

A Case of Rapidly Progressive Primary Sclerosing Cholangitis Requiring Liver Transplantation

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Primary sclerosing cholangitis (PSC) is a slowly progressive cholestatic liver disease. In cases of PSC, liver transplantation is the only effective treatment that can delay the disease's natural course. We report a case of rapidly progressive PSC requiring liver transplantation. A 52-year-old woman visited our hospital with abdominal pain. There was no evidence of PSC, as there was no elevation in cholestatic liver enzymes at her first visit. Although her total bilirubin was in a normal range at the initial visit, liver dysfunction progressed rapidly. Despite endoscopic procedures and ursodeoxycholic acid intake, total bilirubin levels rose to 18.9 mg/dL, and liver transplantation was performed 17 months after her first visit. PSC was pathologically confirmed after liver transplantation.

Key Words: Primary sclerosing cholangitis, Liver transplantation, Ursodeoxycholic acid, Endoscopic retrograde cholangiopancreatography, Magnetic resonance cholangiopancreatography

중심 단어: 원발성 경화성 담관염, 간이식, 우루소데옥시콜산, 내시경적 역행성 담체관조영술, 자기공명담체관조영술

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic bile duct disease. According to a recent meta-analysis, its incidence was 0.77 per 100,000 person-years(1). It is a rare disease and seems to occur at lower frequencies in Asia and Southern Europe than in America and Northern Europe(2).

PSC is often fatal as there are no effective treatments which can halt its progression with the exception of liver transplant. In the case described here, there was no evidence of PSC except the elevated cholestatic liver enzymes at the initial visit of our hospital. However, 17 months later, the patient's liver dysfunction had rapidly progressed, and a liver transplantation was performed.

Case Report

In September 2010, a 52-year-old woman visited our hospital presenting with abdominal pain which had been present for 1 month. She was taking antihypertensive medication. Her sclera was not icteric, and there was no abdominal tenderness. A liver function test revealed the following: aspartate aminotransferase (AST) 110 IU/L, alanine aminotransferase (ALT) 119 IU/L, total bilirubin 0.3 mg/dL, alkaline phosphatase (ALP) 400 IU/L, and γ -glutamyl transpeptidase (γ -GT) 592 IU/L. Her hepatitis B surface antigen, antibody to hepatitis C virus, antihepatitis A virus immunoglobulin M were all negative. Tumor markers were carcinoembryonic antigen 1.18 ng/mL and CA 19-9 24.3 U/mL. Esophagogastroduodenoscopy, colonoscopy, and abdomen computed tomography showed no abnormal findings. Cholestatic liver diseases such as PSC, primary biliary cirrhosis, or nonalcoholic fatty liver disease were suspected due to the elevated cholestatic liver enzyme levels. For further evaluation, autoimmune markers were checked. Her autoimmune markers: perinuclear antineutrophil cytoplasmic antibody, cytoplas-

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mic antineutrophil cytoplasmic antibody, antinuclear antibody, antimitochondrial antibody, and antismooth muscle antibody were all negative. Immunoglobulin G, A, M quantification were 1,460, 192, and 261 mg/dL, respectively, subclass immunoglobulin G4 level was 139.0 mg/dL. Although the diagnosis was unclear, ursodeoxycholic acid (UDCA) intake was started at 10 mg/kg/day, and serum ALP and aminotransferase levels decreased. However, after 8 months (May 2011), the patient's liver enzyme levels rose to: AST 65 IU/L, ALT 174 IU/L, total bilirubin 1.4 mg/dL, ALP 518 IU/L, and γ -GT 686 IU/L. We performed a liver biopsy and the pathology showed a mild degree of lobular and portal activity, and portal fibrosis suggestive of chronic hepatitis (Fig. 1A). The dose of UDCA was increased to 15 mg/kg/day. After 12 months (September 2011), the patient's total bilirubin rose to 4.0 mg/dL. In order to evaluate the cause of the obstructive jaundice, magnetic resonance cholangiopancreatography (MRCP) (Fig. 2A), and endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 2B) were performed. These findings revealed multiple stones, strictures, and dilata-

