Update on Chronic Hepatitis in Dogs

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The most important and most common primary liver disease in the dog is chronic hepatitis. Chronic hepatitis is not a single disease but rather the inflammatory changes can be due to many of etiologies. The therapy should be directed first at the cause of the inflammation. In most all cases a liver biopsy is required to confirm the diagnosis before effective therapy can be begun.

Chronic hepatitis is an etiologic diverse and morphologically variable condition associated by mixed inflammatory cell infiltrates. It is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration and fibrosis. The proportion and distribution of these components vary widely. Plasma cells, lymphocytes and macrophages predominate with a lesser number of neutrophils. Because we see non-specific mild portal inflammation as a common non-specific reactive change frequently secondary to intra-abdominal disorders like IBD I need the pathologist to tell me the severity of inflammation and chronicity of the disease. The presence of fibrosis in the hepatic biopsy usually denotes to me more serious consequences. As damage progresses cirrhosis can result with diffuse fibrosis, alteration in hepatic lobular architecture with the formation of regenerative nodules and abnormal vascular anastomoses. Cirrhosis, a sequel of some chronic hepatitis cases, is often associated with portal hypertension, ascites and multiple portosystemic collateral veins. Some may show manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites and hepatoencephalopathy. This type of chronic inflammation is uncommon in the cat as their inflammatory disease is directed at bile ducts causing cholangitis.

Etiology

The etiology of this chronic inflammatory condition is generally never determined. To date the best-described etiology of chronic hepatitis is the copper associated hepatitis of the Bedlington terrier (see below copper associated hepatitis). This breed and others are thought to have an inherited copper associated chronic hepatitis. Copper accumulates in hepatocyte from abnormal metabolism to a level that then becomes toxic causing hepatocyte death. There are also likely breeds that have difficulty in handling copper if taken in orally in excess amounts.

Infectious chronic hepatitis in man is most often associated with viral etiologies. The search for a viral etiology of hepatitis in the dog however has been unrewarding. The canine adenovirus type 1 given experimentally to partially immune dogs did caused hepatitis and fibrosis. Others identified a suspected acidophil cell hepatitis virus in dogs that were vaccinated with liver homogenates from dogs dying from chronic hepatitis. The vaccinated dogs developed fibrosis and inflammation in their livers. Subsequent further research or publications into viral etiologies are lacking. Chronic hepatitis has also been associated with leptospirosis with the authors describing "atypical leptopsires" in a colony of dogs having hepatitis. However we have examined over 50 dogs livers havng hepatitis using PCR for Leptospirosis and did not identify a single positive case. Other infectious agents suggested as a possible etiology include *Helicobacter sp*, Bartonella, and Leishmaniasis.

Chronic liver injury has also been reported in dogs with aflatoxicosis as well as various drug-induced hepatitis. Some dogs treated with anticonvulsant drugs primidone, phenytoin and phenobarbital will develop chronic hepatitis. We have also observed some dogs treated with NSAIDs to also have hepatitis which asks the question of NSAIDs being related to hepatitis. In man alpha-1-antitrypsin (AAT- also referred to as alpha one protease inhibitor) deficiency is known to cause chronic hepatitis and cirrhosis. Investigation by researchers in Sweden using immunostaining for AAT in hepatocytes found some dogs with chronic hepatitis to be positive for ATT in the hepatocytes but the dogs differ from man in that serum AAT remained in the normal range while humans have low concentrations. It is not known if the AAT accumulation is the cause or the result hepatocyte damage. The breed most often associated with AAT accumulation is thought to be the cocker spaniel.

Finally immune associated hepatitis may also occur in the dog. Autoimmune liver disease in humans is an important cause of chronic hepatitis and is associated with diagnostic circulating autoantibodies. It appears that autoantibodies (ANA, antimitochrondial antibodies [AMA], smooth muscle antibodies [SMA], liver membrane autoantibodies [LMA]) are markers of autoimmune hepatitis in humans. A number of studies have been performed in dogs looking for liver associated antibodies and cell-mediated responses to support autoimmune disease as an etiology. Findings so far suggest autoimmune liver disease exists but studies fail to conclusively prove its existence. The pathogenesis proposed is that an insulting agent damages the hepatocytes thus releasing liver antigens that initiate a secondary immune response perpetuating chronic hepatitis. Nonetheless, immune-mediated mechanisms are thought to occur in some cases of chronic hepatitis and this is further supported by the fact that some dogs respond favorably to immunosuppressive therapy.

