CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will recognize a progressive cholestatic liver disease associated with inflammatory bowel disease.

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Ulcerative colitis and an abnormal cholangiogram

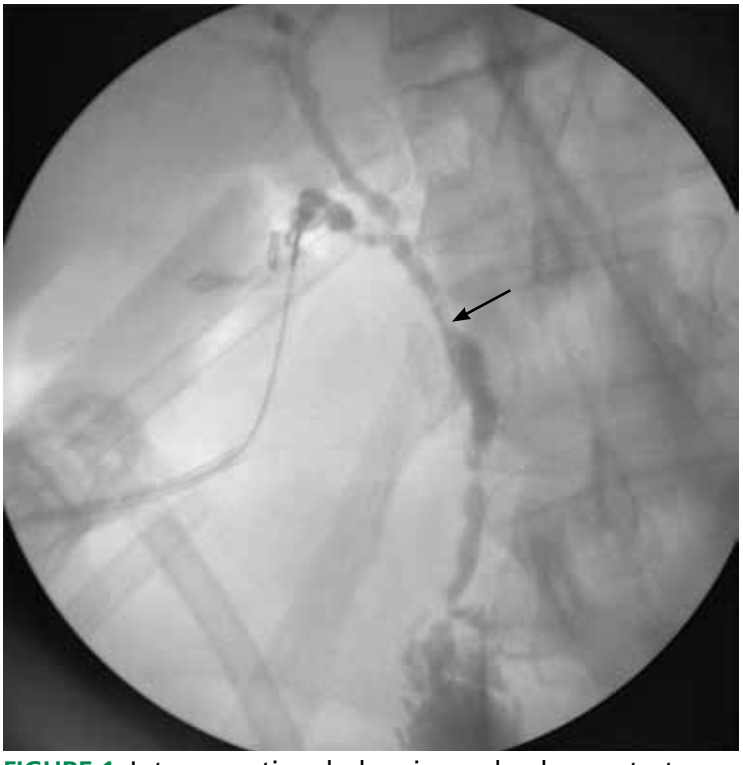

FIGURE 1. Intraoperative cholangiography demonstrates annular, multifocal stricturing and beading of the extrahepatic biliary system (arrow).

A 49-YEAR-OLD MAN has had ulcerative colitis for more than 30 years. It is well controlled with sulfasalazine (Azulfidine). Now, he has come to see his primary care physician because for the past 3 months he has had mild, intermittent pain in his right upper abdominal quadrant.

His physical examination is normal. Routine laboratory testing shows the following:

- Hemoglobin 14.2 g/dL (reference range 13.5–17.5)
- White blood cell count 6.7 × 10^9/L (3.5–10.5)
- Platelet count 279 × 10^9/L (150–450)
- Alkaline phosphatase 387 U/L (45–115)
- Total bilirubin 0.9 mg/dL (0.1–1.0)
- Aspartate aminotransferase (AST) 35 U/L (35–48)
- Alanine aminotransferase (ALT) 30 U/L (7–55).

His physician is concerned about his elevated alkaline phosphatase level, which can be a sign of cholestatic liver disease (ie, involving blockage of the flow of bile). He sends him for ultrasonography, which reveals mild thickening of the gallbladder wall. The patient is referred to a general surgeon, who decides to remove the gallbladder. The procedure goes well, but when contrast dye is injected into the biliary system during cholangiography, the image is markedly abnormal (FIGURE 1). The patient is referred to Mayo Clinic for further evaluation.

WHAT IS THE DIAGNOSIS?

1 Based on this information, which of the following is the most likely diagnosis?

- ☐ Autoimmune hepatitis
- ☐ Primary sclerosing cholangitis
- ☐ Primary biliary cirrhosis
- ☐ Idiopathic adulthood ductopenia

Primary sclerosing cholangitis

The most likely diagnosis is primary sclerosing cholangitis, a chronic cholestatic liver disease characterized by diffuse inflammatory destruction of intrahepatic and extrahepatic bile ducts, resulting in fibrosis, cirrhosis, and liver failure. Its cause is unknown, but it is

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likely the result of acquired exposures interacting with predisposing host factors. Current diagnostic criteria include:

