

Inflammatory Feline Liver Diseases:
Acute and Chronic Cholangiohepatitis
Lymphocytic Portal Hepatitis

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INTRODUCTION

Cats are prone to a relative short differential list of primary hepatic diseases. Cholangiohepatitis is the second most commonly diagnosed feline liver disease. Cholangiohepatitis accounts for approximately 26% of histopathologically confirmed liver diseases in cats. Hepatic lipidosis is the most common, comprising 49% of cases, with neoplastic liver conditions third, at 10%. Less commonly diagnosed feline hepatic diseases include portal vascular anomalies, acute hepatic necrosis, extrahepatic bile duct obstruction and benign hepatic cysts.

The cholangiohepatitis complex has typically been divided into three forms based on histological appearance: Acute (suppurative) cholangiohepatitis, chronic (non-suppurative) cholangiohepatitis, and the end-stage of chronic cholangiohepatitis, biliary cirrhosis. Other pathologic descriptions used to describe the chronic form include chronic lymphocytic cholangitis, progressive lymphocytic cholangitis, pericholangiohepatitis, and sclerosing cholangitis. Recently, investigators at the University of Minnesota have suggested a fourth variant of feline inflammatory liver disease exists and have termed it, lymphocytic portal hepatitis. Preliminary evidence suggests that this disease is etiopathologically distinct from acute (suppurative) or chronic (non-suppurative or “mixed inflammatory cell”) cholangiohepatitis.

Cholangitis refers to inflammation that is confined to the intra or extrahepatic bile ducts. Cholangiohepatitis refers to diseases in which the inflammation extends beyond the bile ducts into adjacent hepatic parenchyma inducing hepatocellular injury as well. It has been presumed, but never proven, that acute cholangiohepatitis progresses to chronic cholangiohepatitis which may progress to biliary cirrhosis as the end stage of this chronic inflammatory disease process.

SUPPURATIVE CHOLANGIOHEPATITIS

Etiopathogenesis

Suppurative cholangiohepatitis is an uncommon disease. It is considered by most investigators to be caused by bacteria of intestinal origin which ascend the common bile duct, eventually involving smaller intrahepatic bile ducts and periportal hepatocytes in the inflammatory process. In addition to ascending infections, generalized septicemia may also result in bacteria localizing within bile ducts or periportal hepatocytes. Bacteria isolated include *E. coli* (most common), *Clostridia*, *Bacteroides*, *Actinomyces*, and alpha-hemolytic streptococcus. Rare infectious agents, other than intestinal coliforms, have also been identified as causes for cholangiohepatitis. These include an organism resembling *Hepatozoan canis*, a coccidia like organism, likely from the protozoan family *Eimeridae*, toxoplasmosis, and *Bacillus piriformis*. The cat liver fluke, *Amphimerus pseudofelineus* can also invade the bile ducts and produce cholangiohepatitis.

Although bacteria are considered the primary cause for the inflammation of this disease, spontaneous ascending bacterial infections are not thought to occur with any frequency. Rather, some predisposing condition exists in the liver or adjacent organs (pancreas) that allows normal GI flora to ascend into the bile ducts which then produces cholangiohepatitis. Conditions considered in this category include any disease leading to cholestasis, the presence of choleliths or inspissated bile, cholecystitis, hepatic fluke infestations and anatomical abnormalities of the gallbladder or major bile ducts. Although

infectious agents appear to be the primary cause, other coexisting non-hepatic conditions are also seen in a high number of cats with suppurative cholangiohepatitis and may also be responsible in some way for ascending bacterial infections. These abnormalities include chronic pancreatitis, and inflammatory bowel disease (IBD). A recent retrospective evaluation of cats with inflammatory hepatic disease identified coexisting IBD in 83%, chronic (mild) pancreatitis in 50% and both IBD and pancreatitis in 33% of cases. Whether these latter diseases actually predispose to cholangiohepatitis or are a result of this disease is unresolved.