There are also a number of breeds that have an increased incidence of chronic hepatitis and are thought to be inherited. Some of these breeds have copper associated chronic hepatitis and are discussed below. Other breeds not yet associated with copper include the standard poodle, Cocker spaniel, Springer spaniel and Scottish terrier. The pathogenesis of the hepatitis is yet unknown. Cocker

spaniels both English and American tend to be more commonly males and ATT accumulation may play a role in their disease. More recently in Europe English Springer Spaniels have been reported to have a breed associated hepatitis. Standard poodles are more commonly females and tend to have prolonged survival with immunosuppressive therapy. We are currently studying the standard poodle at Colorado State University.

Clinical findings

The incidence of chronic hepatitis makes up approximately one fourth of the cases having liver biopsies at Colorado State University (based on a review of 150 consecutive liver biopsies). Chronic hepatitis is more common in female dogs. The average of presentation ranges from 4 to 10 years. It is interesting to note that in both our series and in studies by others it is uncommon to observe chronic hepatitis/cirrhosis in dogs older than 10 years of age. As a general rule old dogs (> 11 years of age) don't generally present with chronic hepatitis/cirrhosis or if they do they are at or near end stage disease.

The clinical signs parallel the extent of hepatic damage. Early in the disease there are usually no or minimal clinical signs. Only after the disease progresses do the clinical signs specific for liver disease becomes evident. Frequent early signs are gastrointestinal associated with vomiting, diarrhea and poor appetite or anorexia. Ascites, jaundice and hepatic encephalopathy may then occur as the disease progresses. With development of these late signs the long-term prognosis is generally poor.

The laboratory findings include consistently elevated ALT and ALP. The magnitude of rise need not be marked however. One report found 75% of the cases with abnormal bilirubin elevation (mean elevation of 2.6 mg/dl). Serum proteins are variable. As the lesions become more severe albumin levels decline. Serum bile acids are abnormal in most cases having significant chronic hepatitis and measurement of bile acids appear to be a good screening test for the patient with unexplained elevations in ALT and ALP. In our study all dogs evaluated with chronic hepatitis had abnormal bile acid concentrations. In a second study only 8/26 dogs with chronic hepatitis had normal fasting bile acids. However, postprandial samples were not determined in these cases. Determining postprandial bile acids has been shown to increase the sensitivity of this test.

A presumptive diagnosis is made based on the clinical features and persistent increases of ALP and ALT values. A definitive diagnosis requires a hepatic biopsy showing characteristic morphological patterns. Needle aspirates are not helpful in making the diagnosis of chronic hepatitis because it is important to see the architecture of the liver and location and extent of the inflammation. One must work with the pathologist when making the diagnosis of chronic hepatitis and to be certain that characteristic abnormalities found in chronic hepatitis are present.

Prognosis

There is little information of the prognosis with and without therapy. The prognosis in dogs with advanced chronic hepatitis and cirrhosis is guarded. In a study by Strombeck found mean survivals ranging from 6 to 16 months with therapy. This study also identified that dogs with hypoalbuminemia, hypoglycemia and coagulopathies have very guarded prognostic factors and many died within 1 week of diagnosis. A second study of 79 dogs found that dogs with cirrhosis had a survival of less than one month and dogs with chronic hepatitis had a mean survival in the range of about 20 to 30 months. Most of these dogs were not advanced in their disease and had concurrent corticosteroid treatment.

Treatment

I have four general goals in therapy: 1) remove the etiology, 2) provide an adequate diet, 3) give specific therapy and 4) providing general liver support. First step in the therapy for chronic hepatitis and other liver diseases involves removing the primary etiology if it can be identified. Short of treating the primary etiology all other therapies suggested are unproven in the management of liver disease in dogs. Much of the therapy is directed at providing adequate liver support. This often involves the use of multiple therapies.