tions of intrahepatic ducts, suggestive of PSC. Endoscopic sphincterotomy was done and an endoscopic nasobiliary drainage tube was inserted by ERCP. After 15 months (December 2011), the patient's total bilirubin and direct bilirubin rose to 13.9 and 11.1 mg/dL, respectively, and so MRCP was performed again. The mucosal irregularity had not changed from what was seen in the previous MRCP. To relieve the jaundice, stones were removed from the common bile duct and intrahepatic ducts by ERCP and percutaneous transhepatic cholangioscopy (PTCS), respectively. A biopsy was performed using PTCS on an intraductal mucosal lesion showing nodularity in the hilum, and the result showed fibrous exudates with chronic inflammatory cell infiltration. Despite extracting the stones, total bilirubin rose again to 18.9 mg/dL (Fig. 3), and direct bilirubin rose to 15.4 mg/dL. Although there were no complications such as ascites, hepatic encephalopathy, bleeding, and hepatorenal syndrome, there was no treatment of choice to halt progression of liver dysfunction except liver transplantation. The patient's MELD score was 26, and Child-Pugh score was 9. A

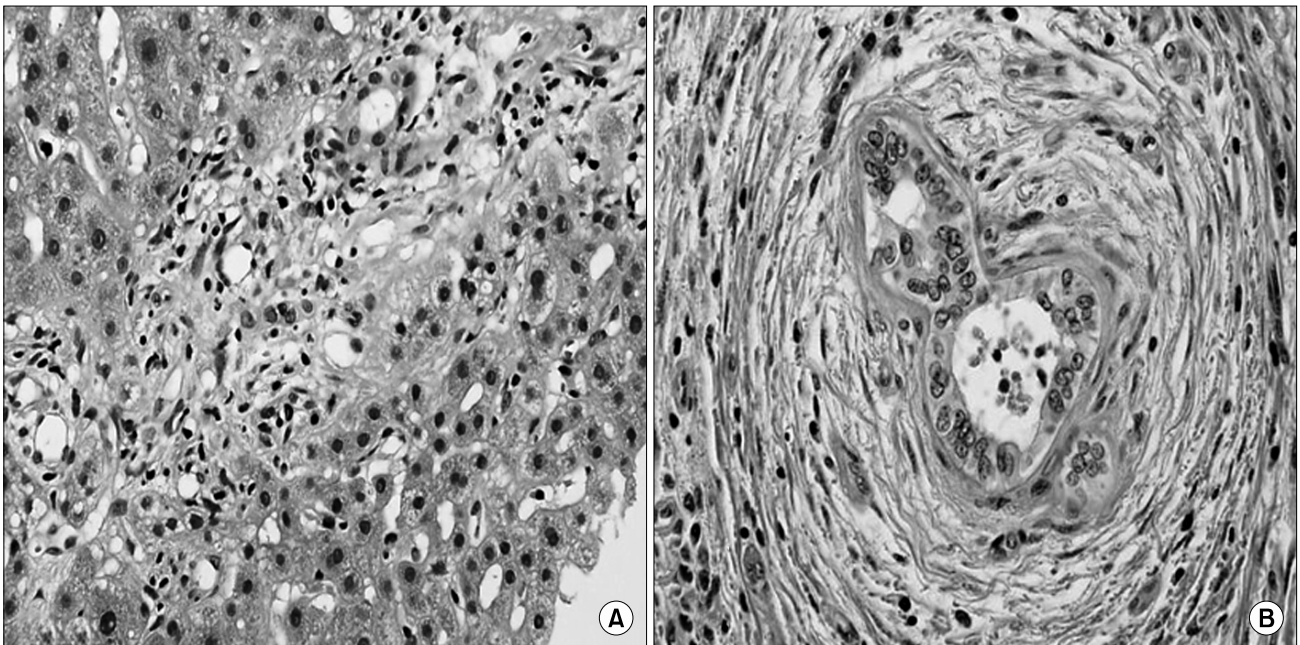


Fig. 1. (A) Eight months after the initial diagnosis of primary sclerosing cholangitis (PSC), the patient's liver biopsy showed a mild degree of lobular and portal activity, and portal fibrosis suggestive of chronic hepatitis (HE stain, $\times 400$). (B) After liver transplantation, which was done 17 months after the initial diagnosis, surgical pathology showed periductal lamellar fibrosis, called "onion-skin," a typical finding of PSC (HE stain, $\times 400$).

