

# Unusual presentation of primary sclerosing cholangitis

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BC PINEAU, LP PATTEE, S MCGUIRE, A SEKAR, LJ SCULLY. Unusual presentation of primary sclerosing cholangitis. *Can J Gastroenterol* 1997;11(1):45-48. A 23-year-old man presenting with acute pancreatitis and autoimmune hemolytic anemia was diagnosed with primary sclerosing cholangitis (PSC) without evidence of ulcerative colitis. This constellation of rare associations constitutes a unique mode of presentation of PSC. Within two years he also developed ankylosing spondylitis with sacroiliitis. Disordered immune regulation as a major factor in the mechanism of injury in PSC is supported by its increased association with other immunologically mediated disorders, most notably ulcerative colitis. Autoimmune hemolytic anemia, however, has been reported to be associated with PSC on only two occasions, and ankylosing spondylitis in the absence of ulcerative colitis is also unusual. In addition, the presentation of PSC with acute pancreatitis has rarely been described. This patient presented with several unusual features of PSC.

**Key Words:** *Acute pancreatitis, Ankylosing spondylitis, Autoimmune hemolytic anemia, Sclerosing cholangitis*

## Présentation inhabituelle de la cholangite sclérosante primitive

**RÉSUMÉ :** Un jeune homme de 23 ans atteint de pancréatite aiguë et d'anémie hémolytique auto-immune a par la suite reçu un diagnostic de cholangite sclérosante primitive (CSP), sans signe de colite ulcéreuse. Cette constellation d'associations pathologiques rares constitue un mode unique de présentation de la CSP. En deux ans, le patient a également manifesté une spondylite ankylosante avec sacro-iliite. Le dérèglement immunitaire comme facteur principal du mécanisme pathologique de la CSP est appuyé par son association marquée avec d'autres troubles d'origine immunologique plus précisément avec la colite ulcéreuse. L'anémie hémolytique auto-immune a toutefois été signalée en association avec la CSP à deux occasions seulement. La spondylite ankylosante en l'absence de colite ulcéreuse est également inhabituelle. De plus, le tableau de CSP avec pancréatite aiguë a rarement été décrit. Ce patient présentait donc plusieurs caractéristiques inhabituelles de la CSP.

Accumulating evidence suggests that primary sclerosing cholangitis (PSC) may be a disease of altered immunity. Although its pathogenesis is unknown, an autoimmune mechanism is supported by increased association of PSC with other immunologically mediated disorders, most notably ulcerative colitis. Autoimmune hemolytic anemia, however, is rarely associated with PSC, with only two reported cases previous to this report (1,2).

The natural history of PSC is variable. In some it remains a subclinical condition for years, while others suffer from recurrent episodes of cholangitis, jaundice and pruritus early in the course of their illness (3). We report a case of PSC, unusual because of its presentation with acute pancreatitis and its association with other autoimmune conditions, ie, hemolytic anemia and ankylosing spondylitis but not ulcerative

colitis. The latter associations may suggest that the immunological abnormality may be more generalized in some individuals.

## CASE PRESENTATION

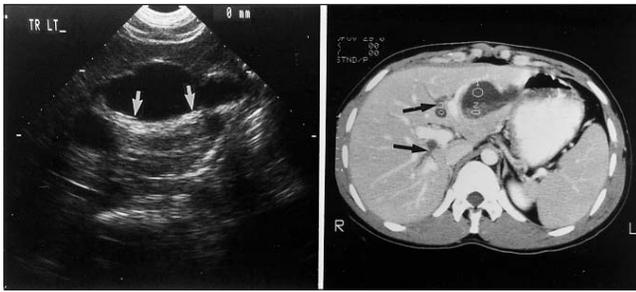
A 23-year-old heterosexual male of East Indian descent was admitted to hospital in December 1990 for evaluation of a three-month history of intermittent epigastric pain associated with fatigue, nausea, vomiting, jaundice and dark urine. There was no fever, chills or weight loss. There was no history of travel, blood transfusions, intravenous drug use, multiple sexual partners or exposure to toxic materials. He was on no medications and consumed alcohol infrequently.

