EDUCATION PRACTICE

A 42–Year–Old Woman With a New Diagnosis of Sclerosing Cholangitis

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Clinical Scenario

A 42-year-old woman is referred to you for severe pruritus, dark urine, and acholic stools. These symptoms have gradually increased during the past 7–10 days. She had previously been in good health with no history of hepatobiliary dysfunction. She complains of right upper quadrant discomfort and a general sense of malaise. Blood tests reveal a normal complete blood count, but her liver enzymes are elevated in a cholestatic pattern. Her alkaline phosphatase level is approximately 3 times the upper limit of normal (ULN) at 428 U/L, the aspartate aminotransferase level is 1.5 times the ULN at 116 U/L, and the total serum bilirubin is 6.4 mg/dL, with a direct bilirubin of 4.8 mg/dL. An antimitochondrial antibody is performed to evaluate for primary biliary cirrhosis and is negative. On examination, she appears unwell with obvious jaundice. She is afebrile, and there are no spider angiomas noted. She has generalized tenderness with palpation of the right upper quadrant of the abdomen.

Abdominal imaging is performed with an ultrasound and reveals focal dilation of the intrahepatic bile ducts in the right and left hepatic lobes. Also noted is diffuse wall thickening of the distal hepatic and common bile duct. There is no obvious hepatic mass and no evidence of cholelithiasis or choledocholithiasis. The gallbladder and pancreas appear normal, and there is no splenomegaly or ascites.

The Problem

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease of unknown etiology. Potential causes include disordered immunoregulation, infections, or bacterial products with portal bacteremia. The disease leads to diffuse inflammation and fibrosis of the biliary tree, which ultimately causes biliary cirrhosis and portal hypertension.

Patients with PSC might present with incidentally noted elevated liver enzymes in a cholestatic profile. Others present with symptoms of cholestasis including fatigue, jaundice, acholic stools, dark urine, hyperpigmentation, or pruritus. A subset will have evidence of cholangiocarcinoma (CCA) at the time of initial presentation. Fifteen percent to 44% of patients might be entirely asymptomatic (Table 1). Autoantibodies such as an antinuclear antibody or antineutrophil cytoplasmic antibody might or might not be present.

The diagnosis of PSC is typically made in the setting of a cholestatic clinical picture and an abnormal cholangiogram. The evaluation of a patient with new cholestasis might include laboratory work, cross-sectional imaging, and a cholangiogram (Figure 1). Endoscopic retrograde cholangiopancreatography (ERCP) has been the preferred method of evaluating for PSC; however, this procedure is not risk free. Potentially serious complications such as pancreatitis and bacterial cholangitis can occur in up to 10% of patients undergoing ERCP. Magnetic resonance cholangiography (MRCP) is a noninvasive method of evaluating the biliary tree and is increasingly being used. The MRCP image in Figure 2 shows changes of PSC.

In the setting of PSC, the bile ducts typically demonstrate a "beaded" appearance when imaged. Often, there will be areas of significant stenosis alternating with focal bile duct dilation. The disease might be diffusely spread throughout the biliary tree or confined to the intrahepatic ducts (<25% of all PSC patients). Approximately 5% of patients with cholestatic changes will have a normal-appearing biliary tree cholangiographically but have changes histologically that are consistent with PSC, a condition termed small-duct PSC. It might be that some of these patients will eventually develop disease of the large bile ducts as well, but this progression is unpredictable. A liver biopsy might be helpful in confirming the diagnosis of PSC and in providing prognostic information, but it is not necessary in all cases. Histologic features might include periductal fibrosis, a paucity of bile ducts, and variable degrees of fibrosis encasing the intralobular bile duct (Figure 3). This is described as "onion skin" fibrosis. Often, however, only nondiagnostic histologic changes are seen. Secondary sclerosing cholangitis is characterized by a similar process but is typically due to causes such as long-term bile duct obstruction, surgical trauma, or infection.

The majority of patients with PSC (75%) will have coexisting inflammatory bowel disease (IBD). Of these patients, 70% will have chronic ulcerative colitis. A subset of these will demonstrate evidence of IBD affecting the right side of the colon with rectal sparing. The diagnosis of IBD might or might not precede the diagnosis of PSC.

