Experimental & Laboratory Note—

Caroli's disease associated with liver cirrhosis
An autopsy case

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Summary

Caroli's disease is one of the rare congenital conditions associated with the cystic dilatation of intrahepatic bile ducts. This is a case report of a 41-year-old Japanese male who complained of jaundice and general fatigue at the age of 34 for the first time. He was clinically diagnosed as having Caroli's disease by physical examination and image analyses study. The patient died after seven years and three months from the onset of the disease on account of renal function impairment. An autopsy was performed, revealing cystic dilatation of the intrahepatic bile duct, associated with a cirrhotic liver and also evidence of portal hypertension, substantiated by esophageal varices and splenomegaly. The liver weighed approximately 2,200 g. A histological investigation revealed typical morphological evidence of cirrhotic glomerulopathy and tubular degeneration with the presence of calcium casts in the dilated tubuli. The lung revealed diffuse alveolar damage with partial organization associated with remarkable polymorphonuclear and macrophagic infiltration. In this paper, the pathogenesis of the cirrhotic change, biliary duct abnormality and potential malignant transformation in the liver are discussed in relation to Caroli's disease.

Introduction

Caroli reported the first case of liver disease associated with congenital dilatation of the intrahepatic bile ducts in 19581). According to the Caroli's description, the congenital dilatation of the intrahepatic bile ducts can be classified into two types2,3). The first type is extremely rare and is associated neither with portal hypertension nor liver fibrosis4). The second type is much more common, affecting especially children, and is associated with liver fibrosis. However, the associated dilatation of the segmental bile ducts sometimes remains latent and is discovered incidentally by postmortem examination in adulthood.

Clinically, intravenous cholangiography is the most useful diagnostic procedure for these conditions. Caroli's disease reveals clinical signs of fever, hypochondralgia and portal hyperten-
Fig. 1a ERCP shows multiple cysts communicating with biliary trees.

Fig. 1b Abdominal CT scan shows multiple cystic dilatation of the intrahepatic bile ducts.

sion. In this particular case, the patient showed evidence of liver dysfunction at the age of 34 as the first manifestation of Caroli's disease, later confirmed by physical examination and image analyses study. In this paper, the authors discuss the possible causative mechanism of the dilatation of the intrahepatic bile ducts and the added complication of liver cirrhosis in Caroli's disease.

Case Report

A 41-year-old Japanese male, restaurant manager was admitted to the Nippon Medical School Hospital (Sendagi) on March 23rd, 1989 on account of general fatigue. Except for a past history of osteomyelitis when he was 8 years old, the patient had enjoyed good health until the age of 34, when he showed some evidence of renal dysfunction. On previous admission, the physical examination demonstrated hepatosplenomegaly and abnormal dilatation of the intrahepatic bile ducts ascertained through endoscopic retrograde cholangiopancreatography (Fig. 1a), ultrason sounds, gastrointestinal series, intravenous cholangiography and computed tomography (Fig. 1b). Upon admission in March 1989, evidence of hepatic failure was demonstrated by physical examination and laboratory investigations. Renal functional impairment was also revealed (Table 1). The patient responded poorly to various therapeutic attempts and expired on July 15, 1989 on account of the renal functional impairment. His total clinical course lasted seven years and three months.

Anatomic Pathological Findings

A post mortem examination was performed approximately seventeen hours after expiration. A moderately developed, well nourished male weighing 63 kg and measuring 173 cm in height.
Table 1 Laboratory data of the reported case of Caroli’s disease

