J Vet Clin 23(1) : 72-76 (2006)

Journal of Veterinary Clinics
www.ksvc.or.kr

Hepatic Cirrhosis Secondary to Chronic Hepatitis in an English Cocker Spaniel (ECS) Dog

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(Accepted: February 28, 2006)

Abstract: A 1-year-old, female English cocker spaniel (ECS) dog was presented with 3-month history of vomiting and retaking of the vomitus, and chronic weight loss. The client had noticed mild abdominal distension 10 days before. The dog was diagnosed as chronic hepatitis with hepatic cirrhosis based on complete blood count (CBC), serum chemistry profiles, radiography, ascites assessment, bile acid evaluation, and liver biopsy through exploratory laparotomy and necropsy. CBC and serum chemistry profiles revealed mild anemia, slightly elevated hepatic enzymes (ALT and AST), increased creatinine kinase (CK), hyperammonemia, and hypoproteinemia with hypoalbuminemia. Ascites was transudate according to analysis of components. Bile acid assessment (fasting; 174.4 μmol/L and postprandial; 198.4 μmol/L) showed strongly suspected hepatic insufficiency. On radiological findings, ascites was evident. Atrophied liver (especially left side lobes) and distended mesenteric vasculatures were observed by exploratory laparotomy. Histopathological examination of marginal lesion of left lateral lobe of liver by biopsy revealed the necrosis of hepatic cells, dilation of sinusoids, infiltration of neutrophils in sinusoids, and vacuolation of hepatic cytoplasm. The patient had been managed with careful low protein diet and specific supportive therapy (ursodeoxycholic acid, prednisolone, vitamine E, and interferon). Vomiting and ascites disappeared with medical management. The dog was monitored periodically by CBC, serum chemistry and radiographic examination. The dog survived more 18 months with medical therapy. After spontaneous death, necropsy and histopathologic examination were performed.

Key words : chronic hepatitis, hepatic cirrhosis, English cocker spaniel, ascites.

Introduction

Chronic hepatitis (CH) is a heterogenous group of inflammatory-necrotizing diseases of the liver (8). CH is often perceived as a frustrating disease with inevitable progression to cirrhosis and thus a poor prognosis. However, the liver has remarkable regenerative capacity, as has been repeatedly demonstrated in canine hepatectomy models (24,25) and recent observations in humans have even suggested that fibrosis and cirrhosis may be reversible given the right conditions and treatment (4). The majority of cases of CH in human have a defined etiology and prognosis and well-understood treatment recommendations are usually based on large trials and meta-analysis (10,20). This allows an 'evidence-based' approach to treating human CH. By contrast, veterinary understanding of the causes of canine CH has changed very little in the last 30 years, with the exception of copper storage disease in the Bedlington terrier (11,14,15,22,27,30). Although there are many potential causes of CH in dogs, the cause, pathogenesis, natural history, and optimal treatment of these disorders in dogs are unknown. The majority of cases remain 'idiopathic', the treatment non-specific, empirical, and symptomatic and the prognosis unclear. Therefore, evidence-based medicine is almost impossible to apply for the therapy of canine CH.

This report describes a case of CH followed by hepatic cirrhosis in an English cocker spaniel (ECS) dog.

Case

A 1-year-old, intact female, ECS dog was presented to the Veterinary Medical Teaching Hospital of Konkuk University for 3-month history of vomiting and retaking of the vomitus, chronic weight loss, malodorous urine, and recent abdominal distension. The owner reported that 10 days prior to presentation, the client detected the suspended abdomen after trimming.

On presentation to the veterinarian, the patient was mildly depressed but alert and responsive. The dog had a body condition score of 2 out of 5 and weighed 7.12 kg. The dog's

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abdomen was flexible and distended. She was feverish (39.48°C) and gallop rhythm was checked during auscultation.

