

Seymour Katz, M.D., Series Editor

Primary Sclerosing Cholangitis and Inflammatory Bowel Disease



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Primary sclerosing cholangitis (PSC) is an immune mediated, chronic, cholestatic liver disease causing inflammation and fibrosis of the intrahepatic and extrahepatic biliary tree. PSC is strongly associated with inflammatory bowel disease, especially ulcerative colitis, predominantly affects males and can lead to the development of portal hypertension, cirrhosis and its complications and cholangiocarcinoma. Patients are usually asymptomatic and present with abnormal liver chemistries in a cholestatic pattern with abnormal imaging of the biliary tree. Currently there are no effective medical therapies to prevent disease progression and treatment is primarily for symptomatic relief. Advanced liver disease is treated with liver transplantation. Due to the high risk of the development of cholangiocarcinoma in patients with PSC, screening of the biliary tract and evaluation of suspicious findings should be performed regularly.

INTRODUCTION

Primarily sclerosing cholangitis (PSC) is an immune mediated, chronic, cholestatic liver disease characterized by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts leading to cirrhosis, portal hypertension and hepatic decompensation.¹ PSC is a

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male-predominant disease, with a male:female ratio of approximately 2:1. The diagnosis is established by cholangiography (usually magnetic resonance cholangiopancreatography [MRCP]) often in patients with inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC), but it is also who present with abnormal liver tests in a cholestatic pattern. PSC is a premalignant disease with a high prevalence of hepatobiliary and colonic malignancy.²

Presentation/Diagnosis

While half of the patients with PSC are asymptomatic, some patients can present with pruritus, right upper quadrant pain or icterus.³ The most common laboratory abnormality is an isolated

elevated alkaline phosphatase of two to three times normal, however, a normal alkaline phosphatase level does not exclude the diagnosis. Serum aminotransferase levels may be mildly elevated but are frequently normal. Serum bilirubin levels are usually normal at diagnosis in the majority of patients. Many patients initially present with low grade fever, right upper quadrant pain, and jaundice due to biliary stones or sludge.

The diagnosis of PSC is based on a cholestatic biochemical profile with characteristic bile duct changes such as multifocal strictures and segmental dilatations on imaging.⁴ Clinical and cholangiographic findings resembling PSC have been described in patients with choledocholithiasis, surgical trauma of the biliary tree, intra-arterial chemotherapy, recurrent pancreatitis, cholangiocarcinoma, diffuse intrahepatic metastasis, eosinophilic cholangitis, hepatic inflammatory pseudotumor, histiocytosis X, IgG4-associated cholangitis, ischemic cholangitis, mast cell cholangiopathy, portal hypertensive biliopathy and recurrent pyogenic cholangitis. Often it is difficult to distinguish PSC from secondary sclerosing cholangitis and the distinction requires a careful review of the clinical history, cholangiographic findings, and whether or not IBD is present. Patients with PSC, in whom other causes of biliary strictures have been ruled out, lacking classical cholangiographic changes on imaging, are classified as having small duct PSC. MRCP is the diagnostic test of choice but endoscopic retrograde cholangiopancreatography (ERCP) can be performed in equivocal cases.^{5,6}

Approximately 50% of PSC patients are asymptomatic at the time of diagnosis. Up to 80% of patients with PSC have IBD, mostly ulcerative colitis and usually pancolitis, with more active disease in the right colon. 13% patients with PSC have concomitant Crohns disease (CD), which usually involves the colon in addition to the small bowel. Conversely, PSC has been diagnosed in 2.4 - 7.5% of patients with UC and 3.4% of patients with CD. The true prevalence of PSC in IBD and in the general population is difficult to assess as it requires cholangiography to be performed. IBD may be diagnosed at any time during the course of PSC. In the majority of cases, the diagnosis of IBD precedes that of PSC, even by several years,⁷⁻⁹

but they may be diagnosed concomitantly.¹⁰ Onset of IBD can occur years after the diagnosis of PSC, and de novo IBD may present after liver transplantation for PSC.¹¹ PSC may be diagnosed at any time during the course of IBD, and may present several years after proctocolectomy.^{7,10} PSC patients who have an ileal pouch anal anastomosis (IPAA) are at an increased risk of pouchitis compared to IPAA patients with UC and without PSC.^{8,12,13} Predisposing factors for this complication are unknown. One report suggests that patients with PSC and IPAA run an increased risk of the development of dysplasia in the ileal pouch mucosa compared with UC patients without PSC and these patients should undergo aggressive cancer screening.¹⁴

Various autoantibodies can be detected in patients with PSC. These autoantibodies are not diagnostic.¹⁵ Perinuclear antineutrophilic cytoplasmic antibodies (pANCA), antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) are most commonly found. Recent studies relating to bile and serum metabolome to establish pathogenesis of PSC and understand the distinctive metabolic signature to aid the diagnosis of patients with UC and PSC have showed interesting results.^{16,17} Liver biopsy is not required to establish a diagnosis of large duct PSC as imaging is sufficient to make the diagnosis. Liver biopsy is required to diagnose small duct PSC and for the assessment of possible overlap syndromes.