Clinical Features

Affected cats are of variable age but tend to be younger with acute (5.7 yrs) than with chronic cholangiohepatitis (9.7 yrs), and no breed predisposition is recognized. Clinical signs usually include depression, anorexia, weight loss, vomiting, fever, polydipsia, hypersalivation and icterus. Physical examination findings are unremarkable except for mild icterus and dehydration. The radiographic assessment of liver size is normal in 50% of cases, with hepatomegaly noted in the other 50%.

Hematologic, biochemical and urinalysis findings are not unique for acute cholangiohepatitis when compared to other feline hepatic diseases. Hemograms often indicate the presence of a neutrophilia, with variable presence of immature WBC's. Anemia is uncommon and usually mild. Poikilocytosis is evident on stained blood smears in approximately 25% of cases. Biochemical abnormalities include mild to moderate hyperbilirubinemia (mostly conjugated), mild increases in SAP (two to four times), and moderate rises in ALT, gamma glutamyl transpeptidase and serum bile acid concentrations. In the majority of cases (75%), the gamma glutamyl transpeptidase (GGT) elevation will be significantly greater than the proportional rise in serum alkaline phosphatase (ALP) concentrations. This is in contrast to hepatic lipidosis in which the ALP typically is significantly greater than the proportional rise in GGT. Hepatic enzymes (ALT, ALP) are normal in some cats. Fasting serum bile acid concentrations are elevated in approximately 50% of cats. Post-prandial serum bile acid concentrations are typically elevated. Urinalyses may be positive for bilirubin and urobilinogen.

Hepatic ultrasound is useful for assessment of inflammatory liver diseases to rule out focal neoplasia, identify the presence of cholecystitis, cholelithiasis, inspissated bile, determine whether extrahepatic bile duct obstruction exists, and identify coexisting active pancreatitis. Ultrasonographic findings typical for cats with cholangiohepatitis include: either normal echotexture (50%), or diffuse hypoechogenicity with prominent portal vascular markings being common. Over 50% have abnormalities of the bile ducts or gallbladder (cholecystitis, thickened gall bladder wall, inspissated bile, cholelithiasis, thickened bile ducts, extrahepatic bile duct obstruction). The ultrasonographic finding of inspissated bile can be normal in many cats without evidence for hepatic disease, so this finding alone is of little diagnostic value.

Diagnosis requires hepatic biopsy. Fine needle aspiration biopsies can be performed, carry minimal risk for the patient, but have low diagnostic yield in cholangiohepatitis. Ultrasound guided transhepatic cholecystocentesis with a 22 ga spinal needle may be beneficial in providing culture and cytologic data if a surgical biopsy is not done. Since this disease process is diffuse, biopsies obtained by percutaneous needle

techniques, laparoscopy or laparotomy will all be diagnostic. However, biopsy via laparotomy has the advantage of allowing for evaluation of the extrahepatic biliary system and pancreas if ultrasound evaluation is not available presurgically. If choleliths, inspissated bile, or extrahepatic obstruction exist, they may be corrected at the time of surgery. Hepatic tissue and or bile should be cultured both aerobically and anaerobically.

Unless extrahepatic bile duct obstruction is evident on ultrasound, open biopsies provide little additional benefit over guided needle biopsy and increase the chances of postoperative complications. Cats with advanced cholangiohepatitis may be fragile hematologically and significant bleeding may occur post-biopsy. Recent evaluations of the hemostatic status of cats with various hepatic diseases identified coagulation abnormalities in 82%. Four cats with cholangiohepatitis were in this group. Three of four had significantly prolonged coagulation tests. One had disseminated intravascular coagulation and the other two had coagulopathies compatible with vitamin K deficiency. Supplementation with parenteral vitamin K₁ (5mg/cat/day, IM or SQ) for several days may reverse a severe coagulopathy, allowing for safer biopsy procedures. The vitamin K deficiency is likely the result of impaired absorption of hepatically synthesized coagulation factors that are vitamin K dependent. This occurs secondary to chronic cholestasis and/or extrahepatic bile duct obstruction which leads to malassimilation of fat soluble vitamins. Cats should be evaluated with a prothrombin time and activated partial thromboplastin time prior to biopsy. Fresh whole blood or fresh frozen plasma may be needed pre-biopsy in cats with significantly prolonged coagulation times, or post-biopsy if significant bleeding occurs.