Complete blood count (CBC) analysis demonstrated mild non-regenerative anemia (RI=0.98). The serum biochemical profile revealed elevated alanine aminotransferase (ALT, 192 U/L) and aspartate aminotransferase (AST, 82 U/L), hyperammonemia (348 μmol/L), hypoproteinemia (4.5 g/dl), and hypoalbuminemia (2.3 g/dl). Assessment of ascites showed the characteristics of transudate (total protein; 0.3 g/dl, total nucleated cell count; 720/μl, transparent color). Bilirubinuria, proteinuria, and struvite crystals were observed by urinalysis. On fecal examination, there were no evidences of endoparasitism and intestinal hemorrhage. Serum bile acids test showed marked elevation in concentrations of both fasting (174.4 μmol/L) and postprandial (198.4 μmol/L) serum bile acids. Detection of canine adenovirus type I from the patient's serum by polymerase chain reaction (PCR) was negative. An abdominal radiograph revealed increased fluid opacity within the abdomen causing severe loss of serosal surface visualization (Fig 1). Also, the abdomen was pendulous. The exploratory laparotomy was performed and atrophied liver (especially left side lobes) and distended mesenteric vasculatures were confirmed (Fig 2). Finally, suction of 1.5 liter of abdominal fluid and liver biopsy were accomplished. The histopathology of the liver, however, showed the necrosis of hepatic cells, dilation of sinusoids, infiltrations of mainly neutrophils and a few lymphocytes, and vacuolization of hepatic cytoplasm, meaning hepatic inflammation (Fig 3).

Treatment was just supportive therapy, supplying ursodeoxycholic acid (Usosan®, Korea United Pharm., Korea, 10 mg/kg, P.O., SID), silymarin (Silymarin®, Sin-il Pharm, Korea, 50 mg/kg, P.O., SID), vitamin E (CVS Pharmacy, USA, 600 I.U./day, P.O., SID), prednisolone (Prednisolone®, Korea Pharma Co., Korea, 1 mg/kg, P.O., BID, tapered), and Interferon (α-feron® , 30 I.U./dog, P.O., SID). Prescription diet (k/d, Hill's science, USA) was supplied. There had been no vomiting or regurgitation episodes, and also urine crystals and ascites had disappeared after medical therapy. Even though iatrogenic Cushing's disease occurred due to long-term corticosteroid medication, the dog survived for 18 months with medical therapy. When we tapered the steroid dosage, clinical signs relapsed. We performed necropsy after spontaneous death. Histologically there was a wide range of hepatic structure. Histopathologic evaluation of the liver revealed lymphocytes infiltration in hepatocytes, fatty liver and advanced hepatic cirrhosis around the hepatic lobules (Fig 4). On Rhodanine stain, the copper granules in the liver were not detected.

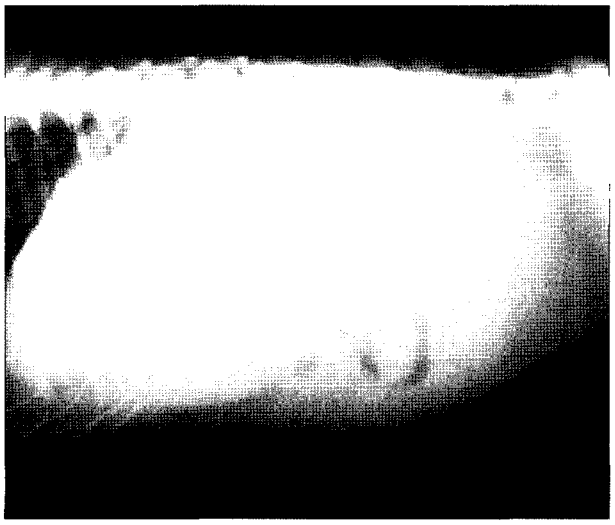

Fig 1. On lateral abdominal radiography, homogeneous fluid opacity is uniformly distributed throughout the abdominal space. There is severe loss of serosal surface visualization.

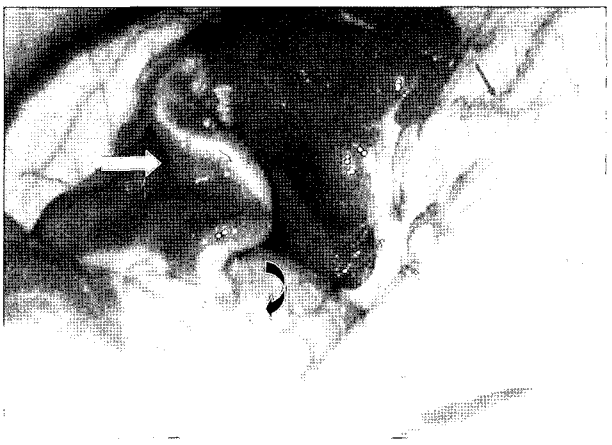

Fig 2. The exploratory laparotomy was performed for definitive diagnosis and atropied liver (especially left side lobes; large arrow) and distended mesenteric vasculatures (small arrow) were shown. Gallbladder was markedly dilated (curved arrow).

