

RETRACTED ARTICLE: Overlap of primary biliary cirrhosis and primary sclerosing cholangitis – a rare coincidence or a new syndrome

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Background: Overlap syndrome has been introduced to the field of hepatology to describe the coexistence of two or more autoimmune hepatic conditions in the same individual. This is a rare clinical case of a patient diagnosed with primary biliary cirrhosis (PBC) who later developed primary sclerosing cholangitis (PSC). This is a unique case as no other cases with a similar pattern have been reported. Overlap syndrome does not include the coexistence of PBC and PSC as a distinctive syndrome so far.

Case report: A middle-aged woman suffering from PBC for 17 years got admitted with clinical and biochemical features of cholestatic syndrome. A provisional diagnosis of worsening PBC was proved wrong by magnetic resonance cholangiopancreatography, which revealed typical benign stricture and dilatation of common bile duct with typical beading appearance suggestive of PSC. The patient was treated and treated with an increased dose of ursodeoxycholic acid (UDCA) which improved her symptoms and the biochemical picture.

Conclusion: This is a rare overlap of PBC–PSC. It is very difficult to say whether it is a rare coincidence or a new overlap syndrome, but there are no clear guidelines for management of these patients. Currently, the treatment involves endoscopic duct dilatation, UDCA, and regular follow-ups to rule out hepato-biliary tumor occurrence.

Keywords: primary biliary cirrhosis, primary sclerosing cholangitis, hepatic overlap syndrome

Introduction

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease with the histological features of chronic inflammation and fibrotic obliteration of the hepatic biliary tree, resulting in bile stasis and hepatic fibrosis.¹ It commonly co-exists with autoimmune hepatitis (AIH) as a part of hepatic overlap syndrome. In our case, it presents on the background of primary biliary cirrhosis (PBC), another autoimmune disorder affecting the hepatobiliary structures.

Case report

A 64-year-old woman with a history of PBC presented with a two-week history of obstructive jaundice. PBC was first diagnosed in 1992 when she presented with lethargy, pruritus, and deranged liver function tests. At that time she had a normal endoscopic retrograde cholangiopancreatography (ERCP) and her antimitochondrial antibody (AMA) was negative, but liver biopsy revealed PBC. She was treated with ursodeoxycholic acid (UDCA). A repeat biopsy in 1996 revealed similar histological appearance (Figure 1) which revealed a portal tract with dense lymphoplasmacytic infiltrate and lymphoid aggregate in addition to interlobular bile ducts showing a focal

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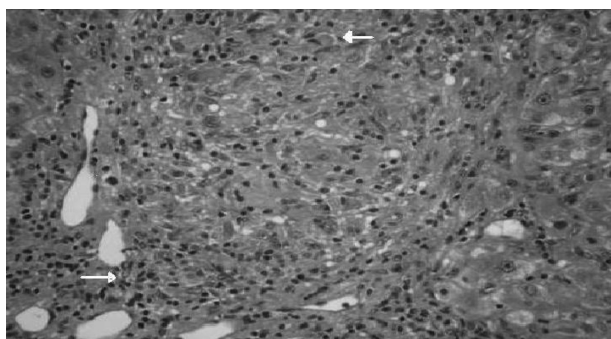


Figure 1 Histopathology periodic acid-Schiff staining reveals lymphoplasmacytic and lymphoid aggregates and damaged bile ducts (arrows).

rupture of its cholangiocytic lining at the site of an adjacent epithelioid granuloma, and no evidence of any dysplasia. For the next seventeen years her baseline alkaline phosphatase, bilirubin, and transaminase levels were stable. She was also suffering from rheumatoid arthritis for which she was on prednisolone and azathioprine.

Current admission was due to two weeks history of jaundice, abdominal pain, loss of appetite, nausea, vomiting, loss of weight, fever, pale stools, and dark urine. She never had these symptoms with PBC.

