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Case Report

Sarcoidosis mimicking primary sclerosing cholangitis requiring liver transplantation

Claudio Tombazzi;[1,2] Bradford Waters;[1,2] Mohammad K. Ismail;[1,2] Pamela B. Sylvestre;[3] Antonio Martinez-Hernandez;[3,4] Caroline A. Riely[1]

Abstract

Sarcoidosis is a systemic granulomatous disease of unknown etiology. The association of the cholestatic pattern usually seen in sarcoidosis, with biliary duct changes resembling primary sclerosing cholangitis (PSC) is rare.[1] Liver transplantation permits the histological evaluation of the complete explanted liver, making the diagnosis more reliable. In conclusion we present our experience with two patients with sarcoidosis requiring liver transplantation, who presented with clinical and radiological findings characteristics of primary sclerosing cholangitis.

Key words: Cholestasis, biliary stricture, granulomas.

Introduction

We are presenting two patients with sarcoidosis but with radiological findings «typical» of primary sclerosing cholangitis. The explanation why some patients with sarcoidosis develop biliary duct changes has been controversial in previous studies. Both of our patients underwent liver transplantation which is different than other reports permitted the examination of the complete explanted liver. With the opportunity to obtain a complete examination of the explanted liver, the radiological findings were considered to be due to sarcoidosis without histological evidence of primary sclerosing cholangitis.

Case reports

From 1993 to 2004 a total of 390 orthotopic liver transplantation (OLT) were performed at the University of Tennessee, Memphis. Two out of eight (25%) patients who underwent (OLT) secondary to sarcoidosis had radiological findings of primary sclerosing cholangitis (PSC), and one of them actually came to transplantation with the diagnosis of PSC.

Case 1

A 49-year-old African American female became symptomatic four years prior to transplantation with weakness; laboratory studies demonstrated persistently elevated alkaline phosphatase, with values between 550-1074 U. Liver biopsy showed non-necrotizing granulomatous inflammation consistent with sarcoidosis. The patient deteriorated progressively over three years with recurrent encephalopathy, pruritus, and complications of portal hypertension including ascites. During a routine follow-up, an abdominal CT showed multiple bile duct strictures with peripheral intrahepatic biliary dilatation. The patient underwent endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography that showed multiple segmental strictures in the intrahepatic biliary tree and a high-grade stricture at the common bile duct *(Figure 1)*; a biliary stent was inserted. In a subsequent ERCP, a persistent common bile duct stricture was seen, and balloon dilatation was performed. Endoscopic brushings from the area of the stricture were negative for malignancy. Serum levels of CA19-9, CEA, and AFP were normal. The patient underwent OLT four years after the initial diagnosis. During transplantation, extensive fibrosis was found in and around the extrahepatic biliary system requiring a roux-en-Y hepatojejunal anastomosis.

[1] Department of Medicine, Division of Gastroenterology and Hepatology.
[2] Medicine Service.
[3] Department of Pathology and Laboratory Medicine. University of Tennessee Health Science Center.
[4] Pathology and Laboratory Medicine Service VAMC, Memphis, TN

Address for correspondence:
Claudio Tombazzi M.D.
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
University of Tennessee Health Science Center
College of Medicine
920 Madison Avenue, Suite 240
Memphis TN 38163
Phone: (901) 448-7302
Fax: (901) 448-7091
E-mail: Ctombazzi@utmem.edu
Claudio.Tombazzi@va.gov

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The explanted liver contained numerous non-necrotizing granulomas, many involving bile ducts, morphologically consistent with chronic intrahepatic cholestasis of sarcoidosis *(Figure 2a)*. The salient feature was the presence of multiple granulomata within the wall of large intrahepatic ducts *(Figure 2b)*; resulting in extensive, severe damage and distortion of the bile ducts, with bile duct loss and fibrosis *(Figure 2c)*. Granulomatous lesions were present throughout the entire liver, including involvement of the hilum and the hilar bile ducts. There were no histologic findings suggestive of PSC. The patient is currently three years and three months post-OLT, asymptomatic, and has normal liver enzymes.