- Characteristic cholangiographic abnormalities of the biliary tree
- Compatible clinical and biochemical findings (typically cholestasis with elevated alkaline phosphatase levels for at least 6 months)
- Exclusion of causes of secondary sclerosing cholangitis: secondary sclerosing cholangitis is characterized by a similar multifocal biliary stricturing process, but with an identifiable cause such as long-term biliary obstruction, surgical biliary trauma, or recurrent pancreatitis.[1]

At presentation, the most common liver enzyme abnormality is an elevated alkaline phosphatase level, often three or four times the normal level.[2] In contrast, aminotransferase levels are only modestly elevated, less than three times the upper limit of normal.[3] At the time of diagnosis, serum bilirubin levels are normal in 60% of patients.[4]

Two large epidemiologic studies (one from Olmsted County, MN,[5] the other from Swansea, Wales, UK[6]) estimated the age-adjusted incidence of primary sclerosing cholangitis to be 0.9 per 100,000 individuals. The median age of the patients at onset was in the 30s or 40s, and most were men. At 10 years, an estimated 65% were still alive and had not undergone liver transplantation—a significantly lower percentage than in age- and sex-matched populations.

It is estimated that more than 70% of patients with primary sclerosing cholangitis also have inflammatory bowel disease.[5] In fact, the most common presentation of primary sclerosing cholangitis is asymptomatic inflammatory bowel disease and persistently elevated alkaline phosphatase—usually first noted on routine biochemical screening, as in our patient.

Imaging of the biliary tree is essential for the diagnosis of primary sclerosing cholangitis. Typical findings on cholangiography include multifocal stricturing and beading, usually involving both the intrahepatic and the extrahepatic biliary systems, as in our patient (**FIGURE 1**). Endoscopic retrograde cholangiopancreatography (ERCP) is considered the gold standard imaging test, but recent studies have shown that magnetic resonance cholangiopancreatography (MRCP) is an acceptable noninvasive substitute,[7] and it may cost less per diagnosis.[8]

Liver biopsy alone is generally nondiagnostic because the histologic changes are quite variable in different segments of the same liver. The classic "onion-skin fibrosis" of primary sclerosing cholangitis is seen in fewer than 10% of biopsy specimens.[9]

Autoimmune hepatitis

Autoimmune hepatitis is chronic and is characterized by circulating autoantibodies and high serum globulin concentrations.[10] Its presentation is heterogeneous, varying from no symptoms to nonspecific symptoms of malaise, fatigue, abdominal pain, itching, and arthralgia. Generally, elevations in aminotransferases are much more prominent than abnormalities in bilirubin and alkaline phosphatase levels[10]—unlike the pattern in our patient.

Primary biliary cirrhosis

Primary biliary cirrhosis is diagnosed if the patient has at least two of these three clinical criteria:

- Biochemical evidence of cholestasis, with elevation of alkaline phosphatase for at least 6 months
- Antimitochondrial antibody
- Histologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts.[11]

In patients who lack antimitochondrial antibody, liver biopsy is necessary to establish the diagnosis. Given that primary biliary cirrhosis involves only small and medium-sized bile ducts, cholangiography is usually normal unless the patient has advanced cirrhosis.

Visualization of the biliary tree is essential for the diagnosis of primary sclerosing cholangitis

Idiopathic adulthood ductopenia

Idiopathic adulthood ductopenia is a rare condition of unknown cause that involves the progressive destruction of segments of the small bile ducts inside the liver ("small-duct" biliary disease).[12] Laboratory findings reveal a cholestatic pattern of liver injury, but biopsy samples show no features diagnostic or suggestive of another biliary disease; cholangiography is typically normal.[12,13]

ASSOCIATION WITH INFLAMMATORY BOWEL DISEASE

2 Which statement best characterizes inflammatory bowel disease associated with primary sclerosing cholangitis?

- ☐ Crohn disease of the small bowel is the most common form
- ☐ Liver disease often precedes the bowel disease
- ☐ Treating the underlying bowel disease improves the long-term prognosis for the liver condition
- ☐ Patients with primary sclerosing cholangitis and chronic ulcerative colitis are at higher risk of colonic dysplasia than patients with chronic ulcerative colitis alone

From 70% to 80% of patients with primary sclerosing cholangitis also have inflammatory bowel disease, usually chronic ulcerative colitis.[14,15] Conversely, 2.4% to 4% of patients with ulcerative colitis and 1.4% to 3.4% of patients with Crohn disease have primary sclerosing cholangitis.[1]

