Abstract

Chronic hepatitis is a relatively common cause of infiltrative hepatic disease in dogs. If diagnosed early enough, many patients can be successfully treated. Biopsy is necessary for diagnosis, but it is critically important to take high quality samples from multiple lobes.

Introduction

Chronic hepatitis is probably one of the main reasons it is a good idea to biopsy dogs’ livers. It is a reasonably common disease, and a lot can often be done for the dog if you diagnose it before the hepatitis causes cirrhosis. Chronic hepatitis can be found in almost any breed of dog, although Doberman pinchers (especially young to middle-aged females) seem to have a very high incidence of the disease. There are several clinical presentations of this disease. First, one may see a chronically ill dog with high ALT and SAP. Second, one may be presented with a dog that was normal until it was stressed (e.g., underwent surgery or anesthesia). Third, one may see a dog that was normal until a few days ago but that now suddenly presents with signs of hepatic failure and is found to have an absolutely end stage cirrhotic liver (see discussion under cirrhosis) even though the clinical signs have only been present for 1-3 days. Finally, one may see a clinically normal dog that has an increased ALT that was fortuitously found during routine health screening or during a preanesthetic work up for a dental. The ALT typically remains increased despite the dog acting and appearing fine. Chronic hepatitis is more common than many people realize and is one reason why it is better to biopsy clinically normal dogs with persistent increases in ALT rather than wait until clinical signs occur.

Treatment of chronic hepatitis usually centers around a) removing the cause, if possible, b) administration of anti-inflammatory therapy (i.e., steroids, azathioprine), and c) administration of supportive therapy (i.e., ursodeoxycholic acid and anti-oxidants).

Two causes of chronic hepatitis that you might be able to remove are drugs and copper. Copper is a bit
confusing in that it can be the cause of chronic hepatitis, it can be secondary to chronic hepatitis but not causing a clinical problem, and we think that it can sometimes be secondary to chronic hepatitis and yet be severe enough to cause disease in and of itself. There has been one report that seemed to show that removing copper from the liver of dogs with chronic hepatitis in which the copper accumulation clearly appeared to be secondary to the hepatic disease was clinically beneficial to the dogs. You can measure copper levels in biopsies, or you can do special stains on hepatic biopsies. If you are in doubt as to how significant the hepatocellular copper is, it is probably best to just remove it. If the decision is made to remove copper, then one may elect oral zinc therapy before meals or copper chelation with d-Penicillamine. Feeding a copper restricted diet is reasonable; but, feeding a copper restricted diet by itself often will not lower hepatic copper concentrations sufficiently. One exception to this may be the Labrador retriever. Chelator therapy or zinc therapy must also be used. D-Penicillamine (10-15 mg/kg bid) is the drug typically used to lower hepatic copper concentrations. This drug occasionally causes vomiting, and administering it with food seems to lessen that problem. Trientine is another copper chelator (Cuprimine) that is also effective (10-15 mg/kg bid) and seems to have fewer side effects than d-penicillamine. If the dog is clearly being intoxicated by very large concentrations of hepatic copper, chelators should be used.

Zinc can be used to prevent copper accumulation, but it can also act as an antifibrotic agent. Various forms can be given, but the idea is to administer approximately 100 mg of elemental zinc daily for 3-6 months and then decrease it to about 50 mg daily. Zinc should be administered on an empty stomach, and generally should not be given with copper chelators. Be aware that zinc administration can rarely cause hemolytic anemia, and periodic blood zinc measurements are not a bad idea in patients receiving zinc therapy.

Dogs with chronic hepatitis not due to copper accumulation or drugs often need anti-inflammatories, and this usually includes glucocorticoids. However, it seems important to use the lowest effective dose of the corticosteroid. If you give too much corticosteroid to a dog with steroid-resistant hepatic disease, you may create a vacuolar hepatopathy in addition to the preexisting hepatic disease. When corticosteroids are used for this disorder, they should typically be used at an anti-inflammatory dose (1 mg prednisolone/kg/day) and then tapered quickly. The steroid treatment should be for relatively short periods of time (i.e., until a week or two after clinical signs substantially diminish or disappear). Severely affected patients and patients that require excessive amounts of corticosteroids may benefit from azathioprine or cyclosporine therapy. Azathioprine may cause severe hepatic disease, but this appears to be an idiosyncratic reaction, possibly due to differences in the rate of metabolism of the drug in different dogs. I do not hesitate to use azathioprine when it seems like it may be helpful. Indications seem to be when steroids are insufficient to control signs, when excessive doses of steroids are required to control signs but cause substantial side effects, and when very severe hepatic disease is found on the initial biopsy. While 1 mg/lb daily is a commonly quoted dose, I typically give azathioprine at the same dose but only every other day, which seems to be much safer.

