Case Report
Destructive Cholangitis in an Adult Jack Russell Terrier

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A 4-year-old female Jack Russell terrier dog exhibited vomiting and severe jaundice of the visible mucous membranes and skin. Ultrasonography revealed diffuse areas of high echogenicity and focal areas of low echogenicity in the left lobe of the liver. On macroscopic observation of the biopsied liver specimen, many scattered irregularly shaped red spots were observed on the liver surface and on the cut surface. Histopathologically, there was loss of the interlobular bile duct and cholangitis accompanied by infiltration of pigment-laden macrophages in the Glisson's capsule. Therefore, in the present case the dog was diagnosed with destructive cholangitis.

1. Introduction
Destructive cholangitis is characterized by the loss of bile ducts in area for Glisson's capsule. This condition induces severe intrahepatic cholestasis, icterus, and eventually, hepatic failure. In humans, bile-duct loss occurs with primary biliary cirrhosis, hepatic allograft rejection, and idiopathic adulthood ductopenia [1–3]. The pathogenesis of bile-duct loss includes immunological, infectious, ischemic, and toxic factors [4]. On the other hand, bile-duct loss is rarely reported in dogs [5, 6]. The present paper describes the clinical and histopathological characteristics of destructive cholangitis in a canine.

2. Case Presentation
A 4-year-old female Jack Russell terrier dog with a history of vomiting for 1 week was admitted to the Animal Teaching Hospital of Gifu University, Japan. The dog was slim, and physical examination revealed severe jaundice of the visible mucous membranes and skin. Routine hematological examination revealed no abnormalities; however, serum biochemical examination revealed increased total bilirubin (T-Bil; 7.0 mg/dL) and C-reactive protein (CRP; 2.5 mg/dL) levels. Ultrasonographic examination revealed areas of diffuse, high echogenicity and areas of focally low echogenicity in the left lobe of the liver. A small gall bladder was observed, but no biliary obstruction was detectable, and a clinical diagnosis of hepatic jaundice was made by the clinician. A histopathological sample from the right median lobe of liver was collected by excisional biopsy with the dog under general anesthesia, 7 days after the first examination. Although the clinical status had improved gradually with the administration of prednisolone and cyclosporine, the dog died 46 days after the first examination. Postmortem examination of the dog was not allowed by the owner.

The liver specimen was fixed in 10% neutral buffered formalin, processed for histology using routine methods,
Figure 1: Gross appearance of the dog’s liver. The surface of the liver presented with many scattered, irregularly shaped red spots.

sectioned (4 \( \mu m \)), and stained with hematoxylin and eosin (HE). In addition, some sections were stained using Prussian blue stain, Schmorl method, Hall’s method, and rhodanine stain. Immunohistochemistry (IHC) on the formalin-fixed paraffin-embedded sections was performed using antibodies against cytokeratin 19 (mouse monoclonal antibody, Vision Biosystems Novocastra, Tyne, UK) and canine distemper virus (CDV; mouse monoclonal antibody, Cosmobio Co., Tokyo, Japan) at 1:100 dilution. Prior to incubation with the cytokeratin 19 primary antibody, we carried out a blockade of endogenous peroxidase activity (0.3% hydrogen peroxidase in methanol for 20 minutes at room temperature) and enzyme digestion (0.05% trypsin in PBS at 37 \( ^{\circ}C \) for 5 minutes). For CDV antigen retrieval, boiling was performed at 121 \( ^{\circ}C \) for 15 minutes in an antigen retrieval solution (Target Retrieval solution, DakoCytomation, Denmark). Subsequently, the sections were incubated with a peroxidase-labeled secondary antibody (Envision+, DakoCytomation) and visualized using diaminobenzidine. Mayer’s hematoxylin was employed for counterstaining. For the negative controls, the primary antibody was omitted and replaced with PBS.