Past medical and family history were negative for inflammatory bowel disease, abdominal surgery, liver disease and

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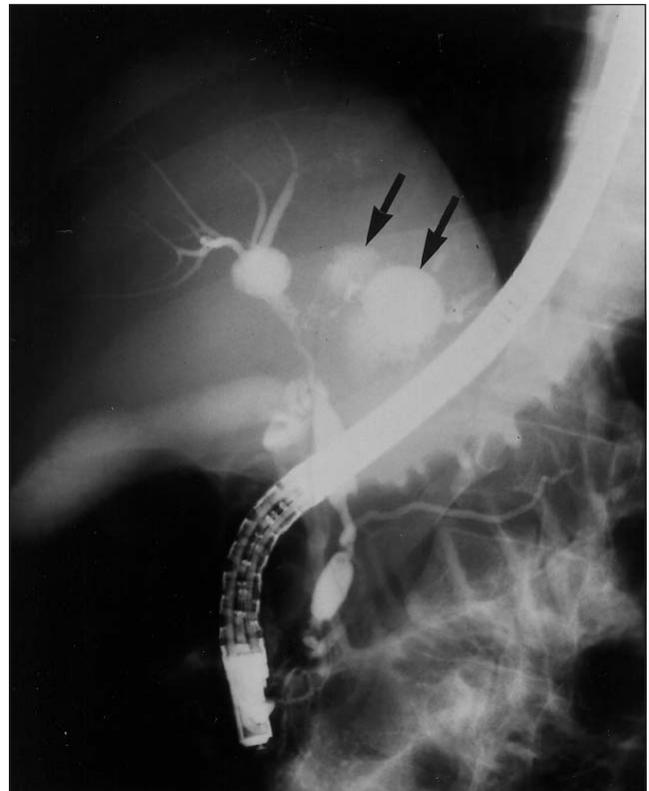
**Figure 1)** *Left* Transverse ultrasound of the left lobe of the liver showing bicameral cystic structure with echogenic debris in its dependent portion (arrows). *Right* Enhanced computerized tomography scan of the liver showing the same cystic structure with debris and intrahepatic ductal dilation (arrows)



**Figure 2)** *Sagittal* ultrasound of the left lobe of the liver showing the thickened wall (long facing arrows) and echogenic debris (short arrows)

cholelithiasis. Apart from jaundice and epigastric tenderness, physical examination was normal and revealed no signs of chronic liver disease.

Normocytic, normochromic anemia was present; hemoglobin was 111 g/L. The peripheral smear showed polychromasia and spherocytes. Reticulocyte count was elevated at 11%. Direct Coombs' test and testing for anti-immunoglobulin (Ig) G antibodies were positive. Serum haptoglobin was 0 g/L. Leukocyte count was  $9.5 \times 10^9/L$  with normal differential and the platelet count was  $452 \times 10^9/L$ . Total bilirubin was 145  $\mu\text{mol/L}$  and conjugated bilirubin was 77  $\mu\text{mol/L}$ . Serum aspartate aminotransferase was 158 IU/L, alanine aminotransferase 154 IU/L and alkaline phosphatase 882 IU/L. Serum amylase was 1835 IU/L while the serum lipase was greater than 4000 IU/L. Serum triglycerides, total cholesterol and calcium were normal. Serological tests for hepatitis A, B and C viruses were negative. Antismooth muscle and antimitochondrial antibodies were not detected. Testing for the human immunodeficiency virus (HIV) by ELISA was nonreactive. Human lymphocyte antigen (HLA) DR typing revealed that he was HLA DW52-, DR8-, DR14-, DRW52- and DQ1-positive.



**Figure 3)** Cholangiogram showing widespread stricturing and saccular out-pouching of the biliary tree; filling of the cystic structures in the left hepatic lobe is also seen (arrows)

Abdominal sonography revealed a bicameral cystic structure consisting of a lobulated 49x37 mm cavity communicating with an adjacent 15 mm similar lesion in the lateral segment of the left lobe of the liver (Figures 1,2) causing deviation of the left hepatic vein and portal triad. The walls were thickened, and echogenic debris was noted in the dependent portion of the largest lesion. There was no apparent connection to the biliary tree. Several similar smaller lesions were seen in the medial segment of the left lobe posteriorly. The pancreas was mildly and diffusely enlarged without evidence of peripancreatic fluid collection or ductal dilation. There was no cholelithiasis.

