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Update on feline cholangitis and cholangiohepatitis

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Inflammation centered on the biliary tree is a common form of hepatic disease, and appears to be the second most common form of liver disease after hepatic lipidosis. Histologic classification of the term “feline cholangitis/cholangiohepatitis” is controversial, with poor consensus amongst pathologists in the nomenclature used. Two major types of inflammatory liver disease were described in 1996 based on histologic features; cholangiohepatitis (acute or suppurative and chronic or non-suppurative) and lymphocytic portal hepatitis. A new simplified classification scheme was proposed by the WSAVA Liver Diseases and Pathology Standardization Research Group in 2002. Three distinct forms of cholangitis have been recognized in cats:

1) **NEUTROPHILIC** (usually referable to ascending bacterial infection but also rarely reported in protozoal infections).

2) **LYMPHOCYTIC** (thought to be immune mediated)

3) **CHRONIC CHOLANGITIS** associated with infection by liver flukes (Amphimerus pseudofelineus, Platynosomum concinnum, etc).

**NEUTROPHILIC (BACTERIAL) CHOLANGITIS** (historically referred to as acute cholangiohepatitis) is characterized by infiltration of large numbers of neutrophils into portal areas of the liver and into bile ducts. Disruption of the periportal limiting plate of the bile duct results in necrosis of hepatocytes adjacent to portal areas and infiltration of neutrophils into hepatic lobules. Neutrophilic cholangitis may begin as an ascending bacterial infection within the biliary tract; however, bacteria are only isolated in a few cases. Organisms include *Bacteroides*, *Actinomyces*, *E. coli*, *Clostridia*, and alpha hemolytic *Streptococcus*. Congenital or acquired abnormalities of the biliary system, including anatomic abnormalities of the gall bladder or common bile duct and gall stones may predispose to cholangitis. Inspsation of bile which may cause partial or complete obstruction of the common bile duct, gall bladder, or intrahepatic bile ducts frequently accompany cholangitis and may require treatment before the cholangitis can be controlled or resolved.

The neutrophilic cholangitis can be divided into 2 categories, namely acute and chronic. Their distinction histologically is based on the presence of increased plasma cells, lymphocytes ± macrophages with the chronic phase.

**LYMPHOCYTIC CHOLANGITIS** is felt to represent a later stage of neutrophilic cholangitis, or may represent a separate disease entity. It is characterized by a moderate to marked infiltration of the portal areas by small lymphocytes ± biliary hyperplasia, portal or periductal fibrosis, or bridging fibrosis.

Diseases frequently associated with lymphocytic cholangitis include inflammatory bowel disease and pancreatitis. Eighty three percent of cats with cholangitis had concurrent inflammatory infiltrates in the duodenum and/or jejunum and 50% had pancreatic lesions. This association has lead to the use of the term “triaditis” to describe affected cats. Inflammatory bowel disease may give rise to retrograde bacterial invasion of the common bile duct with resultant pancreatitis and cholangitis. Despite the high incidence of inflammatory infiltrates in the small intestine, diarrhea is not a frequent finding in cats with cholangitis.

The new proposed histologic classification scheme does not recognize portal lymphoplasmacytic inflammation in which infiltrates are confined to portal areas and not centered on or involving bile ducts as a specific subtype of cholangitis. Sparse lymphocytes and plasma cells may be found in the portal areas of healthy young cats, often in close association with bile ducts. Increased numbers of portal lymphocytes and plasma cells are commonly identified in portal areas of cats over 10 years of age, often in conjunction with extrahepatobiliary disorders.

The new proposed classification scheme also prefers the term cholangitis to cholangiohepatitis, as inflammatory disruption of the limiting plate to involve hepatic parenchyma is not always a feature, and when present, is an extension of a primary cholangitis.

The new classification scheme also does not recognize the previous classification of “lymphocytic portal hepatitis,” and believe that the finding of increased plasma cells and lymphocytes in the portal region not associated with the bile duct epithelium represent a normal phenomenon (see above), or a common finding in older cats in conjunction with extrahepatobiliary disorders (see above).

