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CASE REPORT | BILIARY

Immunoglobulin G4-Seronegative Autoimmune Cholangiopathy With Pancreatic and Hepatic Involvement Mimicking as Primary Sclerosing Cholangitis

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ABSTRACT

Immunoglobulin G4-seronegative autoimmune cholangiopathy is a rare cause of biliary strictures. We describe a 27-year-old man presenting with elevated liver enzymes, recurrent cholangitis/bacteremia, biliary strictures, and normal immunoglobulin G4 levels, who was initially diagnosed with primary sclerosing cholangitis, and later listed for transplantation for recurrent bacteremia. Subsequent surveillance imaging demonstrated morphologic changes consistent with biliary strictures and autoimmune pancreatitis. Initiating corticosteroids resulted in liver enzyme normalization and stricture improvement. Diagnosing seronegative autoimmune cholangiopathy remains challenging given similar presentation to primary sclerosing cholangitis. This case highlights importance of a wide differential for biliary strictures, with increased suspicion in those developing pancreatic changes in this setting.

KEYWORDS: primary sclerosing cholangitis; PSC; biliary strictures; IgG4 cholangiopathy; autoimmune pancreatitis

INTRODUCTION

Immunoglobulin (Ig) G4-sclerosing cholangitis (SC), commonly associated with autoimmune pancreatitis, is a steroid-responsive hepatobiliary inflammatory process characterized by elevated serum IgG4 levels. IgG4-seronegative autoimmune cholangiopathy (AIC; or IgG4-seronegative SC) and autoimmune pancreatitis are rare, with only 4 previous cases reported.[1,2] Diagnosis of IgG4 seronegative AIC with pancreatic and hepatic involvement remains difficult because of similarity in presentation to primary SC (PSC), pancreatitis/pancreatic cancer, and cholangiocarcinoma. This case demonstrates management of a case of IgG4-seronegative AIC mimicking PSC.

CASE REPORT

A 27-year-old White man with a history of asthma, aspirin allergy, and nasal polypoid disease presented with 4 months of daily abdominal bloating, loose stools, and occasional hematochezia. He denied fevers, chills, nausea, or vomiting. His family history was significant for psoriatic arthritis in his father, Celiac disease in his great aunt, and colon cancer in his uncle. He denied drug indiscretions and use of tobacco, though endorsed drinking socially.

Initial evaluation demonstrated negative stool cultures, and serologies were negative for Celiac disease but did reveal elevated liver tests (aspartate aminotransferase [AST] 40 U/L, alanine aminotransferase [ALT] 57 U/L, and alkaline phosphatase [ALP] 158 U/L). Abdominal ultrasound showed mild intrahepatic bile duct and common bile duct thickening without evidence of intrahepatic or extrahepatic bile duct dilatation. A colonoscopy did not show evidence of inflammatory bowel disease, and magnetic resonance

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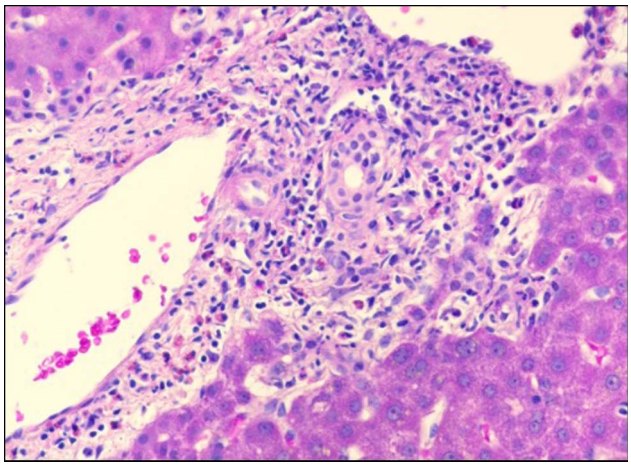

Figure 1. Hematoxylin and eosin (400×)-stained histologic sections of the native liver biopsy demonstrated mild portal inflammation, interlobular bile ducts with lymphocytic cholangitis, portal edema, and ductular reaction compatible with the patient's known diagnosis of primary sclerosing cholangitis (PSC). The presence of lymphocytic cholangitis involving small bile ducts additionally raised suspicion for autoimmune cholangitis or concomitant small duct PSC/exacerbation of PSC.

cholangiopancreatography (MRCP) assessing his biliary tree showed mild intrahepatic biliary ductal dilation with a beaded appearance. Given imaging findings and his significant family history of autoimmune disease, a diagnosis of PSC was made.