On clinical examination she was dry, flushed, febrile, icteric, tachycardic, dyspneic, and scratch marks on her skin. No other clinical signs of chronic liver disease. Chest was clear, and heart sounds were normal and hemodynamically stable. Abdominal examination revealed soft abdomen with right upper quadrant tenderness and normal bowel sounds. No evidence of ascites, splenomegaly, and pedal edema was found. Routine laboratory tests revealed normal renal functions, electrolytes, and bone profile, but C-reactive protein was elevated at 335 mg/L. Liver function tests showed predominantly cholestatic picture with elevated alkaline phosphatase at 2,627 IU/L and bilirubin at 377 $\mu\text{mol/L}$, but the synthetic function of the liver was within normal range. Her full blood count was essentially normal apart from an elevated white blood cell count of 160,000/ml secondary to neutrophilia. Liver autoimmune screen and tumor marker results are listed in Table 1.

An ultrasound scan of the liver and biliary system showed heterogeneous liver texture and irregular margins. Both lobes of the liver showed intrahepatic duct dilatation. No focal lesion was noted. The common bile duct (CBD) was dilated down to the pancreas, but no definite obstructive lesion or stone was found. Mild pancreatic duct dilatation was also noted. Computer tomography imaging (Figure 2) showed similar appearances with change in caliber of distal CBD at the

Table 1 Liver autoimmune and virology screen

AMA M2 negative
Smooth muscle antibodies negative
LKM antibodies negative
Gastric parietal cell antibody negative
Anti-nuclear HEp-2 antibodies positive (Weak)
ANCA MPO negative
ANCA PR3 negative
ds - DNA antibodies negative
ENA antibody screen negative
Immunoglobulin IgG4 negative
Hepatitis serology A,B,C negative
Ca 19-9, alpha feto protein, CEA 125 within normal range
Immunoglobulin IgA, IgG, IgM within normal range

pancreatic level. There was no evidence of pancreatic mass or stone. No fibrosis or calcification was noted in the pancreas. There was a slight concentric wall thickening of the distal duct. ERCP imaging (Figure 3) revealed a low benign-looking stricture with intraluminal dilatation suggestive of PSC and a plastic stent was inserted for biliary drainage. To confirm the above diagnosis ERCP imaging (Figure 4) showcased dilatation of CBD distally measuring up to 1.5 cm tapering at the ampulla. The ducts showed significant typical beading appearance which would go with presumptive diagnosis of PSC.

The patient was treated with intravenous antibiotics, fluids, and a high dose of UDCA. She clinically got better, and liver and infection markers settled. The patient was discharged with regular follow-up arrangements.

Discussion

Overlap syndrome includes various forms of autoimmune hepatobiliary diseases such as AIH, PBC, PSC, and



Figure 2 Computerized tomography reveals dilated intrahepatic biliary ducts.



Figure 3 Endoscopic retrograde cholangiopancreatography reveals dilated intrahepatic ducts with the characteristic beading appearance suggestive of primary sclerosing cholangitis.

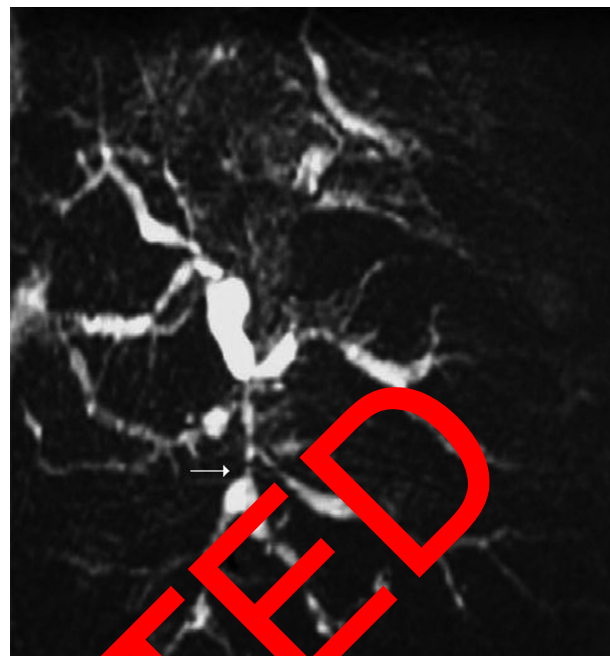


Figure 4 Magnetic resonance cholangiopancreatography reveals typical beading appearance of dilated intrahepatic bile ducts characteristic of primary sclerosing cholangitis.

