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CASE REPORT | BILIARY

Overlap Syndrome between Primary Biliary Cholangitis and Primary Sclerosing Cholangitis

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ABSTRACT

Overlap syndrome indicates the coexistence of 2 or more autoimmune liver diseases in the same individual, occurring simultaneously or sequentially. Cases of overlap of autoimmune hepatitis (AIH) with primary biliary cholangitis (PBC) and of AIH with primary sclerosing cholangitis (PSC) are known and have defined criteria for diagnosis. Overlap between PBC and PSC has been reported in only a few case reports. The cause for the rarity of this entity compared to other overlap syndromes is unclear. We present a case of an overlap syndrome of PBC with PSC in a 35-year-old woman.

INTRODUCTION

The overlap syndromes of autoimmune hepatitis (AIH) with primary biliary cholangitis (PBC) and of AIH with primary sclerosing cholangitis (PSC) are known and have been reported frequently. However, overlap of PBC with PSC has been reported in only few cases. With the health care profession's constantly expanding investigational armamentarium, more cases may be diagnosed.

CASE REPORT

A 35-year-old woman presented with complaints of generalized weakness, easy fatigability, and generalized pruritus for 4 years. She developed ascites and jaundice 4 months prior to presentation. There was no history of hepatotoxic medications, alcohol consumption, previous jaundice, or decompensation. On examination, she had pedal edema, icterus, and ascites. Her investigations are noted in Table 1. Ascitic fluid analysis was suggestive of a high serum albumin to ascites gradient with no evidence of spontaneous bacterial peritonitis.

Liver biopsy showed portal tracts with fibrosis and bile ductular proliferation with mild portal tract inflammation (Figure 1). There was no interface hepatitis. Occasional ductocentric lymphoid aggregates were seen in the vicinity of the hepatic artery. A few portal tracts showed an absence of bile ducts. There were canalicular bile plugs with Mallory hyaline bodies. No onion-skin fibrosis or granulomas were seen.

Magnetic resonance cholangiopancreatography (MRCP), performed due to the features similar to PSC or a PBC-PSC overlap, showed liver parenchymal disease with mild splenomegaly (Figure 2). Smooth, short-segment narrowing was seen in the common bile duct at the porta (1.4 mm diameter) with no upstream dilatation. Left-sided intrahepatic biliary radicles showed irregularity with subtle beading. Central intrahepatic biliary radicle dilatation was seen in the left anterior duct with abrupt cutoff secondary to a stricture. These findings were suggestive of PSC. She underwent endoscopic retrograde cholangiopancreatography (ERCP) and dilatation of the common bile duct stricture with short-term stent placement. Biliary brushings taken

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Table 1. Laboratory values.

Investigations	Values	Serology	Results
Total/direct bilirubin	4.0/3.1 mg/mL	HBsAg ELISA	Negative
AST/ALT	117/41 U/L	antiHCV ELISA	Negative
ALP	1,047 U/L	antiHBc Total	Negative
Albumin	2.4 g/mL	HIV ELISA	Negative
PT/INR	18 sec/1.58	ANA	Positive (1:640)
Creatinine	1.0 mg/mL	ASMA	Negative
Hemoglobin	8.1 g/mL	AMA M2	Positive
Platelets	140,000/mm^3	Total IgG	1,998 (up to 1,500)
Total leukocyte count	4,400/mm^3	CA 19-9	31 U/L
GGTP	353 U/L	IgG4	110 mg%

AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; PT: prothrombin; INR: international normalized ratio; GGTP: gamma-glutamyl-transpeptidase; HBsAg: surface antigen of the hepatitis B virus; ELISA: enzyme-linked immunosorbent assay; HCV: hepatitis C virus; HBc: hepatitis B core; HIV: human immunodeficiency virus; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibody; AMA-M2: antimitochondrial antibody of M2; IgG: immunoglobulin G; CA 19-9: cancer antigen 19-9.

