INFLAMMATORY LIVER DISEASE

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Cholangiohepatitis is a complex of related inflammatory hepatobiliary disorders. They accounted for approximately 26% of the liver diseases reported in cats in one large retrospective study (Gagne, et al. JAVMA, 1999; 214:513). This was second to hepatic lipidosis which accounted for approximately 50% of the cases. Inflammatory liver diseases are characterized by the predominant inflammatory cell infiltrate seen histopathologically. The inflammation is usually seen in the portal areas; and can be characterized as suppurative (neutrophilic), non-suppurative (lymphocytic / plasmacytic), sclerosing lymphocytic cholangitis, or biliary cirrhosis (fibrosis). Cholangiohepatitis is often associated with cholangitis and periportal necrosis. Suppurative cholangiohepatitis can be further subdivided into acute (also termed suppurative by some authors) in which neutrophils are seen and chronic in which a mixture of neutrophils and lymphocytes/plasma cells are seen. Lymphocytic portal hepatitis is the term that has become accepted to describe the histologic classification in which lymphocytes and/or plasma cells are noted to infiltrate the portal areas. This replaces the older term, “lymphocytic/plasmacytic cholangiohepatitis.” Lymphocytic portal hepatitis was more common than suppurative cholangiohepatitis; being seen in 61% of the cats with inflammatory liver disease in the study by Gagne, et al. Significant neutrophilic inflammation, cholangitis and periportal necrosis are not characteristic of lymphocytic portal hepatitis. Whether these classifications represent different stages in the progression of one disease or are separate etiologic entities is not known. Nor is the underlying etiology of inflammatory liver disease in cats. Bacterial, allergic, and immune mechanisms have all been speculated to be involved. Bacterial cholangitis may either initiate the inflammatory process or perpetuate it early in the disease course. Immune mechanisms probably also play a role especially in chronic suppurative cholangiohepatitis and lymphocytic portal hepatitis. Cats with cholangiohepatitis, especially those with suppurative disease, may also have pancreatitis and inflammatory bowel disease. The relationship between these three inflammatory conditions is not well worked out but it has been speculated that the underlying initiator of the inflammatory process may affect the liver, the pancreas, and the small intestine concurrently. The term, “triaditis” has been coined to describe those situations in which inflammation of the liver, pancreas, and small intestine are seen to occur concurrently. While not a very accurate description, the term seems to have stuck.

CLINICAL FINDINGS

The clinical findings seen in cats with inflammatory liver disease are similar to those seen with hepatic lipidosis and other liver diseases. Vomiting, anorexia, lethargy, and weight loss are typical. Fever is occasionally seen. Diarrhea, while not usual, is more common than in cats with hepatic lipidosis and may represent the subset of cats with concurrent inflammatory bowel disease. Affected cats are rarely obese. Cats with cholangiohepatitis are more likely to be severely systemically ill when compared to those cats with lymphocytic portal hepatitis. Any age cat can be affected. Males predominate in populations of cats with cholangiohepatitis as compared to those with lymphocytic portal hepatitis. Suppurative disease often has an acute course while disease characterized by lymphocytic/plasmacytic inflammation may be more chronic. In evaluating liver enzymes, alkaline phosphatase tends not to be as elevated as in cats with hepatic lipidosis and transaminase activities tend to be higher. Neutrophil counts, transaminase activities, and total bilirubin concentrations tend to be higher in cats with cholangiohepatitis when compared to cats with lymphocytic portal hepatitis. All liver enzymes may be normal early in the course of disease, however. Diagnosis is usually dependent on biopsy as FNA is often normal or reveals non-specific changes. Biopsy for both histopathology and culture should be performed if inflammatory liver disease is suspected. The advent of readily available ultrasonography has resulted in Tru-cut needle biopsy becoming the most popular method of obtaining tissue for histopathology. The diagnostic accuracy of Tru-cut obtained biopsies has been questioned (Cole, et al. JAVMA, 2002; 220:1483-90). In this study liver biopsies obtained from dogs and cats by tru-cut techniques were compared to wedge biopsies. Paired 18 g Tru-cut needle biopsies commonly yielded a different diagnosis than wedge biopsy. If it is assumed that the wedge biopsy is the “gold standard” then the 18 g Tru-cut biopsies were highly inaccurate. Larger samples obtained with a 14 g needle may be more accurate. Laparoscopically obtained samples should be considered when feasible. Prior to biopsy, coagulation parameters should be evaluated. PIVKA may be the most sensitive indicator of potential bleeding tendencies. Vitamin K1 (0.5-1.5 mg/kg SQ given within 24 hours of biopsy may decrease the risk of bleeding.

