Immunoglobulin G4–Associated Cholangitis Can Mimic Cholangiocarcinoma on Radiologic and Cholangioscopic Findings

Susana Gonzalez, MD 1
Roger Klein Moreira, MD 2
Elizabeth C. Verna, MD, MS 3
Benjamin Samstein, MD 3
John M. Poneros, MD 4

1Henry D. Janowitz Division of Gastroenterology, Mount Sinai School of Medicine, New York, New York; 2Department of Pathology, 3Center for Liver Disease and Transplantation, and 4Division of Digestive and Liver Diseases, Columbia University College of Physicians and Surgeons, New York, New York

Immunoglobulin G4 (IgG4)-related sclerosing disease (ISD) is a condition characterized by elevated serum IgG4 levels and dense IgG4-positive lymphoplasmacytic infiltrates that cause a marked fibrosis of the affected organs. Autoimmune pancreatitis (AIP) is the pancreatic manifestation of ISD, but multiple organs, including the salivary glands, retroperitoneum, kidneys, and biliary tree, can be involved.1 The biliary manifestation of this disease is IgG4-associated cholangitis (IAC), which can present with bile duct lesions that mimic cholangiocarcinomas.2 Distinguishing benign from malignant disease can be particularly challenging in these cases.

Case Report

A woman, age 27 years, presented with a 3-day history of weakness, pruritus, and choluria. Her medical history was significant only for asthma, and her medications included montelukast as needed for treatment of the asthma. She reported a family history of pancreatic cancer (which was diagnosed in a maternal uncle when he was in his fifties) and gastric cancer (which was diagnosed in her mother, who died at age 45 years, possibly because of the gastric malignancy). Initial laboratory analysis revealed an aspartate aminotransferase level of 246 U/L, alanine aminotransferase level of 442 U/L, alkaline phosphatase level of 301 U/L, total bilirubin level of 2.7 mg/dL, direct bilirubin level of 1.7 mg/dL, and amylase level of 564 U/L, with a normal lipase measure. Serologies for hepatitis were negative except for a positive hepatitis B surface antibody. An abdominal ultrasound was initially performed and demonstrated intrahepatic biliary ductal dilation without evidence of a mass or stone. Further evaluation with magnetic resonance cholangiopancreatography (MRCP) was suggested. MRCP revealed moderate dilation of the intrahepatic biliary ducts with stricturing of the right and left hepatic ducts as well as an amorphous, heterogeneous signal abnormality at the confluence of the right and left hepatic ducts suggesting a neoplastic process, such as a Klatskin tumor (Figure 1).
An endoscopic retrograde cholangiopancreatography (ERCP) with cholangioscopy (SpyGlass, Boston Scientific) was performed for further evaluation. A cholangiogram showed strictures in the common hepatic duct and right main hepatic duct with upstream dilation of the right intrahepatic ducts. Cholangioscopy of the strictures in the common hepatic duct demonstrated irregular mucosa with dilated and tortuous vessels and papillary-appearing mucosal projections (Figure 2). The left intrahepatic branches appeared normal. The right hepatic branches could not be visualized cholangioscopically. Cholangioscopic-directed biopsies of the irregular mucosa, brushings for cytology, and fluorescence in situ hybridization (FISH) analysis were performed. Plastic biliary stents were placed into the right and left hepatic ducts across the strictures.

FISH analysis was negative for aneuploidy, and cytology brushings were benign. Biopsy results showed inflammatory findings. Despite these results, the clinical suspicion for a malignancy remained high. The patient underwent right hepatic vein embolization followed by a laparoscopic right hepatectomy. Pathologic examination of the gross specimen revealed near-complete segmental obstruction involving a large bile duct near the resection margin. Marked thickening with accompanying induration of the bile duct wall was also noted in this region. Bile ducts proximal to this area were dilated and also showed variable wall thickening. The liver parenchyma was essentially unremarkable, with no evidence of fibrosis or nodularity. Histopathologic examination revealed marked chronic inflammatory infiltrate around large-caliber bile ducts. The inflammatory infiltrate was most prominent...
around the area of stricture (Figure 3) and was composed of lymphocytes as well as a large number of plasma cells (Figure 4A). Periductal fibrosis was noted in inflamed areas. Dilated segments of bile ducts also showed intraluminal and intraepithelial neutrophils, which are characteristic of superimposed acute (suppurative) cholangitis. There was no evidence of malignancy. Further evaluation of the inflammatory infiltrate by immunohistochemistry confirmed the presence of a large number of plasma cells (CD138 and IgG-positive), most of which (>80%) expressed IgG4 (Figure 4B). Postoperatively, serum IgG4 levels were checked and were elevated at a value of 168 mg/dL (normal, 21–134 mg/dL).