Supplementation with B-complex vitamins is probably useful. Occasionally a bleeding diathesis is present and you can try supplementing vitamin K₁ (1 mg/kg/day, given SQ). Theoretically, antibiotics may be used to try to decrease the number of bacteria coming out of the intestines and into the portal circulation. Amoxicillin is often used for this purpose.
Patients with hepatic disease may also benefit from supportive therapy, especially those drugs and neutroceuticals that are antioxidants. Antioxidants (i.e., vitamin E, s-adenosyl-L-methionine, silymarin, phosphatidylcholine, vitamin C, N-acetylcysteine) and ursodeoxycholic acid are what should be called “hepatosupportive” therapy. These drugs will generally not cure severe disease all by themselves, but they can substantially help the patient if appropriate therapy is being directed at the primary cause. In general, antioxidants are poorly effective if used as single drugs. Rather, antioxidant therapy is best accomplished if multiple drugs are used simultaneously.

**Vitamin E** (400-500 units per day) seems to have substantial anti-oxidant capabilities and is widely used. The d-alpha form is the effective form; the l-isomer is inactive. We prefer to use the water soluble form, hoping that it has better bioavailability. Vitamin E is very safe as long as it is not grossly overdosed. **Vitamin C** might be helpful, but there is evidence that it might make some forms of hepatic disease worse, especially those with disease due to copper or iron accumulation in the hepatocytes. Therefore, it is very useful to have a hepatic biopsy since some dogs with chronic hepatitis accumulate copper while others do not. **S-adenosyl-L-methionine** (20 mg/kg sid) is a neutroceutical that appears to have benefit in some patients with hepatic disease. It increases hepatic glutathione concentrations as well as enabling a variety of important, intermediary metabolism reactions. The drug appears to have no adverse effects, and there is good evidence that it helps protect against alcoholic hepatitis in people. It should be given on an empty stomach, and the patient should not be feed for 30 minutes. It comes in foil-wrapped, enteric coated tablets. **Phosphatidylcholine** seems to have some potential for preventing fibrosis and protecting hepatocellular membranes. It also appears to increase the bioavailability of other drugs (e.g., silybin). The dose in dogs and cats is unknown, but people generally take 3-9 grams daily, in divided doses. **Milk thistle** (silymarin) (4-8 mg/kg/day OR 50-250 mg/day) is a herbal treatment that has proven efficacy in some diseases (e.g. Amanita mushroom poisoning). There are different active fractions, and silybin seems to be the most active. There is one preparation in which silymarin is complexed with phosphatidylcholine (i.e., Marin by Nutramax) which seems to have increased uptake and bioavailability. **N-acetylcysteine** can be obtained from the health food store. It is an anti-oxidant, and has been given to dogs and cats at a dose of 70 mg/kg tid. It seems to be safe, but should be given on an empty stomach. It seems that s-adenosyl-L-methionine is probably effective in promoting intracellular glutathione concentrations. It is important to note that administering glutathione orally is ineffective; the orally administered drug will not increase intracellular glutathione concentrations. **Superoxide dismutase** has been tried recently, but its effectiveness is very uncertain at this time.

**Ursodeoxycholic acid** (15 mg/kg/day) is beneficial because of its ability to displace more toxic hydrophobic bile acids from the hepatocyte membrane. Like the antioxidants, it generally should not be used as sole supportive therapy. It seems to work best if combined with anti-oxidants.

Copper storage is reported in Bedlington terriers, where it commonly causes chronic hepatitis that progresses to cirrhosis. West Highland White terriers often have excessive hepatic copper accumulation, but it is different than what is found in Bedlington terriers and seldom causes clinically significant hepatic disease. Dalmatians, Labrador retrievers and Skye terriers have recently been reported to have a copper-associated hepatic disease in which accumulation of copper by the liver may be the cause of the clinical disease. Recently, there is increased concern that many dog foods have increased amounts copper that is more bioavailable than

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before, making it easier for some breeds (e.g., Labrador retrievers) to accumulate toxic amounts and develop chronic hepatitis. Biopsy with special stains or preferably quantitated copper analysis performed on frozen hepatic tissue is required for diagnosis.

Cirrhosis is an end-stage hepatic disease that may be caused by various problems, especially chronic hepatitis. In particular, Cocker spaniels seem to have a distinct genetic predisposition to having cirrhosis at inordinately young ages (i.e., < 5 years of age).

**Selected readings:**