the inflammatory cascade.

Ultimately, the mucosal immune response is aimed at eliminating the pathogen completely. Unfortunately, bystander damage of host cells is almost inevitable, although if the antigenic challenge is contained, the danger signals will diminish, and so the mucosa will be repaired and normal tolerance will be restored. However, Kimmel *et al.*(2000) observed, if the danger persists, either because the mucosal barrier remains breached and the pathogenic insult continues, or because of an inherent abnormality in the GALT, a state of chronic inflammation ensues. This may also lead to a breakdown in tolerance to harmless environmental antigens (food components and/or commensal bacteria) and consequent inflammation.

Chronic inflammation ultimately leads to histopathologic changes, which are likely to be similar regardless of the inciting cause. Undiagnosed infection remains a possibility for intestinal inflammation. Recently, Fogle et. al. (2007) identified attachment and invading *E. coli* in histiocytic ulcerative colitis (HUC) of boxers suggests the intestinal inflammation is not idiopathic, and explains the positive response to treatment with enrofloxacin of this rare and specific condition.

Epidemiology

a) Age

No apparent gender predisposition has been reported and, in both dogs and cats, IBD is most common in middle-aged animals, although intermittent signs at an earlier age are sometimes noted. There are reports of intestinal inflammation in much younger animals (≤6 months). However, these may not be true IBD, but cases of intestinal inflammation where the underlying cause has been overlooked.

b) **Breed**

Although IBD can potentially occur in any animal, certain dog breed predispositions are recognized: boxers and Dobermans are reportedly predisposed to EGE; the German shepherd

dog is reported to be predisposed to both EGE and LPE, and a severe form of LPE, sometimes called immune proliferative small intestinal disease, is seen in Basenjis; severe LPE with hypoproteinaemia and extremely low serum cobalamin concentration is recognised in Shar peis (Janeczko *et al.*, 2008). Siamese cats, and perhaps other pure breeds such as Persians and Himalayans may be predisposed to LPE, and in any cat, coexistence of IBD, lymphocytic cholangitis, and chronic pancreatitis can occur; this association has been termed "triaditis".

c) Clinical signs

The most common clinical signs in IBD are vomiting and diarrhoea, but an individual case may show following signs.

i. Idiopathic causes
- Lymphocytic-plasmacytic enteritis (LPE)
- Eosinophilic gastroenterocolitis (EGE)
- Granulomatous enteritis
- Neutrophilic enteritis

i. Food allergy

i. Chronic infection
- Giardia sp.
- Histoplasma sp.
- Toxoplasma sp.
- Mycobacteria sp.
- Prototheca sp.
- Pythium insidiosa
- Pathogenic bacteria

›. Small bowel inflammation associated with other primary gastrointestinal diseases
- Lymphoma
- Lymphangiectasia

In some patients, clinical signs of IBD appear to start with an obvious precipitating event (e.g., stress, dietary change) although signs may spontaneously wax and wane. Postprandial pain and/or eating grass can be significant signs even in the absence of other signs. Gaschen *et al.,* (2008) observed that the weight loss may occur in the absence of overt diarrhoea and, if appetite is normal, is a reflection of SI malabsorption with compensatory colonic reabsorption preventing obvious diarrhoea. Vomiting is reportedly a more common manifestation of IBD in cats than diarrhoea. The presence of blood in the vomit or diarrhoea is associated with more severe disease and EGE.

Severe disease is also associated with weight loss and protein-losing enteropathy (PLE), with consequent panhypoproteinaemia and ascites; PLE is seen much more commonly in dogs than cats. Significant weight loss in the face of polyphagia suggests SI involvement. Mild intestinal inflammation may not affect appetite whereas anorexia occurs with severe inflammation, Inappetence or anorexia has been reported in 34% of cats with IBD. It is not

known how this correlates with acquired cobalamin deficiency, which occurs in feline IBD and can cause loss of appetite because of the development of methylmalonic acidaemia.