TREATMENT

As in cats with hepatic lipidosis, nutritional support is an important aspect of therapy. Total caloric intake should be 80-100 Kcal/kg/day. Protein supplementation is important. Moderate or even high protein diets such as Hills Prescription Diet® p/d™ or a/d™, Iams Veterinary Diets® Nutritional Recovery Formula™/Canine & Feline, or Abbott Laboratories® Feline Clinicare™ or Renal care™ are appropriate initial choices. Switch to a lower protein diet if signs of hepatorenalopathy ensue. Force feeding or enteral feeding is often necessary to maintain appropriate caloric intake. Appetite stimulants may assist the owner who wishes to force feed their cat. Cyproheptadine [Periactin®] 2 mg/cat and oxazepam [Serax®] 1 mg/kg sid-bid may be used. Diazepam (0.1 ml IV) and Midazolam (2-5 mg/kg IV) can result in appetite stimulation. The effect of diazepam is usually short lived and causes significant sedation. Midazolam may cause a more lasting stimulation and less sedation. Care must be taken if benzodiazepines such as oxazepam are used because they may worsen hepatorenalopathy. Enteral feeding while probably needed in most cats with hepatic lipidosis, may not be necessary in all cats with inflammatory liver disease. Esophagostomy, gastrostomy, or nasoesophageal feeding may all be used successfully. Gastrostomy feeding is tolerated well by most cats. The tubes can be placed surgically or percutaneously via endoscopy or blind techniques. Enteral feeding should be continued until the cats appetite improves. This may occur soon after treatment designed to decrease inflammation has been initiated.
In addition to supportive and nutritional support, antibiotics should be used when treating cats with inflammatory liver disease. Metronidazole is effective against anaerobes, some gram-negative aerobes, and has immune modulating effects. Ampicillin, amoxicillin, amoxicillin-clavulanate, and enrofloxacin are excreted in the bile and are also good choices. Immunosuppressive agents should be added to the treatment regime in cats with non-suppurative disease and in cats with suppurative disease that fail to respond to antibiotics alone. Prednisolone (2-4 mg/kg/day initially then slowly tapered to 1 mg/kg QOD) is used most commonly. Other immunosuppressives that may be used in cats responding poorly to glucocorticoids include chlorambucil (1.5 to 4 mg/M² twice a week to q48 hrs; approximately 1 mg < 7 lb cat, 2 mg > 7 lb cat) [probably a safer alternative to azathioprine in the cat], azathioprine (0.3 mg/kg q24-72 hrs) [Note that cats are much more sensitive to the myelosuppressive effects of azathioprine than dogs], methotrexate (0.4 mg divided into 3 doses and given over 24 hours and repeated every 7-10 days has been advocated as a pulse therapy but has not been extensively studied). Ursodeoxycholic acid (Actigall®) 10-15 mg/kg PO SID is a safe treatment alternative that can be used in cats with suppurative or non-suppurative disease.

The drug appears to have multiple actions including shifting the bile acid pool to a less toxic hydrophilic population, a choleretic effect, reducing expression of Class 2 major histocompatibility complex, and an antiinflammatory effect. Vitamin E (aqueous alpha tocopherol, 10-100 IU/kg/day) has been advocated for its antioxidant effects. SAMe (90-180 mg PO SID) is a precursor of glutathione. Glutathione is an important antioxidant that has been shown to be reduced in dogs and cats with liver disease. The nutriceutical SAMe may help replace glutathione. It also may have hepatoprotective effects in preventing programmed cell death (apoptosis) that occurs during inflammatory liver disease. Milk thistle (silymarin) is a nutriceutical that is widely used for its hepatoprotective effects. It may be of benefit as an antioxidant, as an antifibrotic agent, or as an aid in hepatic regeneration. Many studies have evaluated its use in people and show mixed results. Studies in dogs and cats are lacking. Anecdotal evidence would suggest it may be useful at a dose of 50-200 mg/kg PO SID.