REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Pathogenesis of Primary Sclerosing Cholangitis and Advances in Diagnosis and Management

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Primary sclerosing cholangitis (PSC), first described in the mid-1850s, is a complex liver disease that is heterogeneous in its presentation. PSC is characterized by chronic cholestasis associated with chronic inflammation of the biliary epithelium, resulting in multifocal bile duct strictures that can affect the entire biliary tree. Chronic inflammation leads to fibrosis involving the hepatic parenchyma and biliary tree, which can lead to cirrhosis and malignancy. The etiology of PSC is not fully understood, which in part explains the lack of effective medical therapy for this condition. However, we have begun to better understand the molecular pathogenesis of PSC. The recognition of specific clinical subtypes and their pattern of progression could improve phenotypic and genotypic classification of the disease. We review our current understanding of this enigmatic disorder and discuss important topics for future studies.

Keywords: Cholestatic Liver Disease; Cholangiocarcinoma; Autoimmune Disease; Inflammatory Bowel Disease.

Prevalence rates for primary sclerosing cholangitis (PSC) in North America and Europe range from 6 to 16 cases per 100,000 inhabitants.[1–3] Studies of population-based cohorts have estimated the incidence of PSC in many North American locations to be approximately 1 per 100,000 persons.[3,4] The incidence of PSC is similar in North American and Northern European countries.[5] However, the incidence and prevalence vary worldwide, with lower estimates reported in Asia and southern Europe.[6,7] Although PSC may be an uncommon disease, the reported incidence has increased over time.[5]

The median age of patients diagnosed with PSC is 41 years, and it appears to be more common among men.[5] Patients are often diagnosed incidentally, and nearly 50% are asymptomatic. Despite being asymptomatic at the time of diagnosis, patients with PSC have shorter average times of survival compared with matched controls from the general population.[8] Five years after diagnosis of asymptomatic PSC, approximately 22% show clinical symptoms; after 6 years, up to 76% have some evidence of disease progression (biochemical, symptomatic, or radiographic).[8,9] Fatigue is often present at the time of diagnosis. Other presenting signs and symptoms include abdominal pain (37%), jaundice (30%), and fever (17%).[9] When patients are symptomatic on presentation, the median time of survival until death or liver transplantation is 9 years (compared with 12–18 years for all patients with PSC, regardless of symptoms).[8–10]

PSC can present during childbearing years, yet little is known about the progression of PSC during pregnancy or its effects on the fetus and mother. In a case series, fertility was not reduced among women with PSC and there was not a higher proportion of fetal loss or adverse fetal outcomes compared with the general population. Although no serious maternal outcomes were noted, there was an increase in liver enzyme levels among 20% of pregnant women with PSC.[11]

The major risk factor for development of PSC is inflammatory bowel disease (IBD). Sixty to eighty percent of patients with PSC have concurrent IBD (typically ulcerative colitis [UC]), and approximately 4% of patients with UC have coexisting PSC.[12,13] Patients with PSC are most frequently male and have a family history of the disease in rare cases. Smoking has been reported to protect against PSC, even after controlling for underlying UC.[5,14,15]

Abbreviations used in this paper: AIH, autoimmune hepatitis; AIP, autoimmune pancreatitis; CA, carbohydrate antigen; CCA, cholangiocarcinoma; CFTR, cystic fibrosis transmembrane conductance regulator; CRN, colorectal neoplasia; ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence in situ hybridization; FXR, farnesoid X receptor; GBN, gallbladder neoplasia; HCC, hepatocellular carcinoma; IAC, immunoglobulin G4–associated cholangitis; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; JAK, janus kinase; LGD, low-grade dysplasia; LT, liver transplant; LPC, lymphoplasmacytic; MAdCAM-1, mucosal addressin cellular adhesion molecule 1; MDR, multidrug resistance protein; MR, magnetic resonance; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis; Th, T-helper; TLR, Toll-like receptor; TNF, tumor necrosis factor; UC, ulcerative colitis; UDCA, ursodeoxycholic acid; VAP-1, vascular adhesion protein 1.

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Several prognostic scores for PSC have been developed. The revised Mayo risk score is based on a combination of the patient's age; levels of bilirubin, aspartate aminotransferase, and albumin; and the presence of variceal bleeding. These factors can predict survival times without the need for liver biopsy.[16] However, the use of prognostic models is not recommended for management of individual patients with PSC, given the significant variations in disease course.[10,12]

Complications related to PSC, such as intermittent episodes of cholangitis, can occur in 10% to 15% of patients.[17] Portal hypertension and cirrhosis, metabolic bone disease, associated malignancies, and coexisting conditions such as IBD add to the disease burden.