**Discussion**

ISD is a fibroinflammatory disorder that can involve multiple organs, including the salivary glands, lymph nodes, retroperitoneum, kidneys, and biliary tree. IgG4 sclerosing cholangitis is an emerging entity that is a part of the spectrum of ISDs. The typical clinical profile of patients with IAC is that of older men who present with obstructive jaundice, increased serum IgG4 levels, AIP, and abundant IgG4-positive plasma cells in the bile duct biopsy specimens. Studies have found that past or concurrent AIP or extrabiliary organ involvement is a strong clinical predictor of IAC in patients with biliary strictures. The diagnosis of AIP is based on the Mayo Clinic’s HISORt (histology, imaging, serology, other organ involvement, and response to corticosteroid therapy) criteria. Various pathologic findings can be found in the liver in patients with AIP, including portal inflammation with or without interface hepatitis, large bile-duct obstructive features, portal sclerosis, lobular hepatitis, and canaliculic cholestasis and infiltration of IgG4 plasma cells. These abnormalities can be treated with steroid therapy. Hepatic inflammatory pseudotumors with dense lymphoplasmacytic infiltration and obliterating phlebitis also have been previously reported in patients with AIP. Our patient reported no history consistent with AIP and had no radiologic studies suggestive of this diagnosis.

Distinguishing IAC from malignant disease can be challenging. Previously, investigators found that ERCP alone had a sensitivity of only 45% in diagnosing IAC, and they concluded that additional diagnostic strategies would be necessary to accurately distinguish IAC from primary sclerosing cholangitis or cholangiocarcinoma. Additionally, the cholangioscopic appearance of IAC has been reported as smooth, edematous mucosa with a proliferation of dilated and tortuous vessels at the stricture site. Our case did not demonstrate these cholangioscopic findings and was more consistent with a malignant stricture with irregular surface mucosa with dilated and tortuous vessels. Although the IgG4 level was elevated in this case, an elevated serum IgG4 level alone in the presence of a biliary stricture has not been shown to exclude the diagnosis of cholangiocarcinoma. However, a cutoff of 4 times the upper limit of normal has 100% specificity for the diagnosis of IAC. This case highlights the variable presentation of IAC, which should be considered in the differential diagnosis of unexplained biliary strictures. The lack of concurrent AIP should not exclude the diagnosis.

**References**

Review

Immunoglobulin G4–Associated Cholangitis: The Next Great Masquerader

Andrew S. deLemos, MD1
Daniel S. Pratt, MD1,2

1Gastrointestinal Unit and 2Autoimmune and Cholestatic Liver Center, Massachusetts General Hospital, Boston, Massachusetts

Immunoglobulin G4 (IgG4)-associated cholangitis (IAC) refers to the biliary manifestations of IgG4-related systemic (or sclerosing) disease (ISD).1 Recognition of ISD is increasing worldwide, and gastroenterologists and hepatobiliary surgeons who evaluate patients with biliary stricture disease need to be aware of the possibility of IAC. Distinguishing IAC from primary sclerosing cholangitis (PSC) and cholangiocarcinoma remains a dilemma for diagnosticians. Case reports that increase awareness of IAC, such as the one presented by Gonzalez and colleagues,2 in combination with research into the pathogenesis of ISD, promise to provide insight into our understanding of this disease.

History and Epidemiology

Although the exact trigger for ISD is unknown, features of both autoimmunity and allergy are thought to be present. Interestingly, the only medical history of the patient in the case presented by Gonzalez and colleagues was asthma.2 The IgG4 antibody itself is not pathogenic; however, recent evidence suggests that it may play a role in the response to allergens.3 One recent report suggests that patients with ISD have an increased prevalence of allergic rhinitis and asthma.4 Epidemiologically, the diagnosis of IAC in this young female patient is atypical. IAC is associated with the archetypal ISD lesion, type 1 autoimmune pancreatitis (AIP), in 70–92% of patients,5,6 the vast majority of whom are middle-aged or older men. Likewise, this case does not have the typical epidemiologic characteristics of either PSC or cholangiocarcinoma. Male sex predominance (~70%), along with the presence of inflammatory bowel disease (usually ulcerative colitis), characterizes PSC, which is the most important risk factor for the development of cholangiocarcinoma, with an estimated annual incidence rate of 0.6–1.5% per year. Thus, in the absence of other risk factors for cholangiocarcinoma, such as fibropolycystic liver disease, parasitic infection, or Lynch syndrome, the clinical profile of the patient in this case does not provide compelling evidence to support IAC, PSC, or cholangiocarcinoma.

Diagnostic Evaluation

Imaging criteria alone cannot differentiate IAC from either cholangiocarcinoma or PSC.7 Researchers from the Mayo Clinic reported a case series of 53 patients with IAC, of whom 18 (34%) had proximal extrahepatic biliary strictures mimicking cholangiocarcinomas.8 Of note is that isolated extrahepatic biliary strictures were rare, and 13 (72%) of the 18 patients with extrahepatic biliary strictures had other abnormal findings on cholangiograms, such as intrahepatic or intrapancreatic biliary strictures.