Histologic findings in acute cholangiohepatitis include variably increased numbers of neutrophils with lesser numbers of lymphocytes and plasma cells in portal areas. There is also evidence for cholangitis, bile duct degeneration, periportal necrosis and infiltration of neutrophils into hepatic lobules. Variable degrees of hepatic fibrosis, biliary hyperplasia, and suppurative exudate within dilated intrahepatic biliary ducts may also be seen. The presence of primarily neutrophils within intrahepatic bile ducts and in periportal regions is the characteristic feature of this disease and distinguishes acute from chronic cholangiohepatitis. Hepatic copper concentrations are usually normal in cats with acute cholangiohepatitis.

Therapy of suppurative cholangiohepatitis is primarily supportive and symptomatic. This involves maintenance of fluid and electrolyte balance and appropriate nutrition. However, this is one hepatic disease where antibiotics are specifically indicated. The choice should be made based on culture and sensitivity of tissue or bile taken at biopsy when possible. Most cats have negative cultures because of prior treatment with antibiotics or the presence of anaerobes which are difficult to isolate. Drugs such as chloramphenicol, erythromycin, and tetracycline all reach high concentrations in bile, but have disadvantages for use in this disease. Erythromycin has a poor spectrum of activity for gram negative bacteria, and causes frequent gastrointestinal upsets and anorexia. Tetracycline frequently causes anorexia in cats, may induce hepatic lipidosis, and is a hepatic enzyme repressor that inhibits protein synthesis. Chloramphenicol may induce anorexia, bone marrow dysplasia and is a potent repressor of hepatic enzyme systems making it also a poor choice for liver failure. The author currently prefers ampicillin (10-20 mg/kg/IV/PO q8h) or metronidazole (7.5-10 mg/kg q

8 to 12 hrs) because of their effect on hepatic anaerobes and gastrointestinal coliforms. Amoxicillin-clavulanic acid, or a first generation cephalosporin (cephalexin/cephadroxil) may also be considered in initial therapy. Enrofloxacin may be added to increase the spectrum of bacterial coverage. If signs of hepatic encephalopathy are present, oral aminoglycosides (neomycin 10 mg/kg/os TID) and lactulose (2.5-5 ml/os/TID) may be useful as supportive care for cats with hepatic encephalopathy. Aminoglycosides may also be injected parenterally and combined with ampicillin or metronidazole to increase the antibacterial spectrum of activity. Oral antibiotics should be continued for a minimum of 4 weeks or longer depending on whether fever and neutrophilia persist. Some individuals suggest that initial therapy should continue for 3 to 6 months or longer. I continue to treat as long as there is evidence for ongoing cholestasis or inflammation on biochemical profiles. If cats have persistent elevations in liver enzymes, recurrent icterus or fever, chronic cholecystitis may be present and these cats should have ultrasound guided cholecystocentesis with cytology and culture for aerobic and anaerobic bacteria and treated appropriately. Chronic recurrent cholecystitis may benefit from cholecystectomy as well.

While there is no compelling evidence that glucocorticoids are beneficial in suppurative cholangiohepatitis, if animals fail to respond clinically to antibiotics alone in 5 to 7 days, then prednisone or prednisolone (0.5-1mg/lb/day) should be considered as adjunctive therapy. Some cats fail to improve clinically or biochemically until glucocorticoids are added. Therapy is generally continued for a minimum of 2 to 4 weeks initially and the cat monitored clinically and biochemically. Glucocorticoids are tapered off over several weeks with ongoing monitoring of the cats biochemical profiles. Prednisone may be necessary for several months, as with antibiotic therapy.