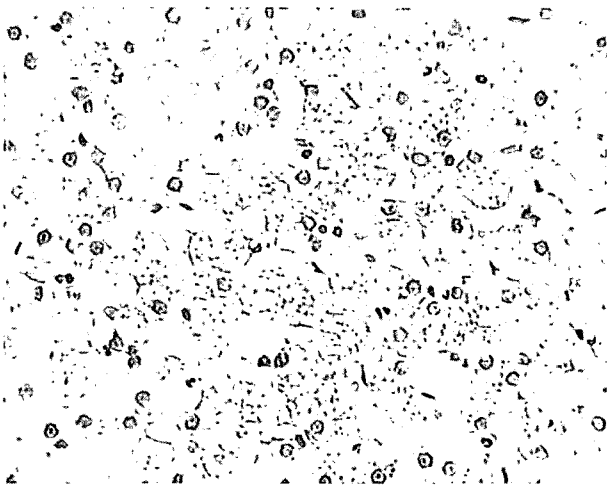

Fig 3. The histopathologic finding of the liver showed necrosis of the hepatic cells, dilation of sinusoids, a few number of neutrophils, and vacuolization of hepatic cytoplasm.

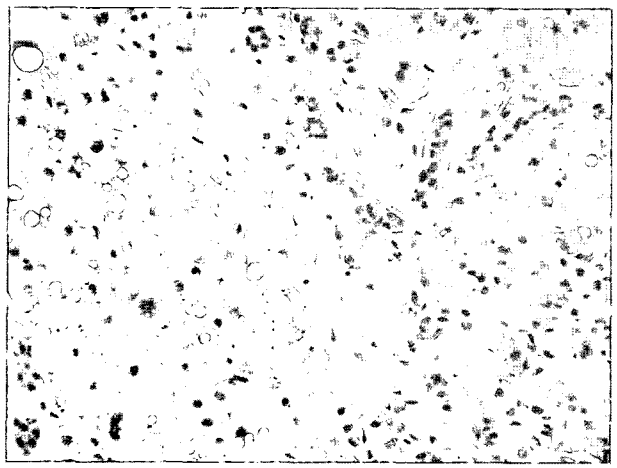

Fig 4. Necropsy was performed after spontaneous death of the patient dog. The cytoplasm of the hepatic cells contains large and small vacuoles which had contained fat and glycogen and dense fibrous tissue extends through the liver.

Discussion

Causes of CH in dogs are usually unknown and the diagnosis is therefore non-specific (31). The current understanding about the underlying etiology of CH in dogs includes 5 categories. '*Infectious causes*' are the first category. Unlike in man, the search for infectious causes of CH in dogs has been largely unfruitful. Two viruses have been suggested as possible causes of canine CH: canine adenovirus type I (6,9,21) and canine acidophil cell hepatitis virus (16,17). Bacterial infection with 'atypical' leptospires may be a significant and underestimated cause of CH in dogs (1,5). Next category is '*Toxic and drug-induced CH*'. Toxins and drug reactions usually cause acute, necrotizing hepatitis (29) but some can cause CH. Third category of causes of CH in dogs is '*Breed-related chronic hepatitis and copper storage disease*'. A familial predisposition to develop CH has been suggested by demographic studies, pathologic surveys, and clinical case series. Breeds of dogs at increased risk for CH include the Bedlington terrier (11,28), West Highland white terrier (26), Doberman pinscher (7,19), American and English cocker spaniel (2,12,23), Skye terrier (13), Labrador retriever (2), and standard poodle (3,18). Even if the cause of CH and liver failure in cocker spaniels is unknown, American and English cocker spaniels have an increased incidence of CH and cirrhosis. Fourth category is '*Other metabolic diseases*'. Accumulation of other metals in the liver has been very little investigated in dogs. Fifth category is '*Autoimmune hepatitis*'. Autoimmune hepatitis is an important cause of non-viral CH in man but has never been demonstrated to exist in dogs.