during ERCP did not show any atypical cells. Colonoscopy was grossly normal, although mapping biopsies revealed the presence of focal active colitis with diffuse lymphoplasmacytic infiltrate in the lamina propria of the entire colon with focal paneth cell metaplasia that was suggestive of changes related to early inflammatory bowel disease (IBD). Serum IgG4 levels were within normal limits, ruling out IgG4-related diseases. With imaging results suggestive of PSC, positivity for antimitochondrial antibody (AMA) of M2 (AMA-M2), liver biopsy findings as described, and features suggestive of early IBD on colonic biopsies, the diagnosis of an overlap between PBC and PSC was proposed.

The patient was subsequently started on diuretics and ursodeoxycholic acid (UDCA) 750 mg daily. On follow-up, her ascites had resolved after 4 weeks. Total bilirubin and alkaline phosphatase reduced to 2 mg/dL and 510 U/L, respectively, and she was continued on UDCA. No episodes of decompensation occurred over 3 months of follow-up.

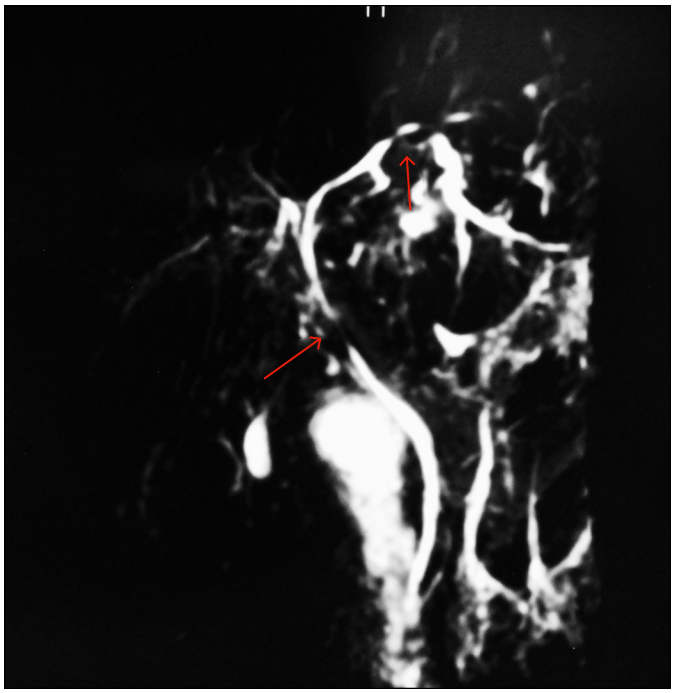

Figure 2. Dominant stricture on magnetic resonance cholangiopancreatography.

DISCUSSION

Overlap with AIH is seen in up to 7% of patients with PBC and up to 14% with PSC, per the revised IAIHG criteria.[1] However, a review of literature revealed that only 10 cases of PBC-PSC overlap have been reported.[2-9] No defined criteria are available for PBC-PSC overlap syndrome, which means that this syndrome is diagnosed when a patient fulfills diagnostic criteria for both conditions. AMA-M2 positivity is seen in our patient, as was seen in all but one previously reported case. AMA-M2 has a sensitivity of 84% and specificity of 97% for PBC, and the positive and negative predictive value are more than 95%.[10] MRCP reveals the presence of dominant stricture in 45–58% patients with PSC, although only 15–20% of patients with dominant strictures experience symptoms. The role of UDCA in patients with PSC is unclear.[11] Our