Ursodeoxycholic acid (ursodiol/Actigall) may have benefit in reducing the chronic cholestasis of cholangiohepatitis and aid in prevention or resolution of inspissated bile. It should NOT be used if there is evidence of extrahepatic biliary tract obstruction. Ursodeoxycholic acid is a naturally occurring bile acid that appears to have unique hepatoprotective effects against other more toxic bile acids. It is known that some bile acids have the potential to be hepatotoxic in high concentrations as would occur in cholestasis of any kind. The hydrophobic, lipophilic bile acids, chenodeoxycholic acid and deoxycholic acid have the greatest potential to cause injury. They are known to increase in the circulation in chronic liver diseases. Conversely, the hydrophilic, lipophobic bile acid, ursodeoxycholic acid, has just the opposite effects. When used chronically by the oral route in humans, ursodiol results in decreased concentrations of hepatotoxic serum bile acids and may modify the rate of progression of chronic cholestatic liver diseases. Ursodiol is proposed to exert this hepatoprotective effect via three mechanisms; 1) inducing hypercholeresis, 2) by a direct hepato-protective effect or by displacing toxic bile acids from the circulation, and 3) via suppression of immune mediated injury that may cause progression of this disease. Only anecdotal evidence regarding the therapeutic efficacy of ursodeoxycholic acid has appeared in the veterinary literature. It does not apparently induce any toxic side effects. However, documented evidence of efficacy is still lacking as well. The current recommended dosage for both dogs and cats is 10 to 15 mg/kg/os once daily. It is only available as 300mg capsules so must be compounded for use in cats. Some authors recommend treating cats with

cholangiohepatitis for life with ursodeoxycholic acid if no specific cause for histologically confirmed cholestasis is found. There is no convincing evidence that such a recommendation changes outcomes in cats with cholangiohepatitis at this time. Particularly if clinical and biochemical evidence for ongoing disease is lacking.

A number of clinical reports have recommended the use of another hydrocholeretic drug, dehydrocholic acid (Decholin), 5 to 7 mg/lb/os (10 to 15 mg/kg/os) three times daily to aid in improving bile flow. This product has only one use in humans—as an irritant laxative. Data to support its efficacy as a choleric in cats are totally lacking. Serum bile acids are already increased in most cats with cholangiohepatitis and would serve as an endogenous choleric anyway. The author cannot recommend the use of this product. Several other compounds stimulate bile flow by what is termed bile salt independent mechanisms. Such drugs stimulate flow by increasing ionic transport of water into bile, causing a choleresis. Drugs known to possess this property are furosemide, ethacrynic acid, theophylline, phenobarbital and hydrocortisone. They would have a more rational basis for use in suppurative cholangiohepatitis than dehydrocholic acid.

The short-term prognosis for cats with suppurative cholangiohepatitis is guarded to fair, but, the long-term outlook is highly variable. Six of 10 cats with suppurative cholangiohepatitis recently reported died of their illness within 6 weeks of presentation. Four others, however, were alive for 21 to at least, 125 months. All the cats in this study received antibiotic therapy and two-thirds also received glucocorticoids.

Some cats appear to undergo complete remission and have long asymptomatic periods. Others respond to specific and symptomatic care but must remain on medication (antibiotics and or glucocorticoids and/or ursodeoxycholic acid) for their signs to be controlled. Still others respond poorly to therapy and die or are euthanized soon after the diagnostic process is completed. Several reports suggest that some cats with suppurative cholangiohepatitis remain asymptomatic, only developing clinical signs when their disease has progressed to chronic cholangiohepatitis.

CHRONIC CHOLANGIOHEPATITIS (mixed inflammatory reaction)

Chronic cholangiohepatitis is the most commonly reported form of this feline disease. Cats range in age from 6 months to 20 years, with the majority being greater than 9 years old. Persian cats were considered to be at increased risk in one report, but this has not been confirmed in others and domestic short haired cats are the most common breed identified. Chronic cholangiohepatitis differs from suppurative cholangiohepatitis in several ways. Cats are generally less ill and ascites occurs more often, with over 50 per cent of the cats in some studies having ascites. Vomiting and lethargy are common, while fever and weight loss are less frequent than in the acute form. Icterus was detected clinically in 10 of 21 cats in one series. On physical exam, significant findings include icterus, ascites and hepatomegaly. Fever was not present in any of 21 cats from one series, but was present in 11% of cats in another report.