He was lost to follow-up until 6 years later, when he presented with a worsening cholestatic profile (AST 85 U/L, ALT 153 U/L, and ALP 644 U/L) and fever concerning for cholangitis. Repeat serologies were negative for the presence of antimitochondrial antibody, anti-smooth muscle antibody, alpha-1-antitrypsin, antinuclear antibody, all subclasses of IgG, cancer antigen 19-9, and perinuclear anti-neutrophil cytoplasmic antibodies. Endoscopic retrograde cholangiopancreatography (ERCP) showed a diffusely diseased biliary system characterized by thin, irregular, beaded ducts without dominant stricture, consistent with PSC.

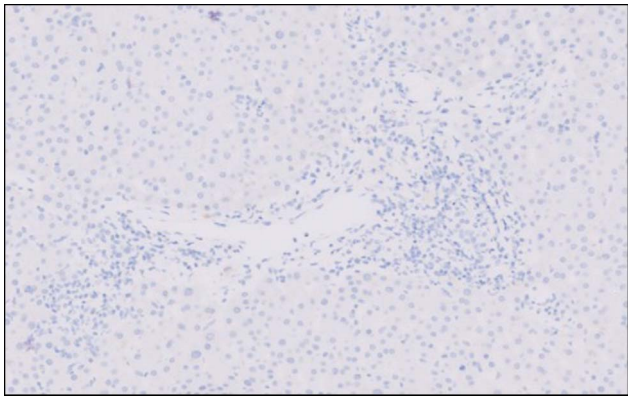

Figure 2. Immunohistochemical staining (400×) for immunoglobulin G4 showing a lack of plasma cell infiltrates, further lowering suspicion for autoimmune pancreatitis given absent immunoglobulin G4 markers seen on laboratory testing.

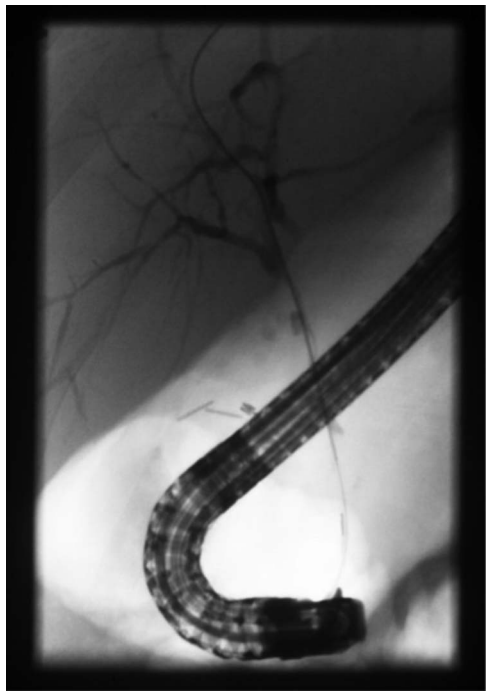

Figure 3. Both right and left intrahepatic biliary systems were notable for multiple segments of stenosis and dilation (beading) consistent with primary sclerosing cholangitis.

After a repeat colonoscopy showed no evidence of inflammatory bowel disease, he returned with fever, jaundice, and an abrupt elevation in liver enzymes (AST 476 U/L, ALT 731 U/L, ALP 588 U/L, and bilirubin 2.0 mg/dL) and a positive antinuclear antibody. Hematoxylin and eosin-stained histologic sections on liver biopsy (Figure 1) demonstrated patchy portal lymphocyte-predominant inflammation admixed with eosinophils and a few plasma cells; associated patchy ductular reaction and portal edema were seen, with negative staining for IgG4-related disease (Figure 2). Given these findings, the leading differential was cholangitis in the setting of PSC. The patient was treated with a prolonged course of ciprofloxacin, and ursodeoxycholic acid was initiated at 500 mg twice daily.

In the next year, he had multiple hospitalizations for recurrent bouts of cholangitis complicated by bacteremia. MRCP indicated new focal strictures and intrahepatic biliary dilatation in the peripheral aspect of segment 5. ERCP a year later showed a 3 mm common bile duct with a 1 mm common hepatic duct stricture extending into the left main hepatic duct (Figure 3); brushings with fluorescence in situ hybridization were negative for malignancy. A stent requiring subsequent exchanges was placed, and he was listed for liver transplantation given recurrent bouts of cholangitis with bacteremia in the setting of PSC.