Case 2

An obese 29-year-old African American female with a history of abdominal pain, jaundice, and cholestatic pattern of liver enzymes presented two years prior to transplantation. Laboratory tests reported total bilirubin 5.8 mg/dL; aspartate aminotransferase 110 U/L; alanine aminotransferase 137 U/L; and alkaline phosphatase 300 U/L. By ERCP she had a normal pancreatic duct, but her bile duct could not be cannulated. Percutaneous transhepatic cholangiography showed irregular multiple segmental narrowings. The peripheral radicles of the hepatic ductal system had a «pruned» appearance. These findings were felt to represent PSC. The liver biopsy showed extensive cholestasis, chronic inflammation in the portal tracts, and no granuloma. The patient was diagnosed as having PSC. Her liver function progressively deteriorated, and she underwent OLT.

At the time of transplantation, she was found to have an enlarged liver with multiple pale, firm areas. Intraoperative frozen section of one of these lesions demonstrated extensive fibrosis around bile ducts but and no evidence of either PSC or cholangiocarcinoma. In permanent sections from the explanted liver there was extensive, non-necrotizing granulomatous inflammation with bile duct involvement, characteristics of chronic intrahepatic cholestasis of sarcoidosis *(Figure 3)*. No histologi-

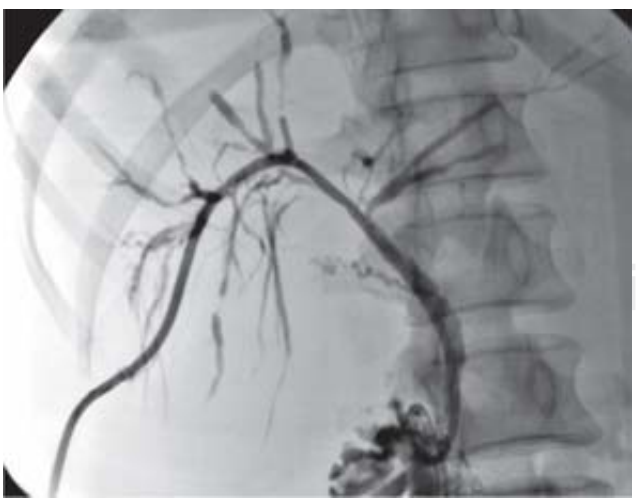

Figure 1. Percutaneous transhepatic cholangiography revealing diffusely multifocal strictures «typical» of primary sclerosing cholangitis.