<table>
<thead>
<tr>
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<th>On admission</th>
<th>On exitus</th>
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<tbody>
<tr>
<td>WBC (x10^3/mm³)</td>
<td>4.300</td>
<td>7.100</td>
</tr>
<tr>
<td>HB (g/dl)</td>
<td>9.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>28.9</td>
<td>17.9</td>
</tr>
<tr>
<td>RBC x10^12/mm³</td>
<td>2.67</td>
<td>1.97</td>
</tr>
<tr>
<td>Plat x10^12/mm³</td>
<td>2.3</td>
<td>4.2</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>1.6</td>
<td>7.3</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>102 (86)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>T. bil (mg/dl)</td>
<td>14.5</td>
<td>32.8</td>
</tr>
<tr>
<td>T. bil (mg/dl)</td>
<td>10.8</td>
<td>12.2</td>
</tr>
<tr>
<td>GPT (IU/dl)</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>GOT (IU/dl)</td>
<td>141</td>
<td>97</td>
</tr>
<tr>
<td>ALP (IU/dl)</td>
<td>780</td>
<td>271</td>
</tr>
<tr>
<td>GTP (IU/dl)</td>
<td>121</td>
<td>12</td>
</tr>
<tr>
<td>LAP (GR)</td>
<td>69</td>
<td>45</td>
</tr>
<tr>
<td>ZTT (IU)</td>
<td>39.4</td>
<td>16.0</td>
</tr>
<tr>
<td>TTT (IU)</td>
<td>27.8</td>
<td>4.9</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Creat (mg/dl)</td>
<td>0.8</td>
<td>7.0</td>
</tr>
<tr>
<td>TP (g/dl)</td>
<td>7.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Alb (g/dl)</td>
<td>1.7</td>
<td>1.5</td>
</tr>
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The liver was markedly enlarged and weighed 2,200 g. The external surface was greenish yellow tinged in color, coarsely and finely granular (Fig. 2a). The cut surface revealed marked bile stasis, irregularly distributed linear fibrosis and multiple cystic lesions of the intrahepatic bile ducts measuring up to 2.3 cm in diameter. Some of them contained dark black bilirubin stones, measuring 2 cm in dimension (Fig. 2b).

Histologically, there was proliferation of the intrahepatic bile ducts; furthermore some were irregularly dilated and lined by thickened mucosa showing papillary or glandular transformation, containing a moderate amount of bile (Fig. 3a). The increase of the periportal connective tissue
Fig. 3a  Cystically dilated bile ducts are observed in the irregularly thickened septa and contain bile plugs. The cystic ducts show mucosal proliferation. (H.E. stain, ×100)

Fig. 3b  Increased reticular fibers and sinus hyperplasia are seen in the congestive spleen. (Silver stain, ×100)

Fig. 4a  Mesangial fibrosis and tubular degeneration are visible in renal tissue. (Masson stain, ×100)

Fig. 4b  Hyaline membrane formation in alveolar spaces are seen, associated with epithelial desquamation and occasional proliferation of fibroblasts. (H.E. stain, ×100)
formed fibrous septa that subdivided the liver into small multiple pseudolobules. Hepatocytes were occasionally degenerated with bile stasis and small round cell infiltration in both the portal triads and the hepatic parenchyma. In the portal areas, the arteries and portal veins were dilated with thickened walls associated with moderate perivascular infiltration of macrophages and lymphocytes. The portal hypertension due to the above liver damage resulted in 900 ml of yellowish abdominal effusion, splenomegaly and esophageal varices. The spleen weighed 995 g and showed marked congestion and atrophy of the white pulps. Histologically, reticulofibrosis with sinus hyperplasia (Fig. 3b) and Gamna-Gandy bodies were observed. In the esophagus, submucosal varices associated with sclerotic veins and plasma cell and lymphocytic cell infiltration were also visible. In the stomach, moderate submucosal hemorrhage and slight lymphocytic cell infiltration were noted in the lamina propria. Each kidney weighed 400 g and had a yellow-tan surface. The renal tissues revealed acute tubular necrosis and dilated tubular lumina containing calcium casts consistent with evidence of the hepatorenal syndrome and Caroli’s disease. The other histological findings were slightly to moderately proliferative glomerulonephritis consistent with cirrhotic glomerulopathy (Bloodworth et al.)⁵ (Fig. 4a) and marked hyperplasia of the juxtaglomerular apparatus with a striking increase of dark fine granules identifiable as renin granules. The right and left lungs weighed 1,080 g and 1,085 g respectively and showed marked congestion, edema and diffuse alveolar cell destruction with exudation of proteinaceous material (Fig. 4b). Hyaline membrane formations were observed on lining walls of alveolar ducts with aggregate of polymorphonuclear leukocytes and alveolar macrophagic infiltration. Partial organization was also demonstrated with occasional proliferation of fibroblasts and dilatation of lymph vessels in the interstitium. The heart showed evidence of slight cardiomegaly, weighing 355 g. Histologically, interstitial edema in the myocardium with slight hypertrophy and disorientation of some myocytes were noted.