Diet

Adjusting diet therapy should be considered in all cases however only general guidelines should be given. First, palatability is important to assure adequate energy requirements are met. Next, there is a misconception about diet and liver disease that liver patients should be placed on a protein restricted diet. Protein restriction should only be instituted in the patient that has clinical evidence of protein intolerance (i.e. hepatic encephalopathy). Diets low in copper are recommended for the dogs that have copper associated liver disease based on biopsy. Most formulated "liver diets" have lower copper concentrations and are often supplemented with additional zinc. Homemade diets can also be prepared that do not to contain excess copper. These diets should exclude liver, shellfish, organ meats and cereals that are all high in copper content. Vitamins or mineral supplements should not contain copper or iron.

Antiinflammatory therapy

Decreasing inflammation as a specific therapy for chronic hepatitis in the dog or cholangitis in the cat is unproven although the author's clinical impression suggests anti-inflammatory therapy is beneficial in some cases. The treatment of chronic hepatitis is quite controversial and there are as yet no good controlled studies in animals to support corticosteroids use in every case. Antiinflammatory therapy is indicated in suspected immune mediated chronic hepatitis. A suggested dose of 1 to 2 mg/kg/day using prednisolone

(prednisone requires hepatic biotransformation) should be instituted. When clinical improvement is suspected or after several weeks the dose is then gradually tapered eventually to a dose of 0.5 mg/kg/day or every other day. The only accurate way to evaluate a response to any therapy is to re-biopsy the patient in 6 months to 1 year because the patient will develop a concurrent steroid hepatopathy with increased liver enzymes making laboratory determination of any improvement impossible. Alternatively one could stop steroids and recheck enzymes in 1 to 2 months. We have more recently been using cyclosporine in many cases with a good clinical response. Our experience using 5 mg/kg bid or q 24 hrs (without steroids) has been very encouraging in dogs that are thought to have immune mediated chronic hepatitis. The veterinary formulation Atopica™ is a microemulsified preparation with the identical properties to Neoral™ (also sold as modified generic cyclosporine) that ensures more consistent bioavailability. With evidence of clinical response at 5 mg/kg bid I will often decrease to once a day therapy. Using cyclosporine alone one can follow the liver enzymes making the need for a liver biopsy less frequently required.

Antifibrotic drugs

Corticosteroids, zinc and penicillamine all have anti-fibrotic effects. Colchicine is a drug that has limited success I chronic hepatitis. Recently it was found that angiotensin II inhibitor Losartan (Zestril™, 0.25-0.5 mg/kg/Day) has effects in reducing or preventing fibrosis in humans by effecting function of stellate (fibrosis producing) cells.

Choleretic drugs

Decreasing cholestasis has been shown to be of benefit in humans and animals having cholestatic hepatobiliary disease. As serum bile concentrations increase (these are predominately cytotoxic bile acids) they can cause cell membrane permeability changes and fibrogenesis. Ursodeoxycholic acid (Ursodiol -Actigall™- 300 mg caps) is a choleretic agent developed to dissolve gallstones but later fond to have positive effects in patients with chronic hepatitis. This drug is a synthetic hydrophilic bile acid that essentially changes the bile acid pool from the more toxic hydrophobic bile acids to less toxic hydrophylic bile acids. Ursodeoxycholic acid has been shown to increase bile acid dependent flow, reduce hepatocellular inflammatory changes, fibrosis and possibly some immunomodulating effects. The hepatoprotective characteristics makes one believe ursodeoxycholic acts as an antioxidant. The dose for ursodeoxycholic acid is 15 mg/kg daily. No toxicity has been observed in dogs and cats at this dose. There has been a concern raised by some that it should not be used if there is any possibility of a bile duct obstruction for fear of biliary rupture. Although with obstruction surgery is indicated ursodeoxycholic acid is not a prokinetic and will not cause a rupture. In fact in experimental bile duct obstructions there was less secondary "toxic" changes in the liver in rats given ursodiol than placebo.

Antibiotics

Antibiotics are indicated for primary hepatic infections. There however may be evidence that bacterial colonization may take place in a diseased liver. Kupffer cell dysfunction could be a reason for secondary bacterial infections. It may be prudent for antibiotic therapy or trial for several weeks in patients having significant hepatic disease (i.e. chronic hepatitis). Amoxicillin, cephalosporin, or metronidazole are suggested. Metronidazole may have some immunosuppressive properties as well as antibacterial mechanisms. For liver disease I would use 7.5-10 mg/kg bid a much lower dose used for other bacterial infections because of hepatic metabolism of the drug.