Diagnosis

Animals with chronic GI signs should always be assessed for non-GI disease.

The term IBD is limited to cases in which histological evidence of inflammation is found without an obvious underlying cause. All other aetiologies, including infectious, diet-responsive, and antibacterial-responsive conditions, must be excluded. House *et al.* (2008) suggested that the before intestinal biopsy is undertaken, laboratory evaluation and diagnostic imaging are performed.

Therapeutic trials with antibiotics and exclusion diets to identify antibiotic-responsive diarrhoea and dietary sensitivity respectively, may also be considered before intestinal biopsy is performed. Such tests cannot prove IBD, as the diagnosis is largely one of exclusion. They do help eliminate the possibility of gross intestinal disease, extra intestinal disease and known causes of intestinal inflammation. Furthermore, by determining whether focal or diffuse intestinal disease is present, the clinician can choose the most appropriate method of intestinal biopsy (Ruaux *et al.,* 2009).

i. Haematology

Haematological examination in IBD is often unhelpful, although sometimes a neutrophilia, with or without a left shift is observed. A mature neutrophilia was reported in 22% of 133 cats. Eosinophilia in dogs may suggest EGE, but it is neither pathognomonic nor invariably present, and in cats is a rare finding. Anaemia may reflect chronic inflammation or chronic blood loss. Thrombocytopenia is seen in 3% of canine cases.

ii. Serum biochemistry

No pathognomonic changes on a serum biochemical profile are seen in IBD, but diseases of other organ systems can be recognized and excluded. Hypoalbuminaemia and hypoglobulinaemia are characteristic of a PLE, such as IBD, alimentary lymphoma (AL) or lymphangiectasia (Kimmel *et al.,* 2000). Hypoalbuminaemia is seen more frequently in canine IBD and has been correlated with a poorer prognosis. Janeczko *et al.* (2008) revealed that only 12% of feline IBD cases show significant hypoalbuminaemia and it is rare for it to be of the magnitude necessary to cause ascites in cats.

Hypocholesterolaemia is seen in about 10% of cats with IBD, and in dogs is quite a good marker of malabsorption. In dogs, hypocalcaemia, and hypomagnesaemia may occur; this is partly a reflection of any hypoalbuminaemia, but there can be reductions in ionized calcium

concentrations, suggesting this change is of clinical significance. Malabsorption of these minerals and/or vitamin D is the most likely mechanism. Kiselow *et. al.,* (2008) evidenced that the intestinal inflammation in dogs may cause a "reactive hepatopathy", with mild elevations in liver enzymes. Increased ALT has been reported in 30% of cats with IBD, but concurrent cholangitis may not have been ruled out.

iii. Faecal examination

Faecal examination is performed to try to eliminate other causes of mucosal inflammation, such as hookworms and whipworms, Giardia, and bacterial pathogens. Given the potential for occult Giardia infection, empirical treatment is recommended in all cases. Additional testing for Histoplasma is indicated in animals originating from endemic areas.

iv. Folate and Cobalamin Estimation

Serum concentrations of both these vitamins may be reduced by both anorexia and intestinal malabsorption (Ruaux et al., 2009). Therefore, IBD can result in subnormal folate (proximal inflammation) or cobalamin (distal inflammation) concentrations or both (diffuse inflammation). Low serum cobalamin can cause abnormal intestinal histology as well as reduced appetite, and poor hair coat.

The degree of hypocobalaminaemia in canine IBD correlates with the degree of histological damage and a poorer prognosis. Although cobalamin deficiency is not diagnostic for IBD, it does require therapeutic correction as it has systemic metabolic consequences. Anecdotally, Ruaux et al., (2009) reported that the cobalamin-deficient cats with IBD require parenteral supplementation to respond optimally to immuno suppressive treatment.

v. Diagnostic imaging

Imaging is used to document whether focal or diffuse disease is present and/or whether other organs are affected. Such information, together with specific clinical signs, aids the choice of the most appropriate biopsy method.