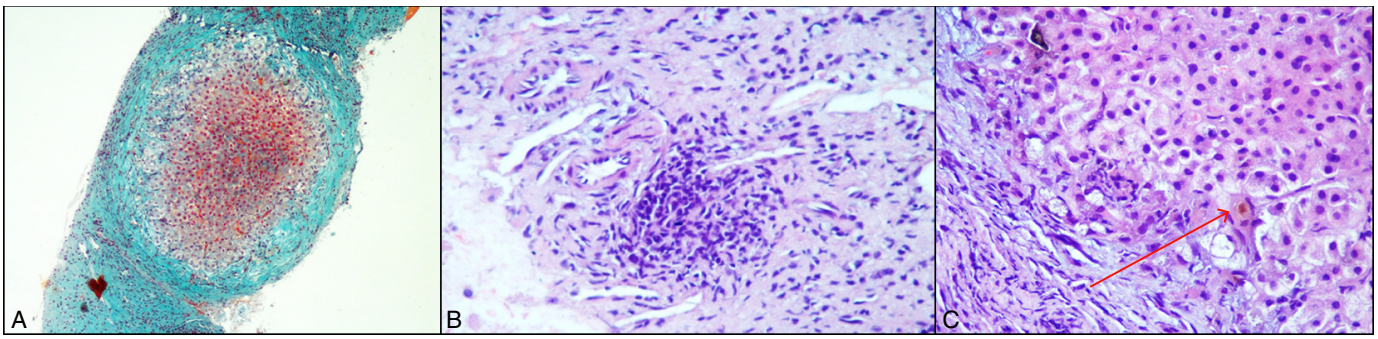

Figure 1. Liver biopsy showing (A) a cirrhotic nodule as a seen with Masson's trichrome, (B) ductocentric inflammation, and (C) canalicular bile plugs with intrahepatic cholestasis.

patient had a dominant stricture with clinical and biochemical response to endoscopic therapy. PSC-like features were seen on imaging in all the cases except one case of overlap between small-duct PSC with PBC.[6] In PBC, UDCA had been the only approved medical treatment to reduce progression of disease until obeticholic acid was approved 2 years ago for use in patients intolerant to UDCA or in combination with UDCA as a second-line agent.[12]

The proposed hypothesis for the pathogenesis of overlap syndromes are that they may represent atypical manifestations of classic diseases, transition stages in the evolution of classic diseases, concurrent diseases in the same individual, or separate pathological entities with their own distinctive pathogenic mechanisms and clinical outcomes.[13] Our patient had dominant stricture with cholestasis suggestive of PSC. The diagnosis of PBC was kept because the patient was positive for AMA and exhibited features of chronic cholangitis with cirrhosis. This led to the diagnosis of PBC-PSC overlap (i.e., predominant PSC with reminiscent features of PBC).

A review of literature suggests that there are 8 case reports or case series describing 9 cases of PBC-PSC overlap syndrome, and one patient with features of all 3 autoimmune liver diseases (i.e., AIH, PBC, and PSC) was described by Kingham et al.[4] All previously described cases involve middle-aged women, with the exception of 1 case report by Rubel et al[2] that involved a middle-aged man. The frequency of PBC-PSC overlap is rare, with only 2 cases (0.7%) out of a cohort of more than 260 patients followed up for more than 20 years as reported by Kingham and Abbasi.[4] These patients presented with fatigue, pruritus, jaundice, or abdominal pain, or were investigated for elevated liver enzymes. Features of other immune disorders were seen in the form of psoriasis with arthropathy in one patient, and scleroderma with vasculitis and Hashimoto's thyroiditis in another patient.[7,9] Up to 70% of patients with PSC have known association with IBD, which may present before, at the same time as, or after PSC.[11] There were histopathologic features of IBD in one of the previously reported cases, although colonoscopic evaluation was normal.[9] In 6 previous case reports, patients showed clinical, biochemical, and histological features of PBC initially, and subsequently went on to develop cholangiographic changes indicative of PSC. With regard to treatment, the literature suggests that patients with PBC-PSC overlap syndrome were treated with UDCA at varying doses, and in some cases the patients responded satisfactorily. Our case adds to the limited existing literature on PBC-PSC overlap syndrome, which may be a separate pathological entity with its own distinctive pathogenesis and outcomes that are yet to be further elucidated.

DISCLOSURES

Author contributions: All authors contributed equally to the manuscript. S. Sundaram is the article guarantor.

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Informed consent was obtained for this case report.

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