**CHRONIC CHOLANGITIS**

Chronic cholangitis secondary to fluke infestation is characterized by severe ectasia of the bile ducts, mild to severe hyperplasia of the biliary epithelium, severe concentric periductal fibrosis, and the occasional presence of adult flukes and/or operculate eggs within bile duct lumina.
Clinical signs

Clinical signs associated with inflammatory liver diseases are variable and nonspecific and are frequently similar to those associated with hepatic lipidosis. Partial or complete anorexia is the most common, and sometimes the only, clinical sign. Other less frequently observed clinical signs include weight loss, depression, vomiting, diarrhea, and fever. Cats with neutrophilic cholangitis tend to be younger (mean age 5.7 years) than cats with lymphocytic cholangitis (mean age 9.0 years), or hepatic lipidosis (mean age 6.2 years). Male cats are more frequently affected with neutrophilic cholangitis. Cats with neutrophilic cholangitis are more acutely and severely ill than cats with most other types of liver disease. Prominent clinical signs in neutrophilic cholangitis include fever, depression, and dehydration.

Jaundice and altered liver size are frequently the only findings that direct attention to liver disease. In severe cases, ecchymotic hemorrhages and/or prolonged bleeding from venipuncture sites may occur. Jaundice is most easily observed in the sclera but may also be observed in the soft palate or under the tongue. When liver size is evaluated radiographically, hepatomegaly is a frequent finding in feline liver disease but cannot be used to differentiate amongst the various causes.

Laboratory evaluation

Hematologic and biochemical testing are essential to establish a diagnosis of liver disease. Although there are trends that differentiate inflammatory liver diseases from hepatic lipidosis and hepatic neoplasia, liver cytology or histopathology is essential to establish a definitive diagnosis. Laboratory changes typically seen with neutrophilic cholangitis include mild to moderate neutrophilia and left shift, normal to slight increase in serum bilirubin and serum alkaline phosphatase (SAP) and a substantial increase in alanine aminotransferase (ALT). This profile tends to differentiate neutrophilic cholangitis from lymphocytic cholangitis, hepatic lipidosis, and hepatic neoplasia. Laboratory changes typical of lymphocytic cholangitis include substantial increases in serum bilirubin, SAP, and ALT. Other associated changes may include mild nonregenerative anemia, hyperglobulinemia, lymphocytosis, and hyperglycemia. When cats with inflammatory liver diseases are compared to hepatic lipidosis, hepatic lipidosis cases tend to have higher total bilirubin concentrations, and higher ALT and SAP. The hallmarks of hepatic lipidosis include clusters of hepatocytes in which the cytoplasm is distended with lipid-filled droplets. Malignant lymphoma cells readily exfoliate and can be diagnosed by cytologic evaluation. Cytologically, hepatic lipidosis is characterized by clusters of hepatocytes in which the cytoplasm is distended with lipid-filled droplets. Malignant lymphoma cells readily exfoliate and can be diagnosed by cytologic evaluation. Cytologic diagnosis of inflammatory liver diseases is hampered by blood contamination, which introduces variable numbers of blood leukocytes into the samples. Therefore, the cytologist is left to determine whether leukocytes are of blood origin or represent inflammatory lesions within the liver.

Liver imaging

Abdominal ultrasonography is often helpful in evaluation of extrahepatic disorders associated with cholangitis. Most cats with neutrophilic or lymphocytic cholangitis or with lymphocytic portal hepatitis have variable or no detectable alterations in the echogenicity of the hepatic parenchyma. Conversely, most cats with hepatic lipidosis have hypoechoic hepatic parenchyma. Bile duct abnormalities may be observed in cholangitis. These abnormalities include gall bladder and/or common bile duct distention, choledolithiasis, cholecystitis, and bile sludging. The normal gall bladder is anechoic and appears round in the transverse scan and pear-shaped in the longitudinal scan. It is important to remember that gallbladder filling occurs normally with fasting, therefore, caution must be exercised in interpreting gall bladder enlargement in an anorectic or fasting cat. The common bile duct can usually be seen as an anechoic, tortuous, tubular structure 2 to 4 mm in diameter with an echogenic wall. Distention of the gall bladder and common bile duct (i.e., greater than 5 mm in diameter) occurs as a result of cholecystitis, or biliary obstruction. The gall bladder wall may become thickened as a result of inflammation or edema. The thickened gall bladder wall has a layered or “double-walled” appearance. Bile sludge within the gall bladder or common bile duct appears echogenic.
be done to produce good quality slides for cytologic evaluation. In a clinically unstable patient, ultrasound-guided fine needle aspiration is recommended. Sonography can be used to monitor for excessive hemorrhage 5 to 10 minutes after aspiration or biopsy.