Computerized tomography (CT) of the abdomen suggested that the cystic lesions seen on ultrasound were focal biliary ductal ectasia with associated intraductal debris (Figure 1). There was mild dilation of the intrahepatic ductal system; the extrahepatic bile ducts, however, appeared normal. The pancreas was enlarged with no calcification.

Endoscopic retrograde cholangiopancreatography (ERCP) subsequently showed the biliary tree to have widespread stricturing and proximal dilation in both the intra- and extrahepatic ducts, including the cystic duct (Figure 3). There were two dominant strictures, one in the distal common bile duct showing the characteristic saccular out-pouchings typical of sclerosing cholangitis and the other located in the common hepatic duct. The cystic structures were in commu-

nication with the biliary tree. The pancreatic duct was normal.

Prednisone 100 mg daily and folic acid 5 mg daily were begun to treat the hemolytic anemia. Three days following admission the amylase normalized and clinical status improved. He was discharged on a tapering course of prednisone but required readmission four weeks later for acute onset abdominal pain, obstructive jaundice and fever. Hemoglobin on admission was 137 g/L while on prednisone 30 mg daily. Leukocyte count was  $14.4 \times 10^9/L$  and the amylase was elevated to 622 IU/L. Repeat abdominal sonography showed a slight decrease in the size of the cystic lesions. The patient recovered well following intravenous antibiotics.

Abdominal sonogram performed in September 1991, nine months after initial presentation, showed partial resolution of the cystic structures; the largest one was  $34 \times 25$  mm, while some of the others completely disappeared.

Following two more episodes of acute pancreatitis a 12 cm, 7F stent was positioned in the common bile duct in October 1991 and replaced with a larger stent four months later. There has not been any recurrence of acute pancreatitis since the first stent insertion. In August the stent was removed, and a cholangiogram revealed almost complete resolution of the extrahepatic strictures with intrahepatic duct disease remaining. In November 1992 he was started on ursodeoxycholic acid in an attempt to slow the progression of the liver disease. A flexible fiberoptic sigmoidoscopy at that time was normal.

The patient also developed significant low back pain and stiffness, and was found to have roentgenographic evidence of sacroiliitis. He is HLA-B27-positive, and a diagnosis of ankylosing spondylitis was made. He had an excellent response to nonsteroidal anti-inflammatory drug therapy.

At present the patient has no PSC symptoms. The autoimmune hemolytic anemia is quiescent off corticosteroids and the ankylosing spondylitis is well controlled.

## DISCUSSION

PSC is an uncommon condition of unknown etiology characterized by chronic progressive inflammatory fibrosis of the intra- and extrahepatic biliary tracts, frequently leading to biliary cirrhosis, portal hypertension, liver failure and premature death (4-6). Most cases of PSC are detected by abnormal liver enzymes, jaundice and, less commonly, symptoms of cholangitis (3). This patient had an unusual clinical presentation with acute pancreatitis, possible hepatic abscesses and autoimmune hemolytic anemia.

Initial abdominal sonography revealed cystic structures that were not obviously connected to the biliary tree. However, while CT scan demonstrated these structures to be focal ectasia of the intrahepatic biliary tree, it failed to show the abnormal extrahepatic ductal system. These findings suggested a diagnosis of Caroli's disease among other less likely possibilities such as multiple hepatic abscesses or necrotic metastases. The importance of ERCP in the diagnosis of PSC is exemplified by this case; ERCP demonstrated widespread severe stricturing and proximal dilation of both

the intra- and extrahepatic ducts, which facilitated exclusion of Caroli's disease and confirmation of PSC.

Although multifocal cholangiocarcinoma or cholangiocarcinoma complicating sclerosing cholangitis could not initially be excluded, the patient's young age, lack of progressive jaundice and prolonged survival make these unlikely. A sclerosing cholangitic process can be found in patients with AIDS (7); however, this patient has continued to have negative serology for HIV.

