Introduction

Regional enteritis is a chronic inflammatory bowel disease of unknown causes, rarely described in veterinary literature both in dogs (DiBartola and others, 1982; Lewis, 1995) and in other domestic species (horse, cat) (Lindberg, 1986; Schumacher and others, 1990; Wilcox, 1992; Barker and others, 1993).

The distribution of masses in the gastrointestinal tract and the histopathology of the lesions of regional enteritis in dogs has similarities to Crohn’s disease in human beings (regional enteritis or segmentaria). This pathology was described for the first time in 1932 by Crohn, Giuzburg and Oppnheimer; it was widespread mainly among the young population of the north Europe (Gasbarrini and others, 1993) and its etiopathogenesis is still uncertain.

As in human beings, it is characterized by a transmural granulomatous inflammation which may involve distal ileum, cecum, colon and rectum. Stomach, duodenum, regional lymph nodes and adjacent mesentery may be also affected. Macroscopically, the affected bowel is generally thickened and narrowed.

In the present report, the Authors describe the clinical and pathological findings in a dog affected by a regional enteritis extended also to the stomach.

Case Report

A 8-year-old intact male mixed-breed dog was referred to the authors' clinic with a history of episodes of recurrent anorexia, vomiting, watery diarrhoea with melena and colic pains (“prayer attitude”) of a 2 years duration. Vaccination were current as was anthelmintic control. Treatment with cephalothin sodium, fenbendazole, lactated Ringer Solution did not result in any improvement. Two weeks prior to presentation, the frequency of vomiting (often containing blood) and of diarrhoea had increased to once per day and the dog had lost weight.

On physical examination the dog was anorexic, cachectic, depressed, mildly dehydrated, and febrile (39.3 °C). Intestinal loops were markedly thickened on abdominal palpation.

Abnormal laboratory findings included leukocytosis (34,800 x mm³) due to neutrophilia (87%) and marked hypoproteinemia (4.5 g/dl). Serum levels of trypsin-like immunoreactivity (TLI) (6.80 ng/ml), cobalamin (363 pg/ml) and folates (12.00 ng/ml) were within normal reference range (TLI: > 5.20 ng/ml; cobalamin: > 200 pg/ml; folates: 3.00-13.00 ng/ml). Urinanalysis was normal and fecal flotation and direct fecal smears were negative for parasites. A lack of abdominal fat and increased amounts of gas in the cecum, large bowel and distal portion of the small bowel were observed on plain radiographs of the abdomen.

Endoscopic examination of the stomach, performed with an Olympus GIF P20 endoscope, showed rugal folds of the greater curvature covered with several streaks of bile-tinged fluid as well as multifocal superficial erosions associated with thickening and irregularity of the gastric mucosa. Duodenal endoscopy also revealed superficial erosion with haemorrhage and mucosal irregularity. Multiple biopsies from stomach and duodenum were obtained.

Biopsy of the stomach and small intestine were fixed in 10% neutral buffered formalin, embedded in paraffin wax, sectioned (6 µm) and stained with haematoxylin and eosin (HE). Histopathological examination revealed active chronic gastritis and enteritis with infiltration of the mucosa by neutrophils and lymphocytes. Focal areas of epithelial erosion were also observed.
The dog was treated with fluid therapy, tylosin (20 mg/kg, PO, b.i.d.), metronidazole (25 mg/kg PO, b.i.d.), cimetidine (5 mg/kg, IV, t.i.d.) and prednisone (1 mg/kg PO, every 12 hours) for one week without improvement. For this reason the client addressed to a private vet lab for an exploratory laparatomy that revealed a thickening of the pylorus and of the proximal duodenum mimicking a neoplasm. The owner elected euthanasia. The Vet sent only the above mentioned lesions to our laboratory for histopathological examination.