Macroscopic examination of the liver specimen revealed many scattered irregularly shaped red spots on the liver surface and on the cut surface, resembling nutmeg liver (Figure 1). Histopathologically, brown pigmentations were observed in approximately the entire Glisson’s capsule and part of the hepatic lobule at low magnification (Figure 2(a)). There were many pigment-laden macrophages and some neutrophils, lymphocytes, and plasma cells present in most portions of Glisson’s capsule and part of the hepatic lobule at low magnification (Figure 2(a)). Although interlobular arteries and veins of the liver were present, interlobular bile ducts and bile ductules were not observed (Figure 2(b)). Some clumps composed of irregularly disposed epithelioid cells containing light cytoplasm at the boundary division between Glisson’s capsule and the hepatic lobule were present. Septal bile ducts, which have their own bile duct wall and are lined by a single layer of high columnar epithelium and hepatic duct, were observed. In the hepatic lobule, there was minimal parenchymal necrosis, brown pigmented hepatocytes, and mild intrahepatic cholestasis. The brown pigments stained blue with Prussian blue stain (Figure 2(c)), dark green with Schmorl method, and they did not stain with Hall’s method. There was no evidence of positive staining with rhodanine or immunohistochemical labeling for CDV. The epithelial cells at the boundary division between the Glisson’s capsule and the hepatic lobule and the epithelial cells of the septal bile ducts and hepatic duct were confirmed by positive immunohistochemical labeling for cytokeratin 19 (Figure 2(d)). However, lumen formation composed of cytokeratin 19-positive cells was not observed.

Canine cholangitis is classified into 4 types: neutrophilic cholangitis, lymphocytic cholangitis, destructive cholangitis, and chronic cholangitis associated with liver fluke infestation [7]. Neutrophilic cholangitis and lymphocytic cholangitis are characterized by infiltration of neutrophils or small lymphocytes in the area for Glisson’s capsule, especially in the biliary epithelium. The main microscopic feature of destructive cholangitis is the loss of the intrahepatic bile ducts in the area for Glisson’s capsule, associated with the infiltration of pigment-phagocytic macrophages, neutrophils, and eosinophils in the area for Glisson’s capsule. Chronic cholangitis associated with liver fluke infestation is an endemic infection caused by the family Opisthorchidae. The lesions consist of dilated, large bile ducts with papillary proliferation associated with various inflammatory infiltrates. In the present case, there was loss of the interlobular bile duct and cholangitis characterized by infiltration of macrophages ingesting the hemosiderin in the Glisson’s capsule. Therefore, the pathological findings of the lesion were similar to destructive cholangitis in dogs.

3. Discussion

In humans, several drugs, such as flucloxacillin, chlorpromazine, and carbamazepine, and hepatotoxic agents have been reported to cause bile-duct loss [8]. Some of these compounds induce bile-duct injury at a specific anatomical level of the intrahepatic biliary tree [4]. Paraquat induces cytopathic changes in bile epithelial cells ranging from those of bile ductules to large intrahepatic bile ducts and 4,4’ dianinodiphenylmethane causes necrotic cholangitis in small bile ducts [9]. Because the bile-duct loss occurred specifically at the interlobular bile duct with cholangitis, a drug or hepatotoxic-agent-induced cholangitis was suspected in the present case. However, the particular drug responsible in this case was not elucidated because drug use history or hepatotoxic agent exposure was not known.
Although CDV is known to cause bile-duct loss in dogs, a positive reaction for CDV was not detected in the present case [7]. Similarly, the deposition of copper causes bile-duct loss, but there was no copper deposition in this case [7]. In addition, lesions indicative of immune-mediated or ischemic bile-duct loss in humans were not evident [4]. Interestingly, in this case, bile-duct loss occurred at the bile ductules and interlobular bile ducts, but did not occur at the septal bile ducts that had bile-duct walls. In addition, lumen formation was not apparent, although cytokeratin 19-positive cells—evidence of bile-duct regeneration—were observed [10]. We hypothesize that the inhibition of lumen formation in the bile ductules and interlobular bile ducts may be associated with the development of the lesion in this case.

References


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