On follow-up cholangiocarcinoma surveillance, MRCP revealed a sharply demarcated T2 moderately hyperintense, T1 hypointense appearance of the distal 4 cm of the pancreatic tail with early hypoenhancement and delayed hyperenhancement suggestive of inflammation and fibrosis. There was also marked

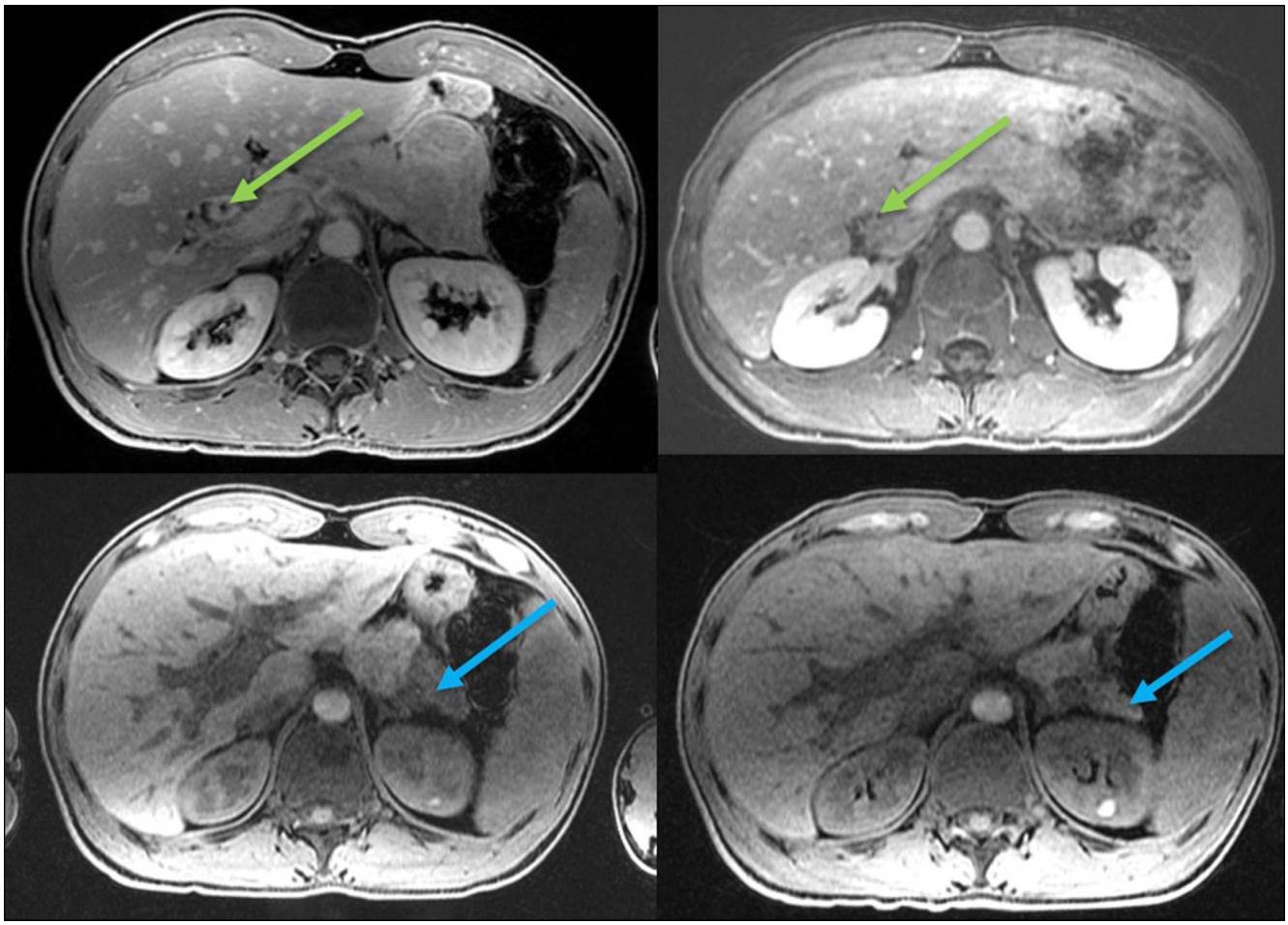

Figure 4. Left, top: Delayed postcontrast T1-weighted fat-suppressed image demonstrates marked peribiliary thickening and enhancement around the common hepatic duct (green arrow). Left, bottom: Axial T1-weighted precontrast fat-suppressed image reveals sharply demarcated abnormal hypointense T1 signal in the pancreatic tail (blue arrow). Right top: Delayed postcontrast T1-weighted fat-suppressed image obtained 6 months after initiation of steroids demonstrates resolution of peribiliary thickening and enhancement around the common hepatic duct (green arrow). Right, bottom: Delayed postcontrast T1-weighted fat-suppressed image obtained 6 months after initiation of steroids shows normalization of the T1 signal in the pancreatic tail (blue arrow).

periductal enhancement of the common hepatic duct with long-segment stenosis consistent with acute on chronic PSC (Figure 4). Endoscopic ultrasound with fine needle biopsy of the pancreas failed to obtain sufficient tissue sample. Given the findings on MRCP, there was suspicion for IgG4-seronegative AIC with pancreatic involvement rather than PSC, and he was started on prednisone 40 mg daily.