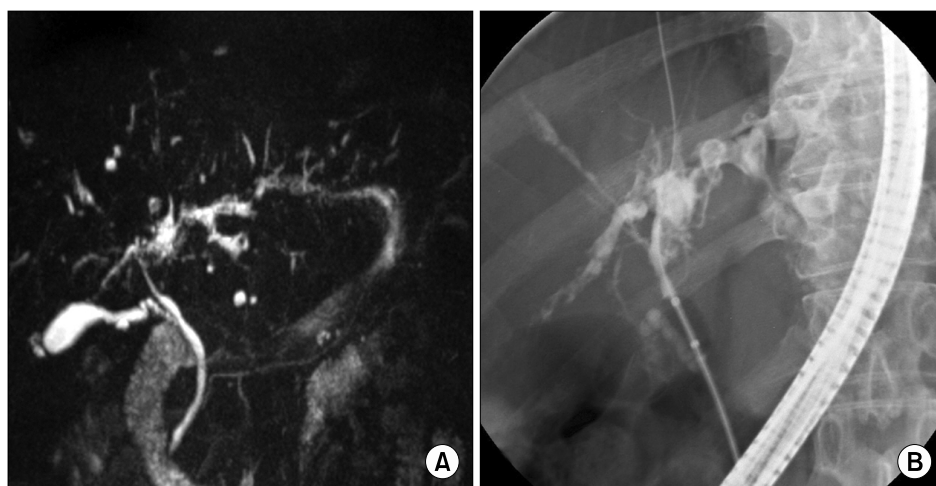


Fig. 2. Twelve months after the initial diagnosis of primary sclerosing cholangitis (PSC), (A) magnetic resonance cholangiopancreatography and (B) endoscopic retrograde cholangiopancreatography findings showed multiple dilations and strictures of intrahepatic ducts, suggestive of PSC.

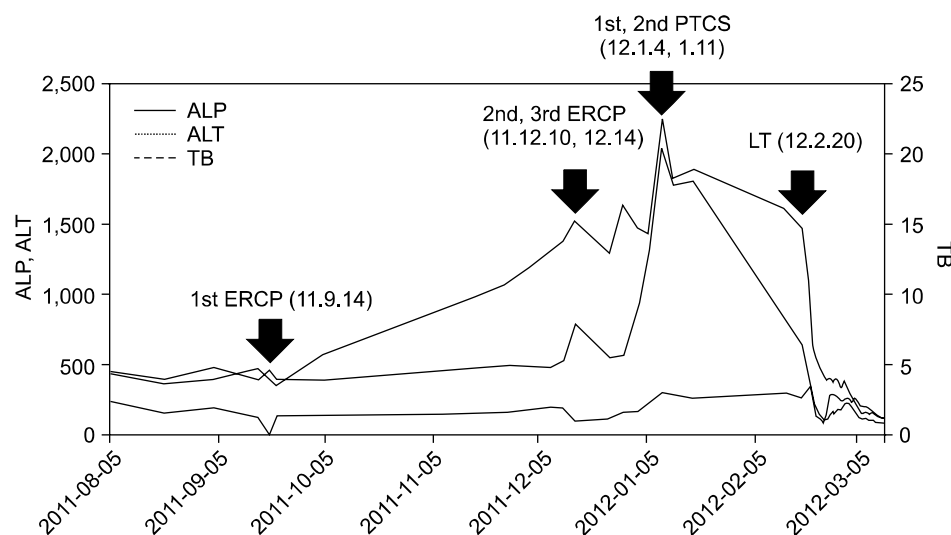


Fig. 3. The trend of total bilirubin, alkaline phosphatase, and alanine aminotransferase (ALT) was described. Abbreviations: PTCS, percutaneous transhepatic cholangioscopy; ERCP, endoscopic retrograde cholangiopancreatography; LT, liver transplantation; ALP, alkaline phosphatase; TB, total bilirubin.

liver transplant from living donor with duct to duct anastomosis was performed at 17 months (February 2012) after the initial visit of our hospital. The explanted liver weighed 1,600 g and measured 24 (right to left) × 15 (superior to inferior) × 12 cm (anterior to posterior) (Fig. 4). The surgical pathology of explanted liver reported a segmental bile duct showing concentric fibrosis suggestive of PSC (Fig. 1B). The patient's human leukocyte antigen (HLA) serotyping was A1, A24, B51, B52, DR1, and DR15. The elevated bilirubin levels rapidly decreased, and were in the normal range by 21 days after surgery. The patient is on tacrolimus hydrate since liver transplantation. General condition of the patients was markedly improved without recurrence of cholangitis. However, at 5 months after liver transplantation, the anastomosis site stricture