Laboratory data in chronic cholangiohepatitis is generally similar to the acute form with a few mild differences. Hemograms are generally unremarkable, except a mild anemia may exist and poikilocytosis is present in 44% of cases. White blood cell counts typically remain normal and little if any left shift is present. Biochemical profiles support

an inflammatory, cholestatic liver disease is present, similar to suppurative cholangiohepatitis. Unique to this syndrome is the presence of hyperglobulinemia and hypoalbuminemia in many cats. The increase in globulins is primarily due to increases in the gamma globulin fraction on electrophoresis. Hyperbilirubinemia and elevations in alkaline phosphatase are more prevalent in chronic than acute cholangiohepatitis. Because of the marked portal lymphocytic inflammatory infiltrate that typifies this disease, a possible immune mediated etiology has been suggested. Tests to detect the presence of antimitochondrial and/or anti-smooth muscle antibodies have been attempted in a few cases. Results were inconclusive in one study and negative in 4 cats in another.

A definitive diagnosis requires hepatic biopsy as with acute cholangiohepatitis. Cautions about bleeding post biopsy are even more likely in the chronic form as the amount of functional compromise of the liver is often greater. Grossly, the liver will be normal to enlarged. The surface may be smooth or finely nodular depending on the duration and severity of the disease, and it may be quite firm if significant fibrosis is present.

Inspissated bile, formed as a result of dehydration and sludging of biliary secretions, may be present in intrahepatic and extrahepatic bile ducts and within the gall bladder. This material must be surgically removed and the entire duct system flushed out to reestablish patency of the biliary system. If patency cannot be reestablished, surgical procedures which will allow bile flow to be normalized must be performed. Cholecystojejunostomy is the biliary bypass procedure of choice in these cats. In some cats "white bile" will be present within the biliary system. This material represents mucus secreted by gall bladder and bile duct epithelium without bile pigments being present; and is considered to be a poor prognostic sign.

Histologic findings are characterized by a mixed inflammatory infiltrate in portal areas. Usually, the majority of the inflammatory cells are lymphocytes and plasma cells with variable, but lesser numbers of neutrophils. Periportal necrosis and extension of the inflammatory cells into hepatic parenchyma is also typical. Fibrous septae may link portal tracts and form complete or incomplete circumscribed nodules (pseudolobule formation) of hepatocytes, distorting normal hepatic architecture. Destruction of small bile ducts by this inflammatory reaction is often marked and bile duct proliferation is typical. In some of the cats with ascites, features of biliary cirrhosis become evident. Biopsies should be cultured, as with suppurative cholangiohepatitis, to determine if specific antibiotic therapy is indicated.

Therapy of chronic cholangiohepatitis is similar to the suppurative form except that the addition of glucocorticoids early in the course appears to improve survival in some cases. The histological features of this disease bear some similarities to an immune mediated disease of man, chronic nonsuppurative destructive cholangitis (primary biliary cirrhosis) in which steroids improve survival. Because of this histologic similarity, glucocorticoids have been utilized as specific therapy in this feline disease. Limited clinical observations seem to indicate that steroids may help some feline cases as well, and relapses may occur when steroids are withdrawn. Immunosuppressive doses of prednisone, 1 to 2 mg/lb/day (2.2 to 4.4 mg/kg/day) have been used initially with doses tapered off over a 30 to 60 day period. Diuretics are useful in controlling ascites.

Ursodeoxycholic acid has good theoretical indications in the chronic form of this disease as well.

The prognosis for cats with chronic cholangiohepatitis is guarded to fair. Many animals will fail to adequately respond to supportive care and will die or be euthanatized. Some have an initial response to therapy but are prone to relapses if steroids and or antibiotics are withdrawn. One cat has been reported to have had multiple relapses but still be surviving over four and a half years. Others appear normal clinically but have persistent biochemical abnormalities, and still others recover completely from their illness. Cats must be followed both clinically and biochemically until all evidence for persistent disease has ceased. Those cats whose illness continues to progress may develop biliary cirrhosis. Mean survival time for 6 cats with chronic cholangiohepatitis was recently reported to be 30 months (range 5-96).