**Treatment**

The major specific therapy for neutrophilic cholangitis is antibiotics. Surgical intervention has been recommended if discrete choleliths or complete biliary obstruction is identified. When complete extrahaepatic bile duct obstruction is identified, surgical decompression and biliary-to-intestinal diversion (i.e. cholecystoduodenostomy or cholecystojejunostomy) is recommended. Bacterial culture and sensitivity testing of bile, liver aspirate or biopsy specimens, choleliths, or gall bladder specimens, should be used to select appropriate antimicrobial agents whenever possible. Antibiotics chosen for treatment of cholangiohepatitis should be excreted in the bile in active form, and should be active against aerobic and anaerobic intestinal coliforms. Tetracycline, ampicillin, amoxicillin, erythromycin, chloramphenicol, and metronidazole are excreted in the bile in active form, however, several of these have significant adverse side effects. Erythromycin is not effective against gram-negative bacteria, tetracycline is hepatotoxic, and chloramphenicol may cause anorexia. As a result, ampicillin or amoxicillin combined with clavulanic acid is frequently used. All are broad-spectrum antibiotics, effective against both gram-negative and gram positive organisms, and are well tolerated by cats. These drugs may be combined with fluoroquinolones to extend the spectrum to anaerobes and more coliforms. Treatment with antibiotics for 2 months or longer is recommended.

Cats with lymphocytic cholangitis typically require antibiotic therapy combined with immunomodulatory therapy. The anti-inflammatory and immunosuppressive properties of prednisolone may be beneficial in limiting hepatocellular injury. Additionally, prednisolone may enhance appetite. An immunosuppressive dose of prednisolone (2.2-4 mg/kg q24h) should be used initially. The dosage is slowly tapered to an alternate day dose (1-2 mg/kg q48h) for long term maintenance. Biochemical values should be monitored prior to each reduction in dosage. If the clinical and biochemical response is satisfactory, doses as low as 0.5 mg/kg q 48 hours may be sufficient for long term maintenance. Long term corticosteroid treatment is well tolerated by most cats and side effects are usually minimal. Chlorambucil can also be used as an immunomodulator (combined with prednisone) at a dose of 2 mg q 4 days for cats with more severe disease. Chlorambucil should be given for at least 8 weeks, prior to tapering based on clinical response and laboratory evaluations. Low dose methotrexate can also be used in cats with lymphocytic cholangitis failing to respond to prednisone and chlorambucil.

Ursodeoxycholic acid (Actigall) is recommended for cats with all types of inflammatory liver disease. It has anti-inflammatory, immunomodulatory, and antifibrotic properties as well as increasing fluidity of biliary secretions. Ursodeoxycholic acid has safely been administered to cats at a dose of 10 to 15 mg/kg q24h PO. Efficacy has not been established for any type of feline liver disease, but clinical trials in human patients with hepatitis support improved quality of life. Adverse effects in cats are uncommon and usually limited to mild diarrhea. Antioxidants such as S-Adenosylmethionine or vitamin E should also be considered to prevent or decrease lipid peroxidation in the hepatocytes. S-Adenosylmethionine is dosed at 20 mg/kg SID for cats, and is available in 90 mg tablets from Nutromax. Vitamin E is typically dosed at 10 to 100 IU/kg administered once daily.

Cats with neutrophilic cholangitis require aggressive supportive care. These cats are frequently acutely ill and have fluid and electrolyte derangements which should be corrected. Treatment with injectable vitamin K₁ (5 mg/cat q 1-2 days IM) can be given if bleeding diatheses develop. Hepatic encephalopathy appears to be relatively uncommon in cats with acquired liver diseases and is manifest most frequently by excessive salivation. Hepatic encephalopathy can be managed by giving lactulose orally (0.5-1.0 ml/kg q8h PO) with or without addition of enteric antibiotics (neomycin 20 mg/kg q8-12h PO).

Response of cholangitis cats to therapy should be monitored through use of serial complete blood counts and chemistry profiles. Persistent increases in ALT activity and serum total bilirubin concentration and/or increasing SAP activity suggest that treatment has been inadequate. Low dose weekly methotrexate therapy has been used in a few affected cats.

**Prognosis**

Limited studies of the response of cholangitis cases to antibiotic treatment suggest that survival of cats with neutrophilic and lymphocytic cholangitis are similar. Approximately half of the cats die or are euthanized within 90 days after diagnosis. The other half has prolonged survival. Hopefully, initiation of standard treatment protocols combined with surgical correction of bile duct obstruction (when needed) will increase the number of cats with long term survival.

Suggested reading list of references available from the author upon request