Subsequent CT scan and sonogram showed resolution of the cystic structures. Whether those structures were abscesses or (more likely) just focal duct dilations is unclear. In our patient the stricturing and beading of the intra- and extrahepatic bile ducts seen on ERCP did not change initially, but were altered only after prolonged stent and bile salt therapy. Therefore these bile duct lesions are unlikely to be secondary to other etiologies. A pattern typical of PSC, which normalizes following percutaneous drainage, has reportedly been induced by hepatic abscesses (8).

Acute pancreatitis, in the absence of cholelithiasis, was a presenting and recurrent complicating factor in our patient. CT scan and pancreatogram did not show any evidence of chronic pancreatitis, an association reported clinically (9,10) and demonstrated endoscopically by changes on pancreatography (the changes resembling those seen in chronic pancreatitis) (11,12). However, pancreatic ductal abnormalities were quite variable, occurring in 0% to 50% of patients with PSC in various series (11,13).

We found only two cases of acute pancreatitis in the setting of PSC. Goldin et al (14) reported a case of severe recurrent acute pancreatitis as a presenting symptom of PSC, whereas Schep and Scully (15) reported acute pancreatitis complicating the course of PSC in a patient with sarcoidosis. Although the pathogenesis of acute pancreatitis in the setting of PSC remains to be elucidated, stricturing of the bile ducts or choledochopancreatic duct junction leading to biliary stasis likely plays a role. A recent prospective study showed biliary sludge to be an underestimated cause of acute idiopathic pancreatitis (16). Considering the physiological and anatomical changes in PSC, it is surprising that acute pancreatitis does not occur more frequently.

Despite its rare association with ulcerative colitis (17), autoimmune hemolytic anemia has been reported on only two occasions in PSC without evidence of ulcerative colitis (1,2). Besides its well recognized association with inflammatory bowel disease (18,19), PSC has less commonly been associated with a variety of other diseases that may also be immunologically mediated, including Riedel's struma, retroperitoneal fibrosis (20), Sjögren's syndrome (21), sarcoidosis (15), hyperthyroidism (2), orbital fibrosis, Peyronie's disease, histiocytosis X, angioblastic lymphadenopathy (22) and immunodeficiency syndromes (7,23).

Although the pathogenesis of PSC has yet to be defined, many immunological abnormalities have been observed such that disordered immune regulation has been postulated as a major factor in the mechanism of injury. HLA-B8 and HLA-DR3 antigens are common in PSC and associated with

an increased incidence of other autoimmune diseases (19,24). Other immunological abnormalities in PSC include elevated levels (25,26) and reduced clearance (27,28) of circulating immune complexes, increased complement metabolism (26,29) and circulating autoantibodies against the colon and the portal tract (30,31).

In addition, disturbances of cell-mediated immunity have also been reported in PSC with enhanced autoreactivity of T lymphocytes (32), inhibited leukocyte migration in response to biliary antigens (33), lymphocyte infiltration in areas of portal damage suggesting immune-mediated destructive processes, and altered lymphocyte subset ratios, yielding a significant decrease in both the absolute number and relative proportions of suppressor/cytotoxic cells (34).

This patient progressed to develop sacroiliitis with ankylosing spondylitis, a well known extraintestinal manifestation of ulcerative colitis, but rarely encountered in PSC. Interestingly, there is no evidence of ulcerative colitis in our patient, who has an entirely normal fiberoptic sigmoido-

scopy. The pathogenesis of ankylosing spondylitis is poorly understood but immune-mediated mechanisms have been implicated.

All these findings suggest an important role for immunoregulatory dysfunction in the pathogenesis of PSC and give support to the increasing association with immunologically mediated diseases such as autoimmune hemolytic anemia and ankylosing spondylitis.

In summary, we report a unique clinical presentation of PSC in which acute pancreatitis and autoimmune hemolytic anemia were simultaneously encountered and ankylosing spondylitis subsequently developed, in the absence of ulcerative colitis.

#### ADDENDUM

Since submission of this paper, another report of this association of diseases has been published (*Can J Gastroenterol* 1996;10:301-303).

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