BILIARY CIRRHOSIS

Biliary cirrhosis appears to be the end stage of chronic cholangiohepatitis in some cats. This is the least common of the 3 histologic patterns comprising this syndrome. These cats are typically icteric, depressed, very thin have ascites and are in functional hepatic failure. Hepatomegaly is usually present, in contrast to cirrhosis in dogs, in which reduced liver mass is expected. In addition to mild to moderate increases in hepatic enzymes, hypoalbuminemia, hyperglobulinemia and coagulopathies are often present. A definitive diagnosis is dependent upon liver biopsy, but, if coagulopathies exist, these cats should receive fresh whole blood transfusions prior to any biopsy procedures. Grossly, these livers will be firm, enlarged and nodular. Histopathologic findings include severe bridging portal fibrosis, bile duct proliferation and hyperplasia, and nodular hepatic regeneration. Inflammatory cells are minimal in this stage of the process, but small numbers of lymphocytes may be present in portal areas. Therapy is supportive and symptomatic, but significant clinical improvement rarely occurs due to the advanced stage of the disease. Survival is usually a few days to weeks following diagnosis.

LYMPHOCYTIC PORTAL HEPATITIS

A fourth type of portal inflammatory infiltrate in cats, believed to be etiopathologically separate from acute and chronic cholangiohepatitis has recently been described. It has been termed lymphocytic portal hepatitis. This inflammatory infiltrate is common in cats, both with and without signs of hepatic disease. It is particularly common in cats over 10 years of age. A group of 25 sick cats with lesions typical for lymphocytic portal hepatitis that had had liver biopsies taken were recently reported. They were from a group of 45 cats that had biopsies evaluated in a 10 year retrospective study. Sixty per-cent had lymphocytic portal hepatitis and 40% had either acute or chronic cholangiohepatitis.

The mean age at presentation is 8 years of age (range 5mo to 17 years). No gender predisposition was noted. The majority were domestic short haired cats. Clinical signs were similar to cats with acute and chronic cholangiohepatitis . Anorexia, and weight loss are present in about 2/3 of cats. Vomiting, lethagy, fever, diarrhea and ascites may also be noted.

The CBC is generally unremarkable although neutropenia was noted in one case and neutrophilia in 4 others. Anemia is uncommon. Biochemical patterns support cholestatic, inflammatory liver disease. Twenty eight percent were hyperbilirubinemic, but most were only mildly elevated (mean 2.3 mg/dl). None were positive for FeLV or FIV of those tested. Half had increased ALT concentrations and 32% had increased ALP concentrations. Hepatomegaly was evident in half the cats and 10% had microhepatica on survey radiographs

Diagnosis was made only via hepatic biopsy. Lymphocytic portal hepatitis differs from acute and chronic cholangiohepatitis by the lack of neutrophilic infiltrates in portal areas. There is also an absence of evidence for bile duct inflammation (cholangitis) and the limiting plate remains intact. Large lymphoid aggregates may develop in portal areas. Significant bile duct hypertrophy and fibrosis may also be seen and varies from mild to severe. Lymphocytic portal hepatitis does not have a tendency to progress to biliary cirrhosis but lesions do appear to increase in severity as cats age.

Therapy utilized for lymphocytic portal hepatitis is similar to that described for chronic cholangiohepatitis. Fluids, electrolytes, nutritional support, antibiotics, glucocorticoids and ursodeoxycholic acid. If cats fail to improve with antibiotic and glucocorticoid therapy, attempts to decrease the inflammation with azathioprine (0.3 mg/kg/os once daily) may be attempted. This immunosuppressive agent is often poorly tolerated in cats and leads to frequent anorexia and blood dyscrasias. Anecdotal mention of therapy with once weekly methotrexate has also been suggested by some authors if cats fail to adequately respond to conventional therapy. No published reports of success with methotrexate have appeared.

The prognosis in cats with lymphocytic portal hepatitis generally is better than in cats with acute or chronic cholangiohepatitis. Approximately 30% will be expected to survive less than one year. However, an additional 44% should survive from 1 to 5 years, with mean survival times for cats alive after one year being 52 months.

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