A Case of Recovery from Canine Destructive Cholangitis in a Miniature Dachshund

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ABSTRACT. A 7-year-old Miniature Dachshund presented with severe chronic jaundice and elevated liver enzymes. Destructive cholangitis was diagnosed according to histopathological findings of remarkable ductopenia with inflammatory infiltrates and fibrosis in the portal areas. Supportive therapy with prednisolone, high-dose ursodeoxycholic acid, human placental extract and antibiotics was tried, and the patient showed recovery of clinical signs 3 months after diagnosis. A second liver biopsy was performed about 1 year after initial diagnosis, and bile duct restoration was confirmed with continuous inflammation around portal areas and inside the lobules. Although we could not determine which treatment was effective in this case, destructive cholangitis in dogs may be recoverable with long-term supportive therapies.

KEY WORDS: canine, destructive cholangitis, ductopenia, jaundice.

NOTE Internal Medicine

Destructive cholangitis in dogs is characterized by destruction and loss of the bile ducts in the small portal areas with mixed cell infiltration and portal fibrosis [2]. Clinical cases of destructive cholangitis have been described in dogs [5, 11]. Although the causes of this disease in dogs remain unclear and many cases are idiopathic, drugs such as sulfonamides and infection by canine distemper virus (CDV) are thought to be responsible for the disease [5, 11]. In general, disease prognosis has been recognized as poor due to a lack of effective treatments.

In human medicine, bile duct loss is one of the basic pathological changes in the intrahepatic biliary tree and is defined by the absence of an interlobular bile duct in ≥50% of small portal tracts [9, 12]. The causes of bile duct loss in humans include immunological, ischemic, infectious, metabolic and toxic processes [1, 4, 9]. Some of these patients undergo progressive and irreversible bile duct loss followed by the development of extensive ductopenia and fibrosis or cirrhosis, while others show biliary epithelial regeneration, with clinical recovery finally occurring within several months or years. The present study describes a canine case of destructive cholangitis with recovery of bile duct structures about 1 year after initial diagnosis.

A 7-year-old, male Miniature Dachshund was referred to the Veterinary Medical Center at the University of Tokyo for evaluation of severe chronic jaundice and elevated liver enzymes. Symptoms of anorexia, nausea, polyuria/polydipsia and occasional white feces had lasted for 5 weeks. The dog had not responded to treatment including ursodeoxycholic acid (UDCA), antibiotics, glycyrrhizin or S-adenosylmethionine at the referring hospital.

On physical examination, the dog was emaciated, and mucous membranes and skin were severely icteric. A complete blood count showed no abnormalities. The dog’s serum biochemical profile (Table 1) revealed marked increases in alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT) and total bilirubin and moderate increases in C-reactive protein. Its coagulation profiles (prothrombin time, activated partial thromboplastin time, fibrinogen and fibrin degradation product) were within the reference ranges.

Abdominal ultrasonography revealed a small gallbladder with a thickened wall containing no bile. The liver parenchyma, common bile duct and pancreas showed a normal appearance. Specific findings were not detected by fine-needle aspiration of the liver parenchyma (data not shown).

Laparoscopic examination with liver biopsy was performed 2 weeks after initial presentation (day 11). Macroscopic findings included an irregular edge of the liver and moderate yellow-brown appearance. Histopathologically (Figs. 1, 2), severe infiltration of neutrophils and fibrosis were apparent in the portal areas. The remarkable characteristic was marked ductopenia, with only 2 bile ducts found in 30 portal tracts. Lymphocytes, macrophages and plasma cells were occasionally seen in some portal areas. The dog was diagnosed as having destructive cholangitis based on these findings. Bacterial culture of aspirated bile was performed, yielding negative results.

The dog was treated with 10 mg/kg of UDCA (Urso tablets; Mitsubishi Tanabe Pharma, Osaka, Japan) and 10 mg/kg metronidazole (Flagyl; Shionogi & Co., Ltd., Osaka, Japan) twice daily after biopsy. However, the dog was hospitalized on day 44 because of progression of lethargy and anorexia. We started treatment with 1 mg/kg prednisolone (Prednisoron; Kawasaki Pharmaceutical, Kawasaki, Japan).
twice daily and 5 mg/kg enrofloxacin (Baytril; Bayer HealthCare, Osaka, Japan) once daily, and then 0.5 ml/head human placental extract (Laennec; Japan Bio Products, Tokyo, Japan) was added once daily to the treatment with intravenous fluids containing vitamin B complex and glycyrrhizin (Stronger Neo-Minophagen C; Minophagen Pharmaceutical, Tokyo, Japan). Subsequently, the dose of prednisolone was tapered to 1 mg/kg and then 0.5 mg/kg once daily on days 49 and 52, respectively. The dose of UDCA was increased to 37 mg/kg twice daily on day 48.