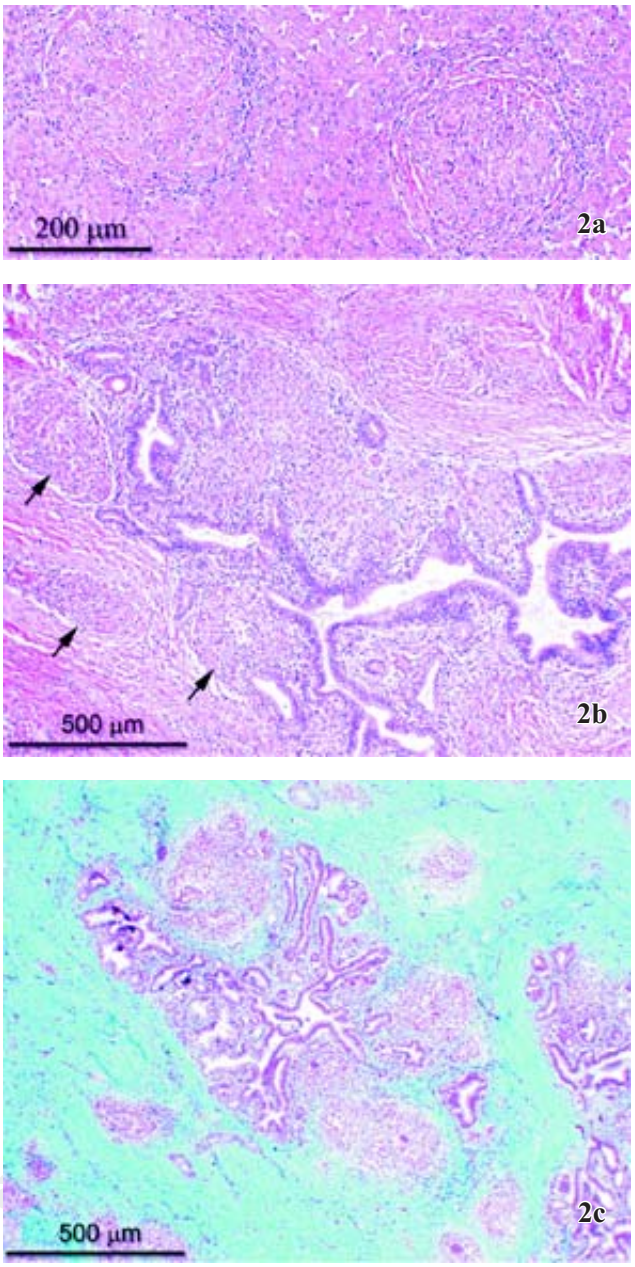

Figure 2. Explanted liver from case **1. 2a.** Two non-caseating granulomas in the hepatic lobule. H+E; Original magnification = x40. **2b.** Multiple granulomas in the wall of a large intrahepatic bile duct. The duct itself appears tortuous and distorted. H+E; Original magnification = x20. **2c.** Large intrahepatic bile ducts contain multiple granulomas in their walls. The bile ducts and the granulomas are immersed in dense fibrous connective tissue (blue). Trichrome stain. Original magnification = x20.