**Discussion**

In a general approach and without referring only to the congenital type described by Caroli, the cystic condition of intrahepatic bile ducts can be divided into four patterns: solitary cysts with or without communication with the biliary system, polycystic lesions from the primarily parenchymal regions and localized and multicystic dilatations of the major intrahepatic ducts. Multiple cysts of intrahepatic bile ducts in Caroli’s disease represent a possibility of malformation in the most distal portion of the ductal system formed from the duct anlage. These cystic lesions may be associated with liver fibrosis and/or other cystic lesions, mostly in the kidney and common bile duct⁶,⁷.

The pathogenesis of the cystic dilatation of the intrahepatic bile ducts has been discussed and studied by many authors. Glenn and McSherry⁸ claimed that the anatomical defect of the bile ducts is eventually induced by disproportionate overgrowth in the proximal portion of the primitive biliary tree during the solid stage in the 4-week-old embryo and results in abnormally dilated structures in the 6th week of the embryonal stage⁹,¹⁰. Possible contributing factors to these abnormal developments of bile ducts include a mechanical resistance of the distal portion of the biliary tract to the bile flow, though other neurological functional impairments may also contribute to the dilatation of the proximal portion of the bile duct (Fig. 5). Caroli’s disease,
which is a primary biliary tract disease\textsuperscript{11}, may be associated with secondary biliary cirrhosis as seen in this particular case. In both primarily and secondarily altered bile ducts, the flow of bile is generally disturbed and causes stasis with the subsequent formation of bile calculi which may in turn contribute to the genesis of bacterial cholangitis. The latter may be complicated by liver abscesses and consequent septic changes. Both the chronic inflammatory process and the bile stasis may induce liver fibrosis and later, cirrhosis. This cirrhotic association may be a possible end-stage of Caroli’s disease. However, most cases are combined only with liver fibrosis at the time of initial clinical diagnosis. Thus fibrosis may be a slowly growing process per se, and may lead to liver function impairment. With the evidence of liver function impairment, further investigations would make possible the clinical diagnosis of Caroli’s disease just before the stage of cirrhosis is clinically attained. Concerning the fibrogenesis in the liver of the combined form of Caroli’s disease, periportal and pericellular fibrosis are thought to be induced by damage to the hepatocytes and mesenchymal cells. Investigations by Kent et al.\textsuperscript{12} and Mak et al.\textsuperscript{13} suggested that mesenchymal cells comprising Ito’s cells, transitional cells and myofibroblasts, play an important role in the genesis of fibrosis in the liver. Since the description by Ito of the precursors of collagen fibrils in the fat storing cells, it is generally accepted that these cells along with hepatocytes are among the principal promotors of pericellular fibrosis\textsuperscript{14}. Yamada et al.\textsuperscript{15} reported recently that mRNA of type III collagen was localized in the mesenchymal cells and hepatocytes per se. The exact stimulant is still unknown but it is believed that bile from the bile ducts and hepatocytes would induce an inflammatory response associated with ductular and mesenchymal cell proliferation which may in turn induce cirrhotic change\textsuperscript{16}. Approximately 10 to 20 cases of malignant transformed Caroli’s disease have been reported in relevant publications. Neoplastic changes such as cholangioma, hepatocellular carcinoma and other adenocarcinoma have been reported by Favre et al.\textsuperscript{17}, Etienne, et al.\textsuperscript{18}, Dayton, et al.\textsuperscript{19}, and Chen et al.\textsuperscript{20}. 

Fig. 5 Pathogenesis of dilatation of intrahepatic bile duct.
The malignant transformation in the liver cells and the ductal epithelium may be facilitated by stasis of the bile and other metabolic substances which contain carcinogenic hydrocarbon and deoxycholic acid. On the other hand, the bile calculi may also contribute to abnormal epithelial cell regeneration and proliferation which may eventually lead to malignant transformation.

**Conclusion**

A rare case of Caroli's disease has been described in this paper. The authors have discussed the pathogenesis of the irregular intrahepatic bile duct dilatation and its interaction with liver fibrosis. The significant interrelation between Caroli's disease and malignant transformation is also discussed.

**References**


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