The concentration of bilirubin was gradually decreased in the first few days, but did not decrease to < 10 mg/dL during hospitalization. Symptoms of anorexia and weight loss were also worsening, and the dog was discharged from the hospital on day 61 because of its poor response to treatment. After discharge, the dog was treated with 25 mg/kg of UDCA twice daily, 0.6 mg/kg of prednisolone once daily and 12.5 mg/head glycyrrhizin (Neophagen C tablet; Taiho Pharmaceutical, Tokyo, Japan) twice daily. The symptoms of anorexia and weight loss gradually improved with decreases in circulating bilirubin levels to 4.5, 2.4 and 0.9 mg/dL on days 89, 105 and 222, respectively. Liver enzymes such as ALT, ALP and GGT were also decreased gradually (Table 1).

A second liver biopsy was performed on day 350. Macroscopically, the liver was smaller and irregular compared with the findings at the first biopsy. Histopathologically, bile duct hyperplasia was observed in some areas, and 46 of 60 portal tracts showed bile ducts with a luminal structure. Moderate to severe infiltration of inflammatory cells (neutrophils and lymphocytes) was still evident not only around portal areas, but also inside the lobules.

The etiology of destructive cholangitis is not fully understood in animals, although drug-induced toxicity, infection and idiopathic processes have been considered responsible [2, 5, 11]. The present case had no history of medication, accidental ingestion of drugs or chemicals and no evidence of CDV infection. Although mixed vaccination was performed 5 weeks before symptoms developed, the relationship is unclear in the present case.

Destructive cholangitis in dogs reportedly shows a poor prognosis, with most cases in previous studies euthanized due to a lack of response to treatment [5, 11]. In a report of 7 dogs treated with prednisolone and ampicillin [11], only 1 dog recovered and survived. The present case also showed little or no improvement after initial medication. However, long-term treatment resulted in clinical recovery and histological restoration of bile ducts with a luminal structure. To the best of our knowledge, this is the first report of canine destructive cholangitis for which restoration of bile ducts with clinical recovery has been confirmed. In human medicine, bile duct restoration is suggested to require several months according to a report of drug-induced bile duct loss,

Table 1. Results of serum biochemical and coagulation profiles of the case

<table>
<thead>
<tr>
<th>Parameters</th>
<th>First visited</th>
<th>Day 44</th>
<th>Day 89</th>
<th>Day 119</th>
<th>Day 350</th>
<th>Reference range</th>
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<tr>
<td>Alanine aminotransferase (ALT; U/L)</td>
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<td>232</td>
<td>305</td>
<td>143</td>
<td>142</td>
<td>17–78</td>
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<tr>
<td>Alkaline phosphatase (ALP; U/L)</td>
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<td>&gt;3500</td>
<td>&gt;3500</td>
<td>2241</td>
<td>238</td>
<td>47–254</td>
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<td>Gamma-glutamyltransferase (GGT; U/L)</td>
<td>127</td>
<td>146</td>
<td>186</td>
<td>123</td>
<td>9</td>
<td>5–14</td>
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<tr>
<td>Total bilirubin (mg/dL)</td>
<td>16.3</td>
<td>18.9</td>
<td>4.5</td>
<td>1.8</td>
<td>0.4</td>
<td>0.1–0.5</td>
</tr>
<tr>
<td>C-reactive protein (CRP; mg/dL)</td>
<td>1.8</td>
<td>0.35</td>
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<td></td>
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<tr>
<td>Prothrombin time (PT; sec)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>6–9</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (APTT; sec)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>11–18</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>245</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>140–420</td>
</tr>
<tr>
<td>Fibrin degradation product (FDP; µg/dL)</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Fig. 1. Histopathological findings from the first liver biopsy (day 11, 4 ×, HE staining). In the portal areas, severe inflammation, mild to moderate fibrosis and loss of bile ducts were observed. Bar: 1 mm.

Fig. 2. Histopathological findings from the first liver biopsy (day 11, 200 ×, HE staining). Infiltrating cells mainly comprised neutrophils, but macrophages were occasionally seen. Bar: 200 µm.
a disease that resembles destructive cholangitis [12]. Considering the time course of clinical recovery and dramatic increase in bile ducts within about 1 year after the initial biopsy in the present case, bile duct restoration in dogs could conceivably take at least several months, as in humans.

No definitive medical treatment is known for human acquired bile duct loss diseases (e.g., primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) and drug-induced cholangitis) except living liver transplantation. UDCA has been widely used in the treatment of cholestatic liver diseases, including several cases of bile duct loss [10]. In some recent studies, UDCA has improved liver histology, cholangiography and survival without liver transplantation in patients with PBC [10, 13]. Furthermore, high-dose UDCA treatment (25–30 mg/kg/day) reportedly shows substantial improvements in biochemical, cholangiographic and histological parameters in PSC [6, 8]. Another report in PSC showed that higher doses of UDCA were associated with improvements in survival probability and a trend toward improvements in liver histology [3]. We used high-dose (50–74 mg/kg/day) UDCA and human placental extract (HPE) for the dog on a trial basis. HPE contains several growth factors including hepatocyte growth factor (HGF) and can stimulate liver regeneration in rats with experimentally induced liver failure [7]. Although the relationship between these treatments and recovery in this case was unclear, no adverse effects associated with high-dose UDCA and HPE administration were encountered.

In conclusion, this is the first report of a case of canine destructive cholangitis showing histopathological recovery. Although we could not determine which treatment was effective in this case, bile duct loss recovered with the provision of long-term supportive therapy.

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REFERENCES