These specimens were routinely processed for histological examination and stained with: HE, Ziehl-Nielsen, Grocott and periodic acid Schiff (PAS). The most consistent histologic finding was represented by a transmural pyogranulomatous inflammation both in the duodenum and in the stomach. In the small intestine, villi were mildly to markedly atrophic and occasionally fused with erosions of the epithelium or clubbed and diffusely infiltrated by neutrophiles, scattered plasma cells and lymphocytes which formed dense aggregates (Fig. 1). Neutrophiles were mostly concentrated under erosive lesions and sometimes were present in the crypts. In the lamina propria epithelioid macrophages were also observed. They were particularly evident as nodular aggregates expanding the submucosa and extending through the muscularis propria to the subserosa (Figs. 2-3). Occasionally, degenerated neutrophiles accumulated in the center of granulomas and lymphocytic infiltration was mild. No giant cells were detected. Peripherically fibroblastic-fibrocytic proliferation was always marked. The lymphoid follicles were hyperplastic with a germinal center and they expanded to the muscularis mucosae. Examination of gastric fundic specimens showed chronic superficial inflammation, while in the pyloric area the same granulomatous lesions were observed. Tissue specimens were examined for mycobacteria by Ziehl-Nielsen and for fungi by Grocott and PAS, but the results were negative. Based on the clinical and histopathological findings a diagnosis of protein-loosing granulomatous enteritis was done.

Discussion

In these last years, the attention of pathologists and clinicians to these rare forms of idiopathic granulomatous enteritis of dogs is raised because of
many analogies with Crohn’s disease, that together with the ulcerative colitis is part of the “inflammatory bowel diseases” (IBD).

The course of Crohn’s disease is usually chronic. It is characterized by a segmental granulomatous inflammation involving the bowel, especially the distal ileum (terminal ileitis). The other parts of ileum, as cecum, colon, jejunum, duodenum and stomach can be involved, therefore the original terminology of “terminal ileitis” (Crohn) has been replaced, over the years, with “regional enteritis”.

Since Crohn’s disease has been discovered, many authors have supposed an infective etiology (bacterial, viral, etc.). At the present time there are no elements that prove the infective etiology, therefore Crohn’ disease remains fundamentally of unknown etiology (Katz and Fiocchi, 1997).

Different studies evaluating the immune response in the case of Crohn’s disease has been conducted, since the alterations of the immunological response are frequently involved in the chronic inflammatory diseases. On the other hand the granulomatous lesions and the response to immunosuppressive therapy suggest that immune-mediated factors play an important role in the pathogenesis of the disease. In fact, a recent theory suggests a deficiency of the cell-mediate immunity: probably, the impaired function of T lymphocytes allows an unsuccessful activation of the macrophages. For this reason the macrophages are not able to oppose to the penetration of bacteria to the intestinal surface (Lanza, 1985). Immunological soluble mediators have been particularly studied; particularly, pro-inflammatory cytokines abundantly revealed both in the serum of the patients and locally, in the intestine. This observation suggests that in this pathology there is an increase in the activation of the intestinal immunity (Katz and Fiocchi, 1997). Besides, by long time some authors have suggested that Crohn’s disease can be a true autoimmune syndrome. Recently it is believed that the intestinal inflammation is a result of epithelial damage due to a cross-reactive antibody reaction toward epithelial antigens of the colon having in common some epitopes with different strain of E.Coli. Actually, this observation is not completely accepted because such antibodies can also represent the effect rather than the cause of the bowel lesions. Other suggestive theories include an increase of intestinal permeability secondary to a genetically determined defect; chronic mesenteric vasculitis causing intestinal multifocal infarct; continuous stimulation of local immunity by enteric bacteria or alimentary antigens; alteration of the composition of the mucus layer (Katz and Fiocchi, 1997). Also in dogs, regional enteritis is placed in the group of chronic idiopathic intestinal disorders that are referred to with the general term of “inflammatory bowel disease” (IBD) and are characterized by infiltration of the intestinal mucosa and sometimes submucosa with inflammatory cells. These disorders are classified histopathologically on the basis of the predominant infiltrating cells as lymphocytic-plasmacytic, eosinophilic and granulomatous enteritis. The causes of IBD in animals remain still unknown, in spite of intensive research into the etiopathogenesis of human ulcerative colitis and Crohn’s disease. Proposed causes include defective immunoregulation of the gut-associated lymphoid tissue; genetic, ischemic, biochemical, and psychosomatic disorders; infectious, and parasitic agents; permeability defects; dietary allergies and adverse drug reactions (Guilford, 1996).

The etiopathogenesis in the dog is still unknown also because of a few reported cases. The most characteristic findings for a diagnosis of granulomatous regional enteritis are granuloma, hyperplasia of lymphoid follicles and mostly transmural inflammation. Clinically, only a diagnosis of chronic enteropathy can be made.

