Chronic Hepatitis/Chronic Active Hepatitis in Dogs

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INFLAMMATORY DISEASES

Inflammation or necrosis characterizes the majority of hepatic diseases diagnosed in clinical practice. From a biochemical standpoint, inflammation is defined as significant elevation in the enzymes associated with hepatocellular injury-serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and arginase. Most hepatic diseases associated with significant functional impairment will have increases in ALT concentrations.

Chronic Hepatitis
Chronic Active Hepatitis

Chronic hepatitis is an important clinical syndrome in dogs. In addition to an idiopathic group, several other disorders are now recognized that present as chronic hepatitis but do not appear to have an immune mediated basis. The most important of these disorders include: chronic hepatitis in Bedlington terriers; copper associated hepatitis in West Highland white terriers; chronic hepatitis in Doberman pinschers; leptospirosis associated hepatitis; lobular dissecting hepatitis; idiopathic hepatoportal fibrosis; and chronic hepatitis associated with infectious canine hepatitis virus. Differentiating between these diseases usually requires hepatic biopsy. Because prognosis and therapy vary widely within this clinically homogeneous group of diseases, clinicians should make every attempt to be as precise in their diagnostic efforts as possible.

Much of what we know about chronic hepatitis in dogs has been extrapolated from findings in humans with chronic liver disease. Whether dogs or cats are truly affected by immune-mediated liver disease remains to be proven. Even more important is whether glucocorticoids and other immunosupressive drugs should be used indiscriminately in the therapy of so-called idiopathic canine chronic active hepatitis.

Chronic active hepatitis (CAH) refers to an etiologically diverse group of diseases which have widely varying clinical, biochemical, and therapeutic responses and are linked solely by histologic similarities. CAH is not a final diagnosis; it is a label for a group of diseases that tend to progress to cirrhosis but that require different therapeutic approaches.

Chronic Hepatitis in Dogs

The complete spectrum of chronic hepatitis in dogs is just beginning to be realized. During the past several years a number of newly recognized causative agents for chronic hepatitis have been identified in dogs. In addition, several breeds of dogs appear to have a genetic predisposition to develop chronic inflammatory liver disease· Lastly, several reports have been published describing an entity in dogs considered similar to idiopathic or autoimmune CAH in humans. There is a great deal of overlap between these three areas

Idiopathic Chronic Active Hepatitis in Dogs

Chronic active hepatitis appears to the disease of the 1980's in veterinary hepatology. Unfortunately, this diagnostic designation has been applied indiscriminately to virtually any inflammatory liver disease that persists for a few weeks and has lesions even remotely resembling those seen in human CAH. This lack of diagnostic specificity results from semantic differences between authors, poor definition of diagnostic criteria, unknown specificity of diagnostic tests, lack of available supportive immunodiagnostic tests, and lack of controlled therapeutic trials. Clinical signs are non specific with depression, weakness, and anorexia present in most dogs. In addition, polydipsia and polyuria, jaundice, and encephalopathy may be seen. Serum ALT concentrations are generally quite high (mean 15 times normal), serum AP concentrations average five times normal and the increase in total bilirubin averages 2.6 mg/dl). The retention of BSP ranges from 6 to 48 per cent (mean = 33 per cent). Hypoalbuminemia and hypergammaglobulinemia are occasionally identified. Hepatic biopsy information is the primary diagnostic test to make the diagnosis of CAH and can be used to determine whether glucocorticoids are utilized.

The designation of a liver disease as chronic is often based on historical information (often unreliable), repetitive biochemical evaluations (often not obtained), or histopathologic findings supporting chronicity (fibrosis), also frequently unavailable. Currently, 12 weeks has been suggested as sufficient time for a chronic designation to be applied to dogs with liver disease. Active liver disease means evidence for continuing inflammation or necrosis, which is most easily determined via laboratory evaluations of serum aminotransferases. Serum alanine aminotransferase concentrations have been stated to average 15 times normal in canine CAH, however, reported cases of presumed canine CAH have had ALT concentrations within the normal range.

Immunologic criteria to support an immune mediated basis for this disease in dogs are also lacking. Some cases have been found to have elevated IgG concentrations, a non-specific finding in many chronic liver diseases. Occasional dogs have titers against nuclear protein (ANA positive) or abnormal LE cell phenomena, but the significance of these findings is unresolved. Measurements of antibodies against mitochondria, smooth muscle or liver specific antigens have not been reported.

Biopsy data provide the most specific information for diagnosing CAH. Lesions compatible with human CAH have been used by most investigators to substantiate this diagnosis in dogs. Unfortunately, biopsy alterations are not pathognomonic for CAH and great care must be taken not to overinterpret histologic findings.