The HISORt (histology, imaging, serology, other organ involvement, and response to therapy) criteria, which were originally developed for AIP,9 were adapted for IAC6 and include the presence of 1 or more strictures anywhere in the biliary tree and migrating strictures seen on imaging. Studies outlining cholangioscopic techniques, including intraductal ultrasound, may offer some clues to the nature of IAC lesions but are currently still largely investigational.9 Histology is a fundamental diagnostic feature of IAC. Unfortunately, too often it is only established after an extensive hepatic resection similar to the one performed in the case described by Gonzalez and colleagues: a resection performed because of suspicion of cholangiocarcinoma.2 Could a core liver biopsy have provided a diagnosis and obviated the need for surgery? The isolated large duct involvement suggests not. The pathology of IAC is typically marked by a lymphoplasmacytic fibrosclerosing cholangitis, findings that also may be present in PSC. Because of the more chronic nature of the condition, features of advanced fibrosis (Ludwig stage 3–4) are more typical of PSC.10 Immunohistochemical staining for IgG4 is essential to diagnose IAC and requires more than 10 but often up to 30–50 IgG4-positive cells per high power field within and around bile ducts. However, IgG4-positive plasma cell infiltrates, albeit to a lesser degree, are also present in the hilar region of liver explants from patients with PSC, signifying that IgG4 staining is by no means definitive.11 Tissue sampling during endoscopic retrograde cholangiopancreatography was performed in this case with brush cytology and fluorescence in situ hybridization to exclude cholangiocarcinoma. Polysomy by fluorescence in situ hybridization in association with a dominant stricture has a sensitivity of 46% and a specificity of 88% for detecting cholangiocarcinoma in patients with PSC.12

Address correspondence to:
Dr. Daniel S. Pratt, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114; Tel: 617-726-3313; Fax: 617-724-6832; E-mail: dpratt@partners.org
Serum testing for IgG4 is a third component of the HISORt criteria. A recent study by investigators at the Mayo Clinic specifically addressed the value of serum IgG4 (sIgG4) levels in discriminating between IAC and cholangiocarcinoma.6 The sIgG4 levels from 2 cohorts of patients with either IAC or cholangiocarcinoma were measured. In a test cohort, 39 (78%) of 47 patients with IAC had elevated sIgG4 levels, and 24 (50%) had a greater-than-2-fold increase in sIgG4 levels. Seventeen (13.5%) of 126 patients with cholangiocarcinoma had elevated sIgG4 levels, and 4 (3.2%) had a more-than-2-fold elevation in sIgG4 levels.

Of the 126 patients with cholangiocarcinoma, 31 (24.6%) carried a concurrent diagnosis of PSC, and within this specific cohort 7 (22.6%) had elevated sIgG4 levels. Based on the results of this study, which were confirmed in an independent validation cohort, an sIgG4 cutoff point of at least 2 times the upper limit of normal was suggested to help distinguish IAC from cholangiocarcinoma. Notably, the postoperative sIgG4 level from the patient in the case reported by Gonzalez and colleagues was 168 mg/dL, which was elevated (normal, 21–134 mg/dL), but not to a degree that could exclude cholangiocarcinoma.2

Treatment

IAC is classically a corticosteroid-responsive condition. Prednisone therapy plays both diagnostic and therapeutic roles and could have been considered for this patient at the outset. However, one has to balance the benefit of avoiding surgery with a trial of corticosteroids with the risk of delaying resection of a potentially curable cholangiocarcinoma. In the Mayo registry, of the 30 patients initially treated with corticosteroids, 29 (97%) responded, and biliary strictures resolved within 6 months of discontinuing corticosteroid therapy. Patients with proximal extrahepatic or intrahepatic disease as well as high sIgG4 levels were found to be at increased risk for recurrent disease. Corticosteroid-sparing agents such as azathioprine are now often used to treat calcificentric cases. Rituximab (Rituxan, Genentech) has been successfully used in patients with IAC unresponsive to corticosteroids and 6-mercaptopurine.14

Conclusions

The case report by Gonzalez and colleagues2 of an unusual presentation of IAC adds to our understanding of the disease entity. The extrapancreaticobiliary manifestations of ISD include involvement of the salivary glands (sialadenitis), retroperitoneum, lymph nodes, aorta, and kidneys, among other systems. This case did not describe findings that would indicate the presence of ISD outside of the biliary system, but it would be critical to seek extrabiliary manifestations when evaluating a patient presenting with a similar clinical scenario. The clinician evaluating a patient with a newly identified biliary stricturing disease must consider the possibility of IAC.

References