Typically, the diagnosis of inflammatory bowel disease is made 8 to 10 years before the diagnosis of liver disease, although cases have also been reported to occur years after the diagnosis of cholangitis.[15,16]

Unfortunately, noninvasive studies do not allow for therapeutic biliary decompression

No association between the severity of bowel disease and liver disease has been reported, and treating the inflammatory bowel disease does not alter the natural history of primary sclerosing cholangitis. Particularly, proctocolectomy, the most aggressive treatment for chronic ulcerative colitis, appears to have no effect on the course of the cholangitis.[17]

In patients with both primary sclerosing cholangitis and chronic ulcerative colitis, the risk of colonic dysplasia is higher than in patients with chronic ulcerative colitis alone.[18] Recent studies have predicted that the risk of colorectal carcinoma in patients with primary sclerosing cholangitis and inflammatory bowel disease is as high as 25% after 10 years.[19,20] Therefore, annual colonoscopy with surveillance biopsy is recommended in patients with both primary sclerosing cholangitis and chronic ulcerative colitis, since screening and early detection improve survival rates.[15]

TREATMENT AND PROGNOSIS

After being diagnosed with primary sclerosing cholangitis, the patient inquires about ongoing medical therapy and long-term prognosis.

3 Which is the only life-prolonging therapy for primary sclerosing cholangitis?

- ☐ Methotrexate (Trexall)
- ☐ Ursodeoxycholic acid (UDCA) (Actigall) at a standard dosage (13–15 mg/kg/day)
- ☐ UDCA at a high dosage (20–30 mg/kg/day)
- ☐ Liver transplantation

Drug therapy has not been shown to improve the prognosis of primary sclerosing cholangitis.

In randomized placebo-controlled trials, penicillamine (Depen), colchicine (Colcrys), methotrexate, and UDCA (13–15 mg/kg per day) failed to show efficacy.[21–23]

In pilot studies, high-dose UDCA (20 to 30 mg/kg/day) initially appeared to bring an improvement in survival probability, with trends toward histologic improvement,[24,25] but larger randomized placebo-controlled trials found no improvement in symptoms, quality of life, survival rates, or risk of cholangiocarcinoma with high-dose UDCA.[26,27] In fact, in 5 years of follow-up, patients on high-dose UDCA had a risk of death or transplantation two times higher than with placebo.[27] One study indicated UDCA may decrease the incidence of colonic dysplasia in patients with primary sclerosing cholangitis and chronic ulcerative colitis.[28] However, more prospective studies are required to better define the routine use of UDCA as a prophylactic agent.

Liver transplantation remains the most effective treatment for primary sclerosing cholangitis, and it improves the rate of survival.[29] Nevertheless, about 20% of patients who undergo transplantation have a recurrence of cholangitis, and it may recur earlier after living-donor liver transplantation, particularly when the graft is from a biologically related donor.[30] Proposed risk factors for recurrence include inflammatory bowel disease, prolonged ischemia time, the number of cellular rejection events, prior biliary surgery, cytomegalovirus infection, and lymphocytotoxic cross-match.[31]

4 In addition to cirrhosis and cholangitis, which of the following is a potential long-term complication of primary sclerosing cholangitis?

- ☐ Colon cancer
- ☐ Cholangiocarcinoma
- ☐ Osteoporosis
- ☐ Fat-soluble vitamin deficiency
- ☐ All of the above

All are potential long-term complications.

Colon cancer. Concomitant chronic ulcerative colitis puts the patient at a higher risk of colonic dysplasia compared with patients with chronic ulcerative colitis alone.[18] According to recent studies of patients with primary sclerosing cholangitis and inflammatory bowel disease,[19,20] the risk of colorectal carcinoma after 10 years of disease is as high as 25%.

Cholangiocarcinoma. Primary sclerosing cholangitis is considered a risk factor for cholangiocarcinoma, with an estimated 10-year cumulative incidence of 7% to 9%.[1,20] In a retrospective study of 30 patients,[32] the median survival was 5 months from the time of diagnosis of cholangiocarcinoma; at the time of diagnosis approximately 19 patients (63%) had metastatic disease.

