A treatable mimicker of cholangiocarcinoma

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CASE PRESENTATION

A 68-year-old female nonsmoker, nondrinker with a medical history of hypertension presented with new-onset painless jaundice and pruritus, a three-month history of 9.9 kg weight loss and chronic diarrhea with four to five loose bowel movements per day. Medications included vitamin D, amlodipine and eprosartan. Physical examination was normal except for jaundice and muscle wasting. Recent colonoscopy had been normal. Total and direct bilirubin levels were 6.84 mg/dL (116.96 μ mol/L) and 9.18 mg/dL (156.98 μ mol/L), respectively. Other results included an international normalized ratio of 1.0, alanine aminotransferase level 247 U/L (normal <33 U/L), aspartate aminotransferase level 139 U/L (normal <32 U/L) and alkaline phosphatase level 524 U/L (normal 35 to 104 U/L). Viral hepatitis serologies, and antimitochondrial antibody and anti-smooth muscle antibody tests were negative. Her alpha-fetoprotein level was 2.4 ng/mL (normal <5 ng/mL), total immunoglobulin (Ig) G was 1880 mg/dL (normal <640 mg/dL), carbohydrate antigen 19-9 was 856 U/mL (normal <33 U/mL) and IgG₄ was 890 g/L (normal <3 g/L). Doppler ultrasound, magnetic resonance cholangiopancreatography and magnetic resonance imaging of the liver were suspicious for a subtly enhancing mass (2.8 cm to 4.2 cm in diameter) in the region of the hilum and porta hepatis, obstructing both the right and left hepatic ducts. Endoscopic retrograde cholangiopancreatography identified strictures in the central portions of the right and left hepatic duct, which was concerning for cholangiocarcinoma (Figure 1). Biliary brushings were negative for malignancy.

Figure 1 Endoscopic retrograde cholangiopancreatography demonstrating a filling defect in the porta hepatis

Figure 2 A biopsy of the ampulla of Vater demonstrating chronic active duodenitis. Hematoxylin and eosin stain, original magnification $\times 40$

Figure 3 A biopsy of the ampulla of Vater demonstrating chronic active duodenitis. Hematoxylin and eosin stain, original magnification $\times 100$

Esophagogastroduodenoscopy was normal. Biopsies of the ampulla of Vater revealed chronic active duodenitis (Figures 2 and 3); an ancillary test confirmed the diagnosis (Figure 4). Treatment with corticosteroids normalized the patient's biochemical and radiological abnormalities within three months.

DISCUSSION

IgG₄ sclerosing cholangitis (IgG₄ SC) falls within the spectrum of IgG₄-related disease. Diagnostic criteria include stenosis and wall thickening of the bile duct, together with one of autoimmune pancreatitis or other IgG₄ disease; or marked fibrosis and prominent infiltration of lymphocytes and IgG₄-positive plasma cells in the bile duct; pancreatic cancer, cholangiocarcinoma and inflammatory bowel disease must be ruled out because IgG₄ SC can mimic these (1). Cholangiography is useful for discriminating IgG₄ SC from primary sclerosing cholangitis, but is not

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Figure 4) Positive immunoglobulin G₄ staining of a biopsy of the ampulla of Vater. Original magnification $\times 200$

useful for discriminating it from cholangiocarcinoma. Therefore, the diagnosis requires an elevated serum IgG₄ level and a tissue biopsy with characteristic IgG₄ histopathological changes. Transpapillary intraductal ultrasonography and bile duct biopsy has high sensitivity and specificity (2), but is invasive and not widely available. Alternatively, positive IgG₄ immunostaining of the major duodenal papilla, as was performed here (Figure 4), is specific and moderately sensitive (3,4), and is less invasive than intraductal manipulation.

Treatment is based on case reports and series. Most patients respond to two to four weeks of glucocorticoid steroids. Patients who are glucocorticoid resistant or dependant may respond to azathioprine (2 mg/kg/day), mycophenolate mofetil (up to 2.5 g/day) or rituximab (5). Potential morbidity and mortality in untreated patients include cirrhosis and portal hypertension, retroperitoneal fibrosis, aortic aneurysms/dissections, biliary obstruction, diabetes mellitus and lymphoma (5).

Patients with IgG₄ SC progressed to liver transplantation in a significantly shorter time than patients with primary sclerosing cholangitis (1.7 years versus 6.5 years; $P=0.0009$) (6). Therefore, IgG₄ SC is an under-recognized, highly treatable condition that has high morbidity if misdiagnosed as malignancy, or if undiagnosed and untreated.

KEY POINTS

- IgG₄ is under-recognized by physicians due to the rarity of the disease. Increased medical awareness has an important value in making the diagnosis.
- Positive IgG₄ immunostaining of the major duodenal papilla is an extremely specific and moderately sensitive tool for the diagnosis of corticosteroid-responsive IgG₄-related disease

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