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Update on the Diagnosis and Management of Feline Cholangiohepatitis

Stanley L. Marks, BVSc, PhD, Diplomate ACVIM (Internal Medicine, Oncology), Diplomate ACVN
University of California, Davis, School of Veterinary Medicine
Davis, CA, USA

Two major types of **inflammatory liver disease** have been described based on histologic features; cholangiohepatitis (acute and chronic) and lymphocytic portal hepatitis.

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 results in necrosis of hepatocytes adjacent to portal areas and infiltration of neutrophils into hepatic lobules. Acute cholangiohepatitis 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 gallstones may predispose to cholangiohepatitis. Inspissation of bile which may cause partial or complete obstruction of the common bile duct, gall bladder, or intrahepatic bile ducts frequently accompany cholangiohepatitis and may require treatment before the cholangiohepatitis can be controlled or resolved.

Chronic Cholangiohepatitis is probably a later stage of acute cholangiohepatitis. It is characterized by a mixed inflammatory infiltrate in portal areas and bile ducts consisting of neutrophils, lymphocytes, and plasma cells. Unlike acute cholangiohepatitis, bile duct hypertrophy and portal fibrosis are prominent. In terminal stages, chronic cholangiohepatitis may progress to biliary cirrhosis (also termed sclerosing cholangitis).

Diseases frequently associated with cholangiohepatitis include inflammatory bowel disease and pancreatitis. Eighty three percent of cats with cholangiohepatitis 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 cholangiohepatitis. Despite the high incidence of inflammatory infiltrates in the small intestine, diarrhea is not a frequent finding in cats with cholangiohepatitis.

Lymphocytic Portal Hepatitis appears to be distinct from acute and chronic cholangiohepatitis. It is characterized by infiltration of lymphocytes and plasma cells, but not neutrophils, into portal areas but not into bile ducts. Variable degrees of bile duct hypertrophy and fibrosis are present; however, lymphocytic portal hepatitis does not progress to biliary cirrhosis. Lymphocytic portal hepatitis is a frequent finding in old cats. This condition is felt to reflect an immune-mediated disease; however, this has not been substantiated to date.

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 acute cholangiohepatitis tend to be younger (mean age 3.3 years) than cats with chronic cholangiohepatitis (mean age 9.0 years), lymphocytic portal hepatitis (8.2 years) or hepatic lipidosis (mean age 6.2 years). Male cats are more frequently affected with acute cholangiohepatitis. Cats with acute cholangiohepatitis are more acutely and severely ill than cats with most other types of liver disease. Prominent clinical signs in acute cholangiohepatitis 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. Fasting bile acids is the test that is most consistently abnormal in all types of inflammatory liver diseases and hepatic lipidosis. Laboratory changes typically seen with acute cholangiohepatitis include mild 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 acute cholangiohepatitis from chronic cholangiohepatitis, hepatic lipidosis, and hepatic neoplasia. Laboratory changes typical of chronic cholangiohepatitis include substantial increases in serum bilirubin, SAP, and ALT. Other associated changes may include mild nonregenerative anemia, hyperglobulinemia, lymphocytosis, and hyperglycemia. Laboratory alterations associated with lymphocytic portal hepatitis include normal to variably increased serum bilirubin, ALT, and SAP. When all 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 jaundice, 10-fold or greater increases in ALT and SAP, without a corresponding increase in gamma glutamyl transferase (GGT). In other forms of liver disease in cats, increases in GGT tend to parallel increases in SAP.

When the clinical chemistry profile reveals evidence of liver disease, hyperthyroidism should be ruled out. Hyperthyroid cats frequently have changes in ALT and SAP that may be indistinguishable from those associated with inflammatory liver diseases. The increased enzyme concentrations normalize with treatment of hyperthyroidism. Pathologic changes in liver associated with hyperthyroidism have not been well characterized.

LIVER IMAGING

Abdominal ultrasonography is often helpful in evaluation of extrahepatic disorders associated with cholangiohepatitis. Most cats with acute or chronic cholangiohepatitis 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 hyperechoic hepatic parenchyma. Bile duct abnormalities may be observed in cholangiohepatitis. These abnormalities include gall bladder and/or common bile duct distention, cholelithiasis, 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.

LIVER CYTOLOGY/HISTOPATHOLOGY

Liver cytology or tissue biopsy is essential in differentiating inflammatory liver diseases from hepatic lipidosis and neoplasia. The use of fine needle aspirates eliminates the need for anesthesia and markedly reduces the chance of hemorrhage. The diagnostic utility of liver cytology is controversial. Several reports indicate that cytologic evaluation is highly efficient in identifying hepatic lipidosis and hepatic lymphoma; however, inflammatory liver diseases are more difficult to identify cytologically. Results of another retrospective study,

however, indicate poor correlation between liver cytology and histopathology. 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.

Ultrasound-guided aspiration and biopsy techniques more consistently produce diagnostic specimens than do blind techniques. Ultrasound-guided fine needle aspiration can be used to sample bile as well as hepatic parenchyma. Such samples can be examined cytologically to look for inflammatory cells and bacteria and can be cultured to confirm bacterial infections. Optimal evaluation, in a relatively stable patient, would consist of 2 or 3 ultrasound-guided liver biopsies and collection of a bile sample under ultrasound guidance. Touch impressions of the liver biopsy specimen may 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 acute and chronic cholangiohepatitis is antibiotics. Surgical intervention has been recommended if discrete choleliths or complete biliary obstruction is identified. When complete extrahepatic 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 metronidazole to extend the spectrum to anaerobes and more coliforms. Treatment with antibiotics for 2 months or longer is recommended.

When cats with chronic cholangiohepatitis fail to respond to antibiotic therapy alone within 2 to 3 weeks, prednisolone is usually added as an empirical treatment. 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.

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.

Cats with acute cholangiohepatitis require aggressive supportive care. These cats are frequently acutely ill and have fluid and electrolyte derangements, which should be corrected. Treatment with injectable vitamin K_1 (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 cholangiohepatitis 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. The approach to treatment of lymphocytic portal hepatitis is based on the hypothesis that the liver injury is immune-mediated. Immunosuppressive doses of corticosteroids are used as described above for chronic cholangiohepatitis. Anecdotal reports indicate prolonged improvement in clinical signs with prednisolone treatment. Others, however, report poor control of disease progression with corticosteroid treatment. Azathioprine (0.3 mg/kg PO q48–72 h) has been tried but side effects, including inappetence and leukopenia, limit its use. Low dose weekly methotrexate therapy has been used in a few affected cats.

Response to treatment for lymphocytic portal hepatitis is difficult to assess because the disease is very slowly progressive. A persistent increase in ALT and/or increasing total serum bilirubin concentration during corticosteroid treatment indicate that the disease is inadequately controlled.

PROGNOSIS

Limited studies of the response of cholangiohepatitis cases to antibiotic treatment suggest that survival of cats with acute and chronic cholangiohepatitis is similar. Approximately half of the cats' die or are euthanized within 1 year after diagnosis, 40% survive between 1 and 5 years, and the rest can be expected to have prolonged survivals beyond 5 years Hopefully, initiation of standard treatment protocols combined, when needed, with surgical correction of bile duct obstruction will increase the number of cats with long-term survival. Cats with lymphocytic portal hepatitis appear to have a better prognosis compared to cholangiohepatitis. Of 23 cats that were available for follow-up, 30% survived less than 1 year, 44% survived between 1 and 5 years, and 26% survived longer than 5 years. Mean survival time for cats surviving longer than 1 year was 51.8 months, with 22% of cats still alive at the time of follow-up.

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