Diagnosis of PSC

Serum Markers

An increased serum level of alkaline phosphatase is the most common biochemical abnormality detected in patients with PSC. In some cases, it is the only biochemical alteration observed, such as in patients with intrahepatic involvement with PSC.[12] However, the level of alkaline phosphatase can vary throughout the disease course and may be normal.[18] Although serum aminotransferase levels are frequently normal, in some patients they can be 2-to 3-fold above the upper limit of normal.[12] Higher values indicate acute biliary obstruction or even an overlap syndrome with autoimmune hepatitis (AIH). Serum levels of total bilirubin are typically normal and increased only among patients with significant biliary obstruction. Serum levels of albumin, international normalized ratios, and platelet counts are typically normal unless cirrhosis and portal hypertension have developed.

Patients with IBD who have increased liver test values that suggest an underlying cholestatic liver disease should immediately be suspected of having concurrent PSC. In rare cases, subjects with IBD undergoing computed tomography or magnetic resonance (MR) enterography have been found to have unsuspected intrahepatic bile duct dilation, even though they had normal results on biochemical analyses of serum samples for liver function. Subsequent MR cholangiopancreatography (MRCP) can identify changes associated with PSC in these subjects.

PSC is associated with a high proportion of nonspecific autoantibodies.[19] Unlike primary biliary cirrhosis, there is no diagnostic serologic test that is specifically associated with PSC. Serologic tests might be useful for patients suspected of having PSC and AIH or immunoglobulin G4–associated cholangitis (IAC) in association with autoimmune pancreatitis (AIP).

Imaging

Cholangiography is the best way to identify patients with PSC (Figure 1). The classic features include multifocal annular stricturing within the intrahepatic and/or extrahepatic bile ducts, with alternating normal or slightly dilated segments.[20] Typically there is diffuse involvement. However, up to 25% of patients have only intrahepatic disease.[20] Although endoscopic retrograde cholangiopancreatography (ERCP) is used to evaluate symptomatic patients with suspected biliary obstruction or cholangiocarcinoma, MRCP has largely replaced ERCP as a diagnostic tool due to improvements in imaging and software-processing technology. Pooled analyses have reported good to excellent diagnostic performance for MRCP compared with ERCP for detection of PSC.[21] MRCP is noninvasive, avoids radiation, and is more cost-effective than ERCP in diagnosis.[22,23] With stronger magnetic fields and availability of 3-dimensional image reprocessing, the ability to visualize third- and fourth-order intrahepatic ducts is now possible, which improves the sensitivity of MRCP when no extrahepatic biliary strictures are present. It is reasonable to consider patient referral if quality MRCP images are not available to exclude or confirm the presence of PSC.

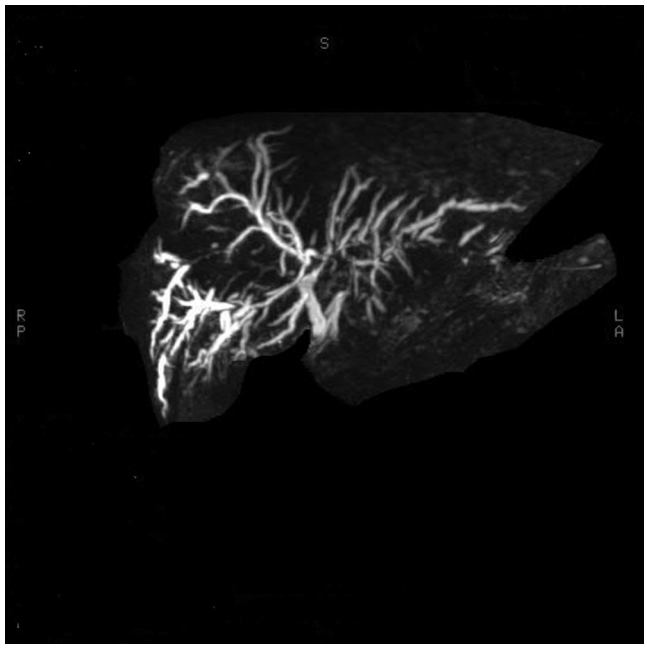

Figure 1. A 3-dimensional postprocessing image from MR cholangiography. Diffusely dilated intrahepatic ducts with multifocal narrowing with diffuse ductal wall thickening and enhancement.

Liver Histology

Typically, a liver biopsy is not required to diagnose PSC unless small duct PSC is suspected or if there are concerns that a patient also has AIH. Histologic features of PSC are often nonspecific and prone to sampling variations due to the heterogeneous involvement of the biliary tree.[24] Unfortunately, the classic description of concentric ductal fibrosis ("onion skinning") involving bile ducts within portal tract areas is rarely encountered in clinical practice (Figure 2).[25] Use of histologic analysis to determine the stage of liver fibrosis requires a specialized scoring system (Batts–Ludwig).[26] However, noninvasive methods to assess fibrosis and cirrhosis, such as elastography imaging, are emerging as useful tools for subjects with PSC.[27]