We ruled out above possible factors of CH in this case report. Then, '*Breed-related chronic hepatitis and secondary cirrhosis*' was strongly suspected.

In this case, the key points of diagnosis were histopathology and serum bile acids test. The bile acids test not only rules out a portosystemic shunt (PSS), but also gives a baseline measurement of liver function. Disruption of the enterohepatic circulation of bile acids results in increases in the concentration of total serum bile acids (TSBAs). Animals with significant extrahepatic or intrahepatic shunting often have normal or mildly elevated fasting TSBAs. This patient's fasting TSBAs revealed 174.4 μmol/L, meaning severe hepatic dysfunction.

CH can progress to hepatic cirrhosis (end-stage liver disease). Hepatic cirrhosis is characterized by fibrosis and regenerative nodules that result in disorganization of the hepatic architecture (8). On first histopathologic examination of liver, the most significant changes in biopsy sample were diffuse inflammation with the necrosis of hepatic cells and sinusoidal dilation. However, cirrhotic changes were not shown. The dog showed definitive progress from CH to hepatic cirrhosis according to final necropsy and histopathological examination. Cholestasis in hepatocytes is increased significantly in dogs with progressed CH. Unfortunately, mesenteric jejunal portography was not able to be performed.

PSSs are vascular problem between the portal and systemic venous systems. Therefore, hepatic histopathology is different from liver of CH. Liver biopsy of PSS patient most consistently reveals hepatocytic atropy with small or absent portal veins and arteriolar hyperplasia, although biopsy abnormalities may be subtle. And signs of hepatic encephalopathy usually predominate.

It is obvious from the inadequacy of our knowledge of the causes of canine CH that treatment is, in most cases, empirical and non-specific (31). Although there are a lot of recommendation of therapeutic medication, there have been no systemic clinical trial of specific therapy.

Conclusion

We report the clinicopathological and histopathological features of CH with hepatic cirrhosis in a dog.

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잉글리쉬 코커스파니엘 견에서 발생한 만성 간염 및 간경화 증례

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요 약 : 1년령의 암컷 잉글리쉬 코커스파니엘 견이 3개월 병력의 구토와 구토물의 재섭취, 그리고 체중감소로 내원하였다. 이 환자는 일반혈액 검사, 혈청화학 검사, 방사선 검사, 복수 분석, 담즙산 농도 측정, 탐색적 개복술, 그리고 사후 부검을 통한 간 생검으로 만성 간염 및 간경화증으로 진단되었다. 혈액 검사상 경미한 빈혈, 경미한 간효소치의 상승, CK치의 상승, 저알부민혈증을 동반한 저단백혈증이 관찰되었다. 복수는 분석을 통해서 누출성 복수인 것으로 판명되었다. 담즙산 농도를 측정해 본 결과(fasting; 174.4 μmol/L and postprandial; 198.4 μmol/L)로부터 간기능 부전을 강하게 의심할 수 있었다. 방사선 검사상 복수가 관찰되었고 결국 탐색적 개복술을 실시하여 좌측엽 부위의 간 위축, 장간막 혈관 구조들의 팽창된 소견이 관찰되었다. 간 좌측 후엽모서리 부위에서 봉합법을 통해 생검을 실시하였다. 간 조직의 조직병리학적인 검사 결과 간 세포의 괴사, 동양 혈관의 확장, 동양 혈관 내 호중구의 침착, 그리고 간세포질의 공포화 등이 관찰되었다. 환축은 저단백 사료 급여 그리고 특수보조제 (ursodeoxycholic acid, prednisolone, vitamine E, and interferon)등을 사용하여 관리했다. 구토와 복수는 치료 후 사라졌다. 환축은 정기적으로 혈액 검사, 혈청 화학 검사, 방사선 검사 등을 실시하였다. 이 환축은 내과적인 치료를 받으며 18개월간 생존하였다가 폐사하였다. 사후 부검을 실시했고 조직병리학적인 검사가 시행되었으며 그 결과 간세포에 림프구의 침윤된 진행성의 간경화증으로 판정되었다.

주요어 : 만성간염, 복수, 잉글리쉬 코커 스파니엘