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Histiocytic ulcerative colitis - What’s new?

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CLINICAL AND HISTOPATHOLOGICAL FEATURES OF CANINE HISTIOCYTIC ULCERATIVE COLITIS

Histiocytic Ulcerative Colitis (HUC) is a form of inflammatory bowel disease which occurs most frequently in young Boxer dogs. It was first described 30 years ago and has since then been reported to occur in many countries, such as the USA, Australia, Japan and Europe, particularly in the UK. Besides Boxers, HUC has also been reported to occur infrequently in other breeds, such as Mastiffs, Alaskan Malamutes, French Bulldogs, English Bulldogs and even in one cat. The onset of disease is predominantly in dogs younger than 2 years of age. The clinical signs are those of severe chronic large intestinal inflammation and comprise diarrhea, tenesmus and excessive mucus in the feces. Weight loss and inappetence can also be seen in severe cases. Endoscopic findings demonstrate sites of severe colonic hemorrhage and ulcerations interspersed with stretches of normal appearing mucosa. Histologically, early lesions can present with a mixed inflammatory infiltrate in the lamina propria, which are subjacent to degenerative epithelium. More extensive lesions and chronic disease, the ulcerations become more visible on histology with severe infiltration of the lamina propria and the submucosal regions with neutrophils, macrophages, lymphocytes, plasma cells and mast cells. There is also usually massive loss of the epithelial surface in biopsies from lesions and loss of goblet cells in the entire colon. The pathognomonic histologic lesion however is the accumulation of large macrophages which stain strongly positive with Periodic Acid Schiff (PAS) in their cytoplasm. This is still the best way to diagnose HUC with certainty. Immunohistochemical studies have shown that HUC lesions are characterized by an increased number of L1 positive cells, as well as MHC class II positive cells, CD3 positive cells and IgG positive plasma cells.

TREATMENT OF HUC

Unfortunately, the prognosis for HUC has been guarded to poor until just recently. Management of HUC consisted of various combinations of dietary management (i.e. increasing fiber content in the diet and specific elimination diets), and anti-inflammatory or immune-suppressive treatment with sulfasalazine, prednisolone and azathioprine. However, these strategies usually failed to improve the clinical signs in affected animals, and most cases had to be euthanased because of refractoriness to treatment. Two recent reports have now sparked hope in treating the disease, as a total of 12 cases have been reported which have shown dramatic response to treatment with enrofloxacin (5mg/kg po once daily for), or a combination protocol with enrofloxacin, amoxicillin (20mg/kg po twice daily) and metronidazole (10-15 mg/kg po twice daily). The response to treatment with enrofloxacin in the more recent reports was dramatic, with all dogs responding within 3-12 days of starting treatment. It is particularly encouraging that several dogs were reportedly disease-free when the drug had been discontinued after finishing a course of 4-6 weeks of antibiotic treatment with enrofloxacin. This implies a possibility of curing the disease in certain cases, even though follow-up times of more than 21 months have not been reported so far and it is possible that some dogs need treatment with enrofloxacin for much longer than 6 weeks or possibly even life-long. In 5 of the reported cases, biopsies were repeated after finishing the course of antibiotic treatment at the time when the dogs were in clinical remission. In all of these 5 dogs, a dramatic improvement in the histological lesions was demonstrated, with disappearance of PAS-positive macrophages in 3 cases and a marked reduction in the number of macrophages in the other 2 cases.

INVESTIGATIONS INTO THE PATHOGENESIS OF HUC

The mechanisms involved in the pathogenesis of HUC in dogs have been debated for decades. The recent success with antibiotic treatment in canine HUC obviously raises the question if HUC could be caused by an infectious organism. It is however not for the first time that this hypothesis has been investigated. The role played by the PAS positive macrophages is intriguing, as PAS stains intracellular phagocytosed material in the macrophages, and early electron microscopic studies have demonstrated so-called “residual bodies”, which resemble bacteria-like organisms in PAS-positive staining macrophages. In a recent publication investigating the possibility of an infectious cause for canine HUC, large numbers of coccobacilli were found by fluorescent in-situ hybridization in the colonic mucosa of Boxers affected with HUC, as opposed to histologically normal tissues and in the mucosa of dogs with other types of colitis. Further studies by culture, cloning and sequencing of the flo-
ra in the colon of Boxers with HUC identified the bacteria to be E.coli. The bacteria could be identified by electron microscopy and localized to the intracellular compartment in PAS positive macrophages in HUC lesions. This finding is exciting, particularly because further classification of the virulence genes and biological behavior of these bacteria in coculture with epithelial cells and macrophages revealed specific adhesive and invasive properties. The E.coli strains associated with HUC were shown to have a similar phenotype and adhesive and invasive behavior resembling E.coli isolates which have recently been associated with Crohn’s disease in people. In several studies, a particular strain of E.coli, so-called E.coli LF82, could be demonstrated in biopsies of 20-35% of ileal lesions in Crohn’s disease, but never in healthy controls or other colitic diseases.

Genetic defects in certain receptors of the innate immunity have been identified in people with IBD. The inflammatory response which is normally only seen as a reaction towards pathogenic bacteria breaching the intestinal barrier is similar to what is seen in the mucosa of people affected with Crohn’s disease and dogs affected with HUC. It is therefore possible that similar defects in pattern-recognition receptors as found in people with IBD could be found in dogs with HUC. A genetic predisposition seems to be one of the obvious mechanisms involved, as most cases described are young Boxer dogs, and in the first report of the disease in 1965, most of the affected dogs could be traced back to a single ancestor. Whether Boxers with HUC carry mutations in pattern-recognition receptors such as TLRs or NODs remains to be determined, however, it seems likely that a defect in the innate immunity renders dogs with HUC more susceptible to specific infections, such as E.coli strains which do not cause disease in normal animals.

References