At present, early detection of cholangiocarcinoma is hampered by the low sensitivity and specificity of standard diagnostic approaches. Carbohydrate antigen 19-9 has been used as a marker, but it has questionable accuracy, since elevations of this antigen can also be a result of pancreatic malignancy and bacterial cholangitis. However, cholangiocarcinoma should be suspected when patients present with progressive jaundice, weight loss, abdominal discomfort, and a sudden rise in carbohydrate antigen 19-9.

Conventional ultrasonography and computed tomography (CT) have poor sensitivity for detecting this malignancy. ERCP with biliary brushings should be considered when evaluating for biliary malignancy. New diagnostic methods such as digitized image analysis and fluorescence in situ hybridization on biliary brushings offer promise to evaluate bile duct lesions for cellular aneuploidy and chromosomal aberrations, which may improve the detection of cholangiocarcinoma.[33] A recent large-scale study of nearly 500 patients showed that fluorescence in situ hybridization had a higher sensitivity (42.9%) than routine cytology (20.1%) with identical specificity (99.6%) for malignancy.[34]

Metabolic bone disease, usually osteoporosis rather than osteomalacia, is relatively common and is an important complication of primary sclerosing cholangitis.[35] Patients with osteoporosis should be treated with vitamin D and calcium supplementation. Bisphosphonates have been used with varying results in primary biliary cirrhosis[36] and can be considered in patients with advanced osteoporosis.

Fat-soluble vitamin deficiency is relatively common in primary sclerosing cholangitis, particularly as it progresses to advanced liver disease. Up to 40% of patients have vitamin A deficiency, 14% have vitamin D deficiency, and 2% have vitamin E deficiency.[37] Patients can undergo simple oral replacement therapy.

A stone is removed, fever develops

Three years after the diagnosis of primary sclerosing cholangitis, the patient develops mild hyperbilirubinemia and undergoes ERCP at his local hospital. A stone is found obstructing the common bile duct and is successfully extracted.

Twenty-four hours after this procedure, he develops severe right-upper-quadrant pain and fever. He is seen at his local emergency department and blood cultures are drawn. He is started on antibiotics and is transferred to Mayo Clinic for further management.

Cholangitis recurs in as many as 20% of patients who undergo transplantation

5 In addition to continuing a broad-spectrum antibiotic, which would be the next best step for this patient?

- ☐ ERCP
- ☐ MRCP
- ☐ Abdominal ultrasonography
- ☐ Abdominal CT

The patient's clinical presentation is consistent with acute bacterial cholangitis. The classic Charcot triad of fever, right-upper-quadrant pain, and jaundice occurs in only 50% to 75% of patients with acute cholangitis.[38] In addition to receiving a broad-spectrum antibiotic, patients with bacterial cholangitis require emergency endoscopic evaluation—

ERCP—to find and remove stones from the bile ducts and, if necessary, to dilate the biliary strictures to allow adequate drainage.

In our experience, more than 10% of patients with primary sclerosing cholangitis who undergo ERCP develop complications requiring hospitalization.[39] The procedure generally takes longer to perform and the incidence of cholangitis is higher, despite routine antibiotic prophylaxis, in patients with primary sclerosing cholangitis than in those without it. However, the overall risk of pancreatitis, perforation, and bleeding was similar in patients with or without sclerosing cholangitis.[39]

MRCP is a promising noninvasive substitute for ERCP in establishing the diagnosis of primary sclerosing cholangitis.[7,8] Unfortunately, as with other noninvasive imaging studies such as abdominal ultrasonography and CT, MRCP does not allow for therapeutic biliary decompression.

The patient undergoes ERCP with stenting

The patient's acute cholangitis is thought to be a complication of his recent ERCP procedure. He undergoes emergency ERCP with balloon dilation and placement of a temporary left hepatic stent. His fever improves and he is discharged 48 hours later. He completes a 14-day course of antibiotics for *Enterococcus faecalis* bacteremia. Six weeks later, he undergoes ERCP yet again to remove the stent and tolerates the procedure well without complications.

TAKE-HOME POINTS

- Primary sclerosing cholangitis is a progressive cholestatic liver disease of unknown etiology that primarily affects men during the fourth decade of life.
- This condition is strongly associated with inflammatory bowel disease, particularly with ulcerative colitis.
- Cholangiocarcinoma and colon cancer are dreaded complications.
- Liver transplantation is the only life-extending therapy for primary sclerosing cholangitis; however, the condition can recur in the allograft.

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