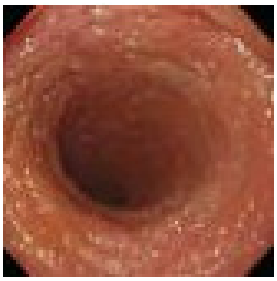
Plain radiographs may be useful for detecting gross disease; contrast studies rarely add further specific information. Gaschen *et al.,* (2008) reported that the ultrasonographic examination is superior to radiography for identifying focal neoplastic disease and AL, where the wall may be grossly thickened and the normal layered structure disrupted. It permits evaluation of intestinal wall thickness and can document mesenteric lymphadenopathy, whilst ultrasoundguided fine needle aspiration (FNA) can provide samples for cytological analysis. However, increased intestinal wall thickness is not a feature of most cases of canine

idiopathic IBD. Thickened intestines are a more common feature in feline IBD, although the mucosa may actually be thinned, with concomitant hypertrophy of the muscular layers.

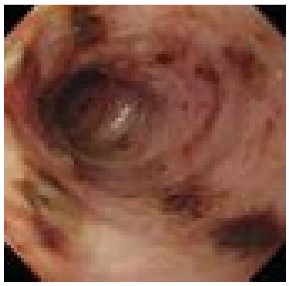
There is also emerging evidence that ileal biopsies are more likely to show abnormalities than duodenal biopsies. House *et al.* (2008) agreed that the histopathologists often is poor, especially when examining endoscopic biopsies. In one study, AL was diagnosed by some pathologists in tissues from healthy dogs, and there was only reasonable agreement between four independent pathologists in about half of the samples examined. Indeed results may differ between ante-mortem endoscopic biopsies and post-mortem specimens from the same patient.

vi.Intestinal biopsy

Intestinal biopsy is necessary to identify intestinal inflammation. Shales *et. al.*, (2005) observed that the endoscopy is the safer method of biopsy (Figure 2a& 2b), but has limitations such as biopsies are small and superficial and usually can only be collected from the stomach, duodenum and LI. In some cases full-thickness surgical biopsy is necessary, although the procedure is more invasive and can be problematic, especially if severe malnutrition and hypoproteinaemia is present. Laparotomy may be more suitable for cats, given the tendency for multi-organ disease.



2a. Increased granularity of the duodenum in lymphoplasmacytic enteritis



2b. Irregularity and ulceration in the duodenum in eosinophilic enteritis

(Photo courtesy: The BSAVA Manual of Canine and Feline Endoscopy and Endosurgery, Lhermette and Sobel, 2008, BSAVA Publications)

Histopathological assessment of GI biopsies remains the gold standard for the diagnosis of intestinal inflammation, but limitations to interpretation are recognized (Evans *et.al*., 2006). The quality of specimens can vary, agreement between pathologists is poor, and differentiation between normal specimens and those showing IBD and even AL can be difficult (Glanemann *et. al.,* 2008)

Therefore the clinician should always interpret endoscopic biopsy results cautiously, and in some cases, repeat biopsy (e.g., by exploratory laparotomy) may be required.

vii. Other diagnostic investigations

Given the limitations of histopathology, other diagnostic tests for reliably diagnosing IBD and distinguishing it from AL would be helpful. Cytological examination of FNAs or squash preparations of biopsies are likely to be less sensitive and specific. Dossin *et. al.* (2007) observed that the immunohistochemistry or flow cytometry can be used to analyze immune cell classes, and RT-PCR can measure cytokine mRNA expression in IBD. The presence of increased serum acute phase proteins, perinuclear antineutrophilic cytoplasmic antibodies (pANCA), increased intestinal permeability and faecal excretion of calprotectin may be useful markers of intestinal inflammation as per the guidelines of Jergens (2003). Clonality testing can be used to distinguish AL from severe IBD.