autoimmune cholangitis (AIC) coexisting in an individual.² They have a combination of hepatic and cholestatic biochemical and histological features of AIH, PBC, PSC, and/or AIC, and usually show a progressive course toward liver cirrhosis and liver failure without adequate treatment. AIH–PBC overlap syndrome has been reported in almost 10% of adults with AIH or PBC, whereas AIH–PSC overlap syndrome was found in 6%–8% of children, adolescents, and young adults with AIH or PSC.³ A small amount of patients may also show a change from stable PBC to AIH, AIH to PBC, or AIH to PSC, as documented by single case reports and small case series. Single cases of AIH and AIC (AMA negative PBC) overlap have also been reported. Transition from one autoimmune hepatopathy to another (eg, from PBC to AIH and from AIH to PSC) have also been reported.⁴ The overlap syndrome appears to be misused when characteristic features of an autoimmune hepatopathy are detected together with those of a second liver disease (eg, chronic hepatitis A). It is not clear whether these overlap syndromes form separate groups or are only variants of the major autoimmune hepatic diseases.⁵ No standard diagnostic criteria for overlap syndromes has been achieved so far.⁶

This case showcases hepatic overlap syndrome with an uncommon combination of PBC–PSC associated with additional autoimmune disorder (rheumatoid arthritis). There has been no other case reported with co-existing PBC histology and PSC structural duct pattern with the background of rheumatoid arthritis. Only one other similar case has been reported with PSC histology and PBC specific antibodies. In our case patient, the AMA were negative with positive

PBC histology suggesting the possibility of autoimmune cholangitis. However, immunofluorescence method was used instead of immunoblotting method which is more sensitive. A study of Japanese patients found the immunoblot was positive in nearly 30% of AMA negative patients by immunofluorescence, suggesting that not all patients with AMA negative immunology are truly negative.⁷

In management of hepatic overlap syndromes there is no clear consensus on treatment. There are no specific management criteria for PBC–PSC that has been published thus far.⁸ In general, all of the overlap syndromes use one or more of the treatment options given below. It includes usage of UDCA if the combination includes PBC, PSC, or AIC. Studies reveal consistent evidence of improved liver biochemistries and improved survival. UDCA is widely used and has shown the ability to produce a reduction in need for liver transplantation. Immuno-suppressive therapies such as corticosteroids, especially prednisolone and azathioprine, are ideal options available. In steroid resistant cases of AIH–PBC, cyclosporine has been tried. Endoscopic stricture dilatation and stenting also plays an important role in relieving the obstruction and helps in good biliary drainage. Liver transplantation is regarded as the treatment of choice in end stage liver disease secondary to overlap syndromes.

Periodic monitoring of liver function tests should be performed at three- to six-month intervals. This helps to detect the rare patients who go on to develop AIH on top

of other combinations and also indicates whether UDCA is improving liver function. Thyroid status should be monitored annually. For patients with known cirrhosis with a Mayo risk score of more than 4.1, upper gastrointestinal endoscopy needs to be performed for assessment of varices every two to three years. Bone mineral density should be assessed every two to four years depending on baseline density and severity of cholestasis. Similarly, fat soluble vitamin levels should be monitored annually in patients with jaundice. Cross-sectional imaging usually with ultrasound and alpha-fetoprotein levels to screen for hepatocellular cancer should be performed every 6–12 months in patients with cirrhosis and older men.

Conclusion

The exceptional rarity of this case scenario with overlap of PBC–PSC when compared with frequency of AIH–PBC and AIH–PSC overlap in patients with major autoimmune hepatobiliary diseases and the incidence is statistically less significant may lead to conclusion that this case would be a pure coexistence of PBC and PSC rather than a new overlap syndrome. UDCA is the only drug option beneficial in both PBC and PSC. Drugs such as chlorambucil, penicillamine, cyclosporine, corticosteroids, and azathioprine have been tested, but none have any benefits over UDCA. Until now there have been no effective studies that have given us any appropriate guidance for investigation, management,

and follow-up of the PBC–PSC patients. There is no clear evidence about risk of hepatobiliary tumors in these patients. For now treatment remains mainly symptomatic. Regular outpatient monitoring with liver-specific laboratory investigations and imaging is essential.

Disclosure

The author reports no conflicts of interest in this work.

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