The situation as it stands today regarding idiopathic chronic active hepatitis in dogs is anything but resolved. A group of dogs exists in which there is biochemical evidence for chronic hepatitis, no cause has been identified, and biopsy features resemble CAH. Establishing a diagnosis of idiopathic CAH should involve several steps. First, it should be confirmed that active liver disease exists. This can be done by using the clinical history and and appropriate biochemical tests (ALT, AST). If no identifiable cause can be found and the patient has mild or intermittent disease, it is likely that only supportive care will be necessary (no steroids). If the dog's signs worsen or there is evidence biochemically of a continuing necroinflammatory process or that the disease is chronic, a liver biopsy should be obtained. Biopsies should be reviewed by pathologists with knowledge of the features of CAH. Veterinarians should send as much pertinent clinical data as are available to assist the pathologist in establishing a diagnosis, since

biopsy data are only one piece of this diagnostic puzzle. If the biopsy findings are compatible with idiopathic CAH, immunosupressive therapy should be considered along with general supportive and symptomatic measures.

Therapy of Canine CAH

The therapy of idiopathic chronic active hepatitis combines supportive and symptomatic care with specific imunosupressive therapy.

Only those drugs unique to the therapy of CAH will be discussed here. These drugs include glucocorticoids, azathioprine, d-penicillamine, and polyunsaturated phosphatidylcholine. Glucocorticoids are used alone or in combination with azathioprine (Imuran). Only one report of clinical usage of steroids in canine CAH has been published. Five of nine dogs treated with steroids were considered to have improved. However, multiple approaches to therapy were utilized in this group of dogs and no control group was evaluated, making conclusions speculative at best. Until results of well controlled clinical trials become available, the author has the following recommendations. Dogs should be given 1 mg/lb/day of prednisone for 10 to 14 days. Dosages are decreased by 25 percent every week thereafter until a maintenance dosage of approximately 0.25 mg/lb/day is achieved (one month), at which time dogs should be reevaluated both clinically and biochemically. If improvement is noted, this dosage should be continued for another month and then decreased to alternate day therapy. A recheck at this time should determine whether continued steroid therapy is indicated. If the dog is active, alert, eating well and biochemical profiles are improving, consider withdrawing steroids. Because of the profound effect of glucocorticoids on canine hepatic enzymes, it may be difficult to determine if the dog's disease is improving or not unless functional tests are also run, e.g., serum bile acids, albumin concentrations, BSP retention, ammonia tolerance. The dog must be reassessed following steroid withdrawal to determine if the disease is reoccurring. If relapses occur, reinitiation of steroid therapy is indicated. The optimal duration of such therapy is totally arbitrary, and good clinical judgement is necessary here.

If glucocorticoids are poorly tolerated by the dog, consideration should be given to decreasing the steroid dosage to one that is tolerated and adding azathioprine at 0.45 mg/lb/day (1 mg/kg/day) to the therapy. Hemograms must be monitored at 2 to 3 month intervals when azathioprine is being used. This regime has been reported to result in clinical remission in dogs with chronic hepatitis.

Ursodeoxycholic acid (Actigal) may also be beneficial in selected dogs with CAH due to its ability to modify the toxic effects of retained bile acids. Five to ten milligrams/kg/os once daily may be added to other therapeutic agents. If the total bilirubin or serum bile acids are within normal limits, Actigal would not likely be of therapeutic benefit.

If significant fibrosis is detected on histopathology of the liver, then the addition of cholchicine at 0.03 mg/kg once daily may also help to reduce progression of fibrosis in some dogs. Gastrointestinal side effects (vomiting, diarrhea) may prevent continuation of this therapy, however.

Therapy using d-penicillamine in the dog for CAH should be considered if steroids and azathioprine are ineffective. No data are available for dogs supporting its efficacy in CAH. It has had limited clinical trials in humans as an antifibrotic drug. Steroids have not been effective in reversing or delaying hepatic fibrosis in human CAH, while penicillamine has been shown to have a beneficial effect. The dosage for this drug in dogs is 4.5 to 6.8 mg/lb (10 to 15 mg/kg) given every 12 hours.

The use of polyunsaturated phosphatidylcholine in canine CAH should be considered experimental. Histologic evidence of significantly decreased disease activity was found in patients receiving this drug in combination with prednisone and azathioprine who had failed to respond to the latter two drugs. Human recommended dosages are 3 grams/day. Experimental animals (rabbits) have been given 45 mg/lb/day (100 mg/kg) in experiments to try and define the mechanism through which this drug alters the immune system.

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