Treatment

Whatever the histological type of IBD, treatment usually involves immunosuppressive drugs with a combination of dietary modification and antibacterial therapy. However, if clinical signs or mucosal inflammation are severe, early intervention with immunosuppression is essential. Future use of disease activity indices will provide more objective comparisons of different treatment regimes.

Supplementation with oral folate and parenteral cobalamin is indicated if serum concentrations are subnormal. Modulation of the enteric flora with prebiotics or probiotics may have benefits in targeting the pathogenesis of IBD; both can reduce intestinal inflammation in mouse models of IBD (Jergens, 2002).

a) Antibacterial therapy

Treatment with antimicrobials can be justified in IBD because of the importance of bacterial antigens in its pathogenesis. Metronidazole is the preferred antibacterial for small animals. Its efficacy, especially in mild feline IBD, may be related to its immunomodulatory effects on cell-mediated immunity. Other antibacterials (e.g., oxytetracycline, tylosin) may also have immunomodulatory effects.

b) Immunosuppressive drugs

The most important treatment in IBD is immunosuppression. Corticosteroids are the mainstay, but alternative, cytotoxic immunosuppressives, such as azathioprine in dogs and chlorambucil in cats, can be used for their steroid-sparing effects.

In dogs, glucocorticoids alone are used most frequently, and prednisolone is the drug of choice. Silva *et al.* (2009) gave an initial dosage of 1-2 mg/kg is given orally every 12 hours for 2 to 4 weeks and then tapered slowly over the subsequent months. Initially signs of

iatrogenic hyperadrenocorticism will occur. However, in some cases therapy can be completely withdrawn or at least reduced to a low dose given every 48 hours, when side-effects will be reversed.

Budesonide is an enteric-coated, locally active steroid that is destroyed 90% first-pass through the liver, and so has minimal systemic side-effects (Craven *et.al*.,2004). A preliminary study showed apparent efficacy in dogs and cats, but limited information is published and a very wide dose range has been suggested. Cyclosporine may show promise for the future in treating canine IBD, given its T lymphocyte–specific effects and its efficacy in canine anal furunculosis. Unfortunately, it is expensive but response to cyclosporine in 11/14 dogs with steroid-resistant enteropathy has been reported.

Finally, anti–TNF-α monoclonal antibody therapy has been adopted in severe cases of human IBD. Species-specific monoclonal antibodies will be needed to treat canine and feline IBD.

Response to Treatment

There is a perception that the treatment of IBD is routinely successful and that full remission usually occurs. Reported cases where there were positive responses to parasiticides, dietary therapy or antimicrobials alone suggest that some were not truly IBD. A poorer prognosis in dogs has been associated with more severe disease, concurrent pancreatic disease, hypocobalaminaemia and hypoalbuminaemia. Whereas Willard *et al.* (2008) correlated with serum albumin may simply reflect the disease severity, but may reflect thromboembolic disease, which is a recognised complication of PLE.

Whereas the response to treatment in feline IBD appears better and remission is often prolonged; metronidazole as a sole therapy in milder cases can be successful and cats are more resistant to the side-effects of chronic steroid usage. Indeed prolonged survival has also been seen with simple prednisolone and chlorambucil therapy in old cats whether the diagnosis was severe LPE or small cell AL. Finally, one unexpected finding has been that clinical improvement is not necessarily accompanied by histological improvement.

Conclusion

Inflammatory bowel disease is undoubtedly a most common cause of chronic vomiting and diarrhoea in dogs and cats, but in reality it is probably overdiagnosed because of difficulties in interpretation of histopathologic specimens and failure to eliminate other causes of mucosal inflammation. It may be that histological remission is slower than clinical remission, but it more likely reflects the difficulty in assessing intestinal inflammation histologically.

Again, it is hoped that a standardized template for assessing histology will improve the reliability of the diagnosis and allow objective assessment of different therapies

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