Abbreviations used in this paper: AASLD, American Association for the Study of Liver Diseases; CCA, cholangiocarcinoma; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2012.02.022

Table 1. Clinical Presentation of PSC

Symptoms	%
Asymptomatic	15–44
Fatigue	75
Pruritus	70
Jaundice	30–69
Hepatomegaly	34–62
Abdominal pain	16–37
Weight loss	10–34
Splenomegaly	30
Ascending cholangitis	5–28
Hyperpigmentation	25
Variceal bleeding	2–14
Ascites	2–10

Management Strategies and Supporting Evidence

Treatment

There is no approved or widely accepted medical therapy for PSC. Multiple agents have been studied with largely negative results. Among these are ursodeoxycholic acid (UDCA) at varying doses (13–15 mg/kg/d to 28–30 mg/kg/d), as well as immunosuppressive agents such as azathioprine, budesonide, methotrexate, mycophenolate mofetil, and tacrolimus. In addition, bezafibrate, colchicine, cladribine, cyclosporine, etanercept, infliximab, oral and transdermal nicotine, D-penicillamine, pentoxifylline, pirfenidone, and silymarin have all been studied. None have provided convincing evidence of benefit, although some have resulted in modest improvement in biochemistries. UDCA at doses of 10–15 mg/kg/d has been associated with biochemical improvement and histologic improvement in small pilot studies. Larger studies have failed to corroborate this finding. Use of UDCA at doses of 28–30 mg/kg/d has been associated with negative outcomes and is not recommended. There are data that show that use of UDCA might be associated with a decreased risk of colorectal neoplasia in patients with PSC and IBD. Continued research would be of value.

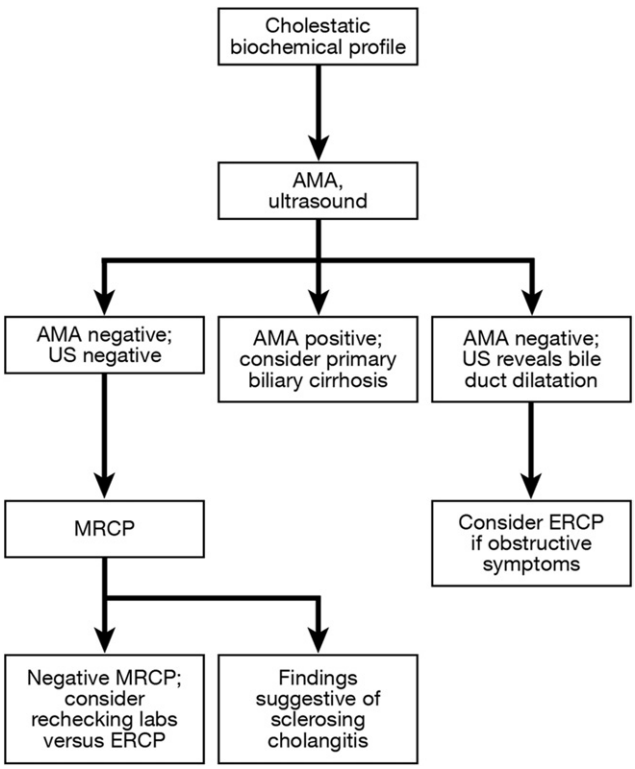

Figure 1. Algorithm for evaluation of cholestatic presentation. AMA, antimitochondrial antibody.

Figure 2. MRCP showing PSC.

Managing Complications

Patients with PSC are at an increased risk for bacterial cholangitis, which requires treatment with broad-spectrum antibiotics. There is little role for surgical management of PSC in the absence of malignancy or liver transplantation. Endoscopic management of symptomatic strictures, which are present in

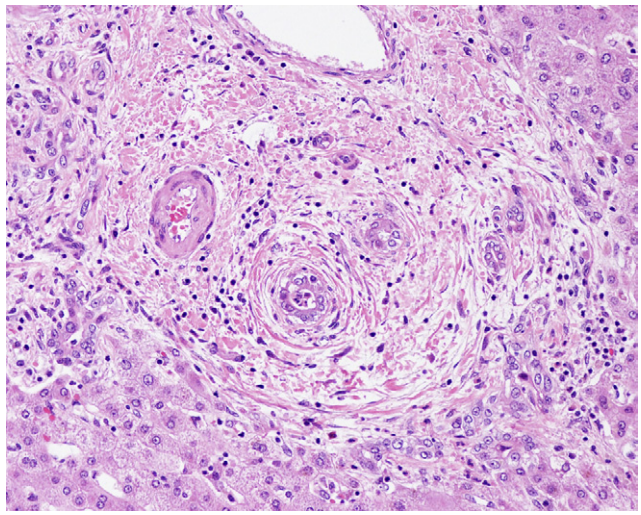

Figure 3. Histologic evidence of PSC. (Note the concentric periductal fibrosis.)