The investigation of specific infectious agents (Histoplasma capsulatum, Prototheca spp., Mycobacterium tuberculosis, Trichuris vulpis) causing granulomatous inflammation gave negative results. This observation confirms the idiopathic nature of the disorder. Histologically, Histoplasma capsulatum and Prototheca spp. are readily identified: Histoplasma capsulatum (2-4 µm in diameter) appear as basophilic dots after staining with HE, PAS positive and black-stained with Grocott. Prototheca organisms (5-20 µm in diameter) are colourless algae with HE, PAS positive, besides endospores can be observed easily in the cytoplasm of the mother cell. Trichuris infections usually cause colitis and typhilitis and granulomatous lesions are uncommon because related to an aberrant localization of ova or larvae, that can be identified to fecal examination (direct and flotation). The differential diagnosis with tuberculosis is very difficult because the granulomatous infiltration is characterized by epithelioid cells and Mycobacterium organisms are rarely seen. Giant cells are poorly present. The lymphocytic-plasmacytic infiltrate in the periphery of the granuloma is marked and neutrophiles are uncommonly seen.

Despite the absence of definite etiopathogenesis, the involvement of the immunitary system in the genesis of chronic enteropathies justifies the use of antiinflammatory and immunosuppressive drugs in the therapy of Crohn’s disease. The drugs commonly used are prednisone, mesalazine and, recently, budesonide, a “topical” glucocorticoid that repre-
sents an attractive alternative with fewer side effects (Guyot and others, 1998). Azathioprine, 6-mercaptopterine, methotrexate and cyclosporin, strong immunosuppressants, are also widely used in severe forms or steroid resistant cases, alone or associated with glucocorticoids. The role of chemioantibiotics is still uncertain; in the “active” phase of the disease, they are associated with the above mentioned drugs and metronidazole and ciprofloxacin are the most employed (Guyot and others, 1998). Other treatments such as cytokines (interleukin 10), anti-TNF α antibodies and 5-lipoxigenase inhibitors have shown promise in the treatment of human IBD (Van Deventer and Camoglio, 1996; D’Haens and others, 1997; Fedorak and others, 1997).

In dogs, the management of IBD is similar to that applied in the human patients suffering form Chon’s disease ulcerative colitis. Drugs most frequently used are prednisone (1-2 mg/kg PO b.i.d.), azathioprine (1 mg/kg PO s.i.d.) and sulfasalazine (15-20 mg/kg PO t.i.d.), associated with chemioantibiotics, such as tylosin (20 mg/kg PO t.i.d.) and metronidazole (10-30 mg/kg PO b.i.d.). The latter is an antiprotozoal agent, inhibits cell-mediated immunity, has a broad spectrum of activity and has positive effects on brush border enzyme levels (Guilford, 1996). As regards regional enteritis of the dog, a suitable therapeutic management can not be precisely established because of few reported cases. The prognosis for dogs with granulomatous enteritis appears to be poor. In 10 reported affected dogs, medical treatment using prednisone, sulfasalazine and trimethoprim-sulfamethoxazole has resulted in remission but not cure (Van Kruiningen, 1976; Di Bartola and others, 1982; Lewis, 1995). The efficacy of tylosin therapy still remains uncertain. Most affected dogs die or are euthanized as a result of their disease. In the present case medical therapy did not produce any improvement because of the serious-ness of illness.

It is expected that further investigations and a greatest number of reported cases in veterinary literature will allow a better understanding of etiopathogenesis of IBD and consequently an improvement in the therapeutic management of this disease.

Summary

Regional enteritis was diagnosed in an 8-year-old male mixed-breed dog with a history of recurrent anorexia, vomiting and diarrhoea. Laboratory findings included leukocytosis due to neutrophilia and marked hypoproteinemia. Histologically transmural granulomatous inflammation involving the pylorus and duodenum was observed.

The Authors discuss the histopathological aspects of regional enteritis because of the manifold similarities to Crohn’s disease in humans. Besides, they explore the etiopathogenetic hypothesis considering the most recent data existing in human literature.

References


Shumacher J. et al. (1990) Effect of intestinal resection on two juvenile horses with granulomatous enteritis. Journal Veterinary Internal Medicine, 4, 153-156.