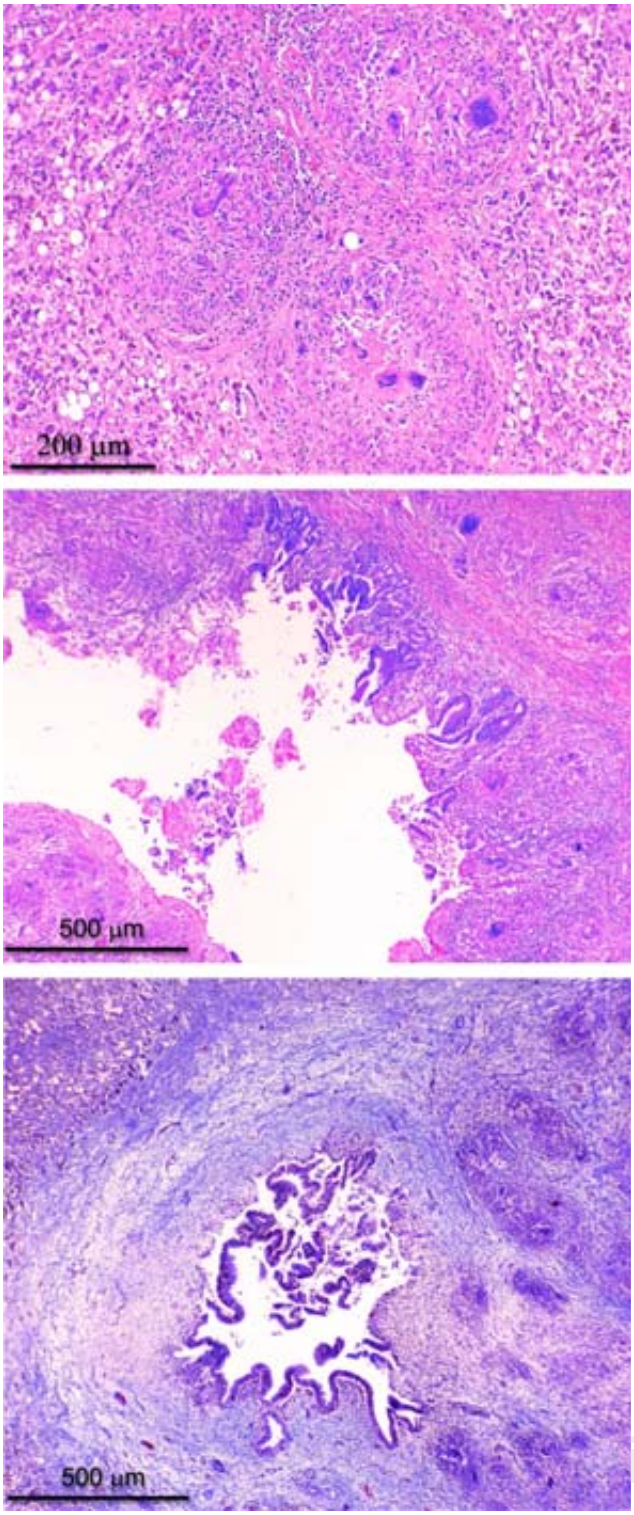

Figure 3. Explanted liver from case **2. 3a.** Several non-caseating granulomas with multinucleated giant cells in a hepatic lobule. . H+E; Original magnification = x40. **3b.** Large intrahepatic bile duct. The ductal submucosa contains a dense inflammatory infiltrate, and several granulomas with multinucleated giant cells. Most of the ductal mucosa has been destroyed by the inflammatory process. H+E; Original magnification = x20. **3c.** Intrahepatic bile duct. The submucosa contains a dense inflammatory infiltrate and several non-caseating granulomas. The ductal mucosa has been damaged at several points. The duct is surrounded by dense fibrous connective tissue.

cal evidence of PSC was identified. Six years after OLT the patient developed a recurrent cholestatic pattern of liver enzymes. Liver biopsy revealed multiple, well-formed, non-caseating granulomas in portal tracts and the hepatic lobules, consistent with recurrent sarcoidosis.

Discussion

Several studies have established that the liver is involved in 95% of patients with sarcoidosis.[2,16] This involvement is often asymptomatic or has only mild symptoms.[3-8] Hepatobiliary disease with clinical, radiological, and biopsy features of PSC has occasionally been reported in patients with sarcoidosis,[5,7,9-13] and some authors have proposed a pathophysiological relationship between these two entities.

A priori, if there was a connection between these two entities, it could be explained by several options: 1) chance occurrence of two etiologically unrelated disorders in the same individual; 2) existence of an (as of yet) uncharacterized immune defect common to both diseases; 3) a new entity with a combination of signs symptoms from these two diseases; or 4) sarcoidosis mimicking PSC.[5,10,14-18]

The chance occurrence of two unrelated disorders in the same individual is obviously possible. However, based on the incidence of each entity in the population it has been estimated (10) that sarcoidosis and PSC may occur by chance in the same individual between 2 to 23 times per billion (10^9). Therefore, if these two entities were associated with any frequency it would be unlikely to be by random chance.

In a few reports the authors postulated a common immunological mechanism involved in the pathogenesis of both entities;[2,19,20] however, the reported cases included neither OLT nor autopsy examination of the entire liver, and to some extent, there was not definitive diagnosis.

In our patients, the entire explanted livers were grossly examined, serially sectioned, followed by microscopic examination of multiple sections. No findings compatible or suggestive of primary sclerosing cholangitis were found. Two hepatopathologists (PBS and AM-H) independently re-examined the pathology slides of the explanted livers and the allograft liver biopsy confirmed the diagnosis of sarcoidosis and the lack of histologic features of PSC.

In practice, the diagnosis of PSC is made following well described radiological criteria. The major criterion is the presence of segmental strictures in the extra-and/or intrahepatic biliary tree. Possible explanations for these radiological findings in patients with sarcoidosis resembling PSC, such as those we are describing, include compression of the bile ducts at the hepatic hilum by enlarged lymph nodes or direct involvement of the bile ducts by the disease.[14,21,22] In both of our cases, the explanted livers

revealed direct involvement of ductal structures with extensive periductal fibrosis and bile duct damage on the intrahepatic biliary tree, correlating with the PSC-like radiological findings.

Conclusion

We report two patients that had biochemical and radiological findings characteristic of PSC. These two cases with radiological findings typical of PSC actually represent biliary tree involvement by sarcoidosis. The biliary tree changes are the result of either primary (granulomas in the ductal wall) or secondary (fibrous adhesions to surrounding lymph nodes) involvement. Therefore, radiographic abnormalities in the biliary tree with a «pruned» appearance should not be considered pathognomonic of PSC, especially in the presence of sarcoidosis. In patients with sarcoidosis presenting with a cholestatic pattern and radiological findings suspicious of PSC, the diagnosis of sarcoidosis mimicking PSC should be strongly considered. The distinction between these two entities, PSC and sarcoidosis, is of more than just academic importance because the two entities have different therapies, follow-ups, and outcomes.

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