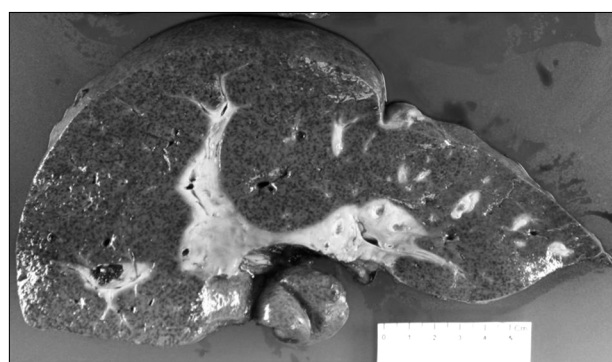


Fig. 4. Gross finding of the explanted liver. The liver was macronodular, and diffusely bile stained.

was found in abdomen computed tomography, and percutaneous biliary tract drainage (PTBD) was inserted. At 11 months after liver transplantation, PTBD was re-

moved, and endoscopic retrograde biliary drainage was inserted.

Discussion

PSC is a chronic cholestatic liver disease leading to liver cirrhosis and liver failure. It is a slowly progressive disease(3) and the median survival from diagnosis to liver transplantation or death is 9.6~12 years(4,5). Previous studies have reported that HLA-DR4 and DRw52a are markers for rapid disease progression in PSC(6,7), but this is still controversial(8). In our patient, HLA-DR4 and DRw52a were not observed, but her liver dysfunction progressed rapidly, and 17 months after her initial diagnosis a liver transplant was necessary.

PSC can be diagnosed when cholangiography shows multifocal strictures and segmental dilatations of bile ducts with elevated cholestatic liver enzyme levels(9). Inflammatory bowel disease is found in 60~80% of PSC patients and can be a clue for PSC diagnosis(9). In this case, the patient first visited our hospital complaining of abdominal pain without any evidence of inflammatory bowel disease, and laboratory results revealed elevated levels of alkaline phosphatase and aminotransferase without any elevation of total bilirubin.

Although liver biopsies can be done to determine the stage of PSC and to exclude coexisting liver diseases, this is not essential for diagnosis. In 98.7% of PSC patients, liver biopsies showed no atypical findings(10). In this case, a liver biopsy was done but only indicated chronic hepatitis. The nodular lesion at the hilum portion of an intrahepatic duct was also biopsied by PTCS to exclude cholangiocarcinoma, which is often concomitant with PSC, and the pathology showed chronic inflammation without malignancy. Nine months after the first liver biopsy, a surgical specimen obtained during the liver transplantation showed periductal lamellar fibrosis, a typical pathologic finding in PSC.

Until now, there has been no definitive treatment for PSC except liver transplantation. Some retrospective studies reported survival benefits in PSC when endoscopic treatments such as sphincterotomy, balloon di-

latation, stent insertion, or stone extraction were performed to relieve dominant strictures(11,12). A dominant stricture is a stenosis with a diameter of ≤ 1.0 mm in a hepatic duct or ≤ 1.5 mm in a common duct(13). However, in PSC, the effectiveness of these endoscopic procedures is still unclear because there have been no randomized controlled studies to report on the benefits(9). Some studies have reported that UDCA improved liver function, but they failed to demonstrate if it halted PSC progression(14-16). Furthermore, recent studies revealed that high-dose UDCA (28~30 mg/kg/day) did not improve patient survival and was associated with severe adverse effects(17,18). Due to this lack of clarity of the effectiveness of UDCA, recent guidelines recommend against the use of UDCA(9).

In summary, we described a patient with rapidly progressive PSC, which was pathologically confirmed after liver transplantation. PSC is a very rare disease in Korea and is typically a chronic disease. The patient visited our hospital because of abdominal pain without jaundice, but after 17 months, liver transplantation was performed due to decreased liver function. Although an endoscopic treatment was performed and standard-dose UDCA was administered, disease progression was not slowed. After liver transplantation, the patient's liver function recovered fully.

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