Over the next year, he experienced normalization of his liver tests (AST 20 U/L, ALT 25 U/L, and ALP 79 U/L; Figure 5),

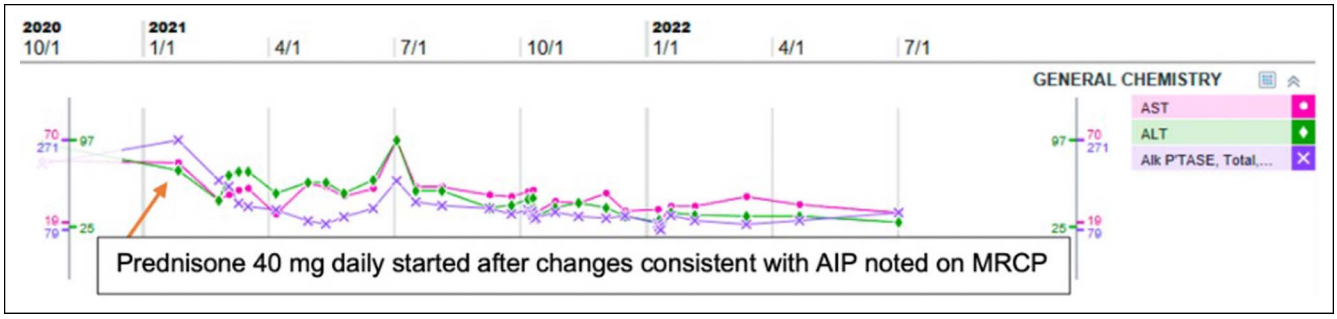

Figure 5. Liver function tests normalize after initiation of corticosteroid therapy in February 2021. AIP, autoimmune pancreatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MRCP, magnetic resonance cholangiopancreatography.

although he did have 2 additional episodes of cholangitis with bacteremia. The final diagnosis was concluded to be IgG4-seronegative AIC with hepatic and pancreatic involvement. Three weeks after initiation of steroids, there was improvement of biliary wall thickening and enhancement on magnetic resonance imaging (Figure 4). ERCP showed marked improvement in biliary tree strictures, and biliary stents were removed. He continues on azathioprine, and a tapered dose of prednisone is no longer pursuing orthotopic liver transplantation.

DISCUSSION

This case highlights the challenges of diagnosing IgG4-seronegative AIC and the difficulty in differentiating PSC from other causes of secondary SC and malignancy.[3] Traditionally, the gold standard for diagnosis of PSC is ERCP showing segmental fibrosis within both intrahepatic and extrahepatic bile ducts separated by normal areas of saccular dilatation, commonly referred to as "beads on a string."[1]

Despite both magnetic resonance imaging and ERCP showing classic PSC findings which were confirmed by liver biopsy with negative IgG4 staining and normal serum IgG4 levels, it was not until a surveillance MRCP demonstrated inflammation and fibrosis of the pancreatic tail, that the differential of IgG4-seronegative AIC with pancreatic involvement was entertained. This case reiterates the importance of continued surveillance in those with PSC. The difficulty in identifying a correct diagnosis is exacerbated by the low incidence rate of PSC[2] (0.5–1.3 cases per 100,000 person-years) and significantly rarer incidence of IgG4-seronegative AIC.[3,4]

Ten years after initial presentation, a correct diagnosis was made for this patient, allowing initiation of therapy that normalized liver tests and improved biliary strictures. He has improved his quality of life substantially and has for now delayed proceeding to liver transplantation. A previous case series describes 3 IgG4-seronegative patients presenting with biliary strictures and pancreatic involvement that responded to initiation of corticosteroid therapy, thus highlighting the benefit of early identification and treatment of IgG4-seronegative AIC with pancreatic involvement. Our case differs in that the initial presentation was with biliary strictures only, with subsequent pancreatic involvement leading to the diagnosis and treatment. Given the rare[1] and steroid responsive nature of this disease, IgG4-seronegative autoimmune cholangiopathy is an important diagnosis to consider when encountering patients with suspected PSC and can present initially without pancreatic involvement.

DISCLOSURES

Author contributions: S. Achalu and R. Berry wrote the manuscript. MT Wei, S. Banerjee, P. Ghanouni, M. Kambham, and PY Kwo critically revised the manuscript. PY Kwo is the article guarantor.

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Informed consent was obtained for this case report.

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