Antioxidants

There has been recent interest in the management of certain types of liver disease using antioxidants. Antioxidants in general provide liver support to promote optimal hepatic function. Considerable evidence shows that free radicals are generated in chronic hepatitis and participate in the pathogenesis of oxidative liver injury in dogs and cats.

Vitamin E, d-alpha tocopherol, functions a major membrane bound intracellular antioxidant, protecting membrane phopspholipids from peroxidative damage when free radicals are formed. Vitamin E is shown to protect against the effects of copper, bile acids and other hepatotoxins. In a small study of dogs having chronic hepatitis we found all dogs had evidence of oxidative damage. In a three-month placebo controlled study treating only with vitamin E there was evidence improvement in the oxidant status of the treated dogs however we did not identify changes in clinical, laboratory or histology during this short treatment period. A suggested vitamin E dose is 50 to 400 IU a day. The d-alpha tocopheryl formulation is much more potent than the most common commercial form (dL-alpha tocopheryl). Since bile acids are required for fat-soluble vitamin E absorption and may be reduced in cholestatic liver disease, a water-soluble formulation is suggested. For a water soluble form I use Twin labs Liqui-E. The vitamin E is derived from TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate) and has a rapid absorption. Because of the potential benefits of vitamin E, the lack of side effects and since the drug is inexpensive I place most all my liver patients on E therapy.

S-Adensosylmethionine (SAMe) is a naturally occurring molecule found in all living organisms and is involved in a number of metabolic pathways that appear to be beneficial to the liver as well as other tissues. SAMe is involved in three major biochemical pathways. It is involved in cell replication and protein synthesis, has a modulating influence on inflammation and plays a role as a precursor of the antioxidant glutathione in the hepatocyte. Research has demonstrated that the exogenous administration of SAMe to have potential beneficial effects for a number of types of liver damage. In one study giving acetaminophen to cats at a sub-lethal dose we observed protective effects of SAMe when measuring markers of hepatic oxidative damage and RBC fragility. Studies investigating naturally occurring liver disease in animals are required to determine the benefit of SAMe administration in liver disease.

I will routinely prescribe SAMe (Denosyl™) in patients having acute liver toxicity and in many cases having chronic liver disease or other liver disorders. A recommended dose range is 20 mg/kg/day. It should be given on an empty stomach and the tablets not broken. There are numerous commercial sources of SAMe each having variable concentration or purity of the compound. Foil wrapped tablets produced by a company that provides reliable purity and potency is recommended.

Milk thistle has been used for centuries as a natural remedy for diseases of the liver and biliary tract. Silymarin the active extract consists of bioflavonoligans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Several recent human clinical trials have assessed the efficacy of silymarin in the treatment of liver disease. The data is somewhat difficult to interpret because of the limited number of patients, poor study design, variable etiologies, lack of standardization of silymarin preparations with different dosing protocols. There is however compelling evidence to suggest silymarin has a therapeutic effect in acute viral hepatitis, alcoholic liver disease, patients with cirrhosis, and in toxin or drug-induced hepatitis. Unfortunately, the purity of commercial products, and therapeutic dosage is unknown. Clinical trials are limited in small animals and reported success is only anecdotal. Dosage of milk thistle ranges from 50 to 250 mg bid. Milk thistle is reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects. To date there is only one published clinical study evaluating the efficacy of silymarin in the treatment of liver disease in dogs. In this placebo controlled experimental study dogs were poisoned with the *Amanita phalloides* mushroom. Researchers showed silymarin to have a significant effect on liver enzymes, the extent of histological liver damage and survival outcome. Based on this canine study and several clinical reports in humans poisoned with *Amanita* and treated with silymarin having a favorable outcome many physicians in Europe now accept silymarin as part of the standard protocol for mushroom poisoning.

General support therapy

The remainder of the therapy for chronic hepatitis involves treatment of secondary complications. These occur as the disease becomes advanced. Hepatic encephalopathy, GI ulceration and ascites are common clinical occurrences in advanced hepatitis or cirrhosis.