Hepatobiliary and Colorectal Malignancies

Cholangiocarcinoma may be seen in up to 15% of PSC patients and up to 50% of cholangiocarcinomas are diagnosed within one year of the diagnosis of PSC.¹⁸ The diagnosis of cholangiocarcinoma in PSC may be difficult to make. Serum carbohydrate antigen19-9 (CA19-9) is useful with a value of >130 U/ml and has a high sensitivity and specificity.¹⁹ Dominant strictures and changes in biliary tract imaging should alert the practitioner to the possibility of cholangiocarcinoma. ERCP with cholangioscopy with brushing and biopsy is useful in assessing and treating dominant strictures. Conventional brush cytology during ERCP has variable sensitivity and specificity for the diagnosis of bile duct neoplasia. Diagnostic accuracy may be increased by the use of fluorescence in situ

Take Away Points on Presentation and Diagnosis

80% of patients with PSC have IBD

Most patients are asymptomatic

An elevated alkaline phosphatase in IBD should make one suspect PSC

MRCP is diagnostic imaging of choice with characteristic bile duct changes such as multifocal strictures and segmental dilatations

Liver biopsy is required to diagnose small duct PSC and overlap syndrome

Key Points: Hepatobiliary and Colorectal Malignancies

Cholangiocarcinoma seen in 7-15% of PSC patients

CA19-9 useful in diagnosing cholangiocarcinoma with a value of >130 U/L

ERCP with cholangioscopy with brushing and biopsy useful for diagnosis

Increased risk of gallbladder disease and gallbladder cancer in PSC

Increased risk of colorectal cancer in PSC specially proximal colon

hybridization (FISH).²⁰ Gallbladder abnormalities are also common in patients with PSC. In a review of 286 PSC patients, gallstones were found in 25%.²¹ Gallbladder stones were diagnosed at a mean of 5 years (± 6.4 years) after the diagnosis of PSC. In this study, a gallbladder mass lesion (mean size 21 \pm 9 mm) was found in 18 (6%) cases. Among these, 10 (56%) proved to be a gallbladder carcinoma. Because of the high prevalence of gallbladder carcinoma in these patients, the American Association for the Study of Liver Disease (AASLD) recommends annual screening with imaging of the gallbladder in patients with PSC.

There is an increased risk of colorectal cancer in PSC patients with IBD over IBD patients without PSC. A meta-analysis indicated that patients with UC and PSC are at an increased risk of CRC and dysplasia compared to patients with UC alone, especially in younger patients.²⁰ Colorectal neoplasia in these patients has a predilection for the proximal colon, therefore annual full length colonoscopy is recommended to detect early dysplasia and initiate proper treatment.²²

Treatment

There is no Food and Drug Administration (FDA) approved medical treatment for patients with PSC. A variety of immunosuppressives and other drug classes have been evaluated, but none have shown

clinically significant benefit. Patients with overlap syndrome with autoimmune hepatitis, however, have been shown to benefit from immunosuppressive agents.^{23,24} The bile acid, ursodeoxycholic acid (UDCA), has been evaluated to treat PSC in varying doses in multiple double-blinded, placebo-controlled, randomized, controlled trials, given its beneficial effect in primary biliary cholangitis.⁶ At doses of 13 to 21 mg/kg, UDCA has been shown in PSC to reduce cholestatic liver enzymes, bilirubin, and albumin, but not to reduce overall mortality, the need for liver transplantation, or prevent liver histologic progression. Higher doses of UDCA at 28 to 30 mg/kg have been associated with increased patient mortality when compared to placebo. Both European Association for the Study of the Liver (EASL) and AASLD guidelines agree that low dose UDCA is safe, but its efficacy is unclear. The current EASL guidelines do not recommend the use of UDCA in PSC.⁵ The AASLD guidelines recommend against the use of UDCA in PSC.⁶

The widespread use of UDCA has inspired research into the mechanisms of action behind the potential protective effects of bile acid interventions in PSC.²⁵ New therapeutic applications have been derived from this research in the form of norUDCA, which appears to enhance general resistance to bile acid induced biliary injury via a bicarbonate rich choleresis, along with local effects in the bile ducts

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Key Points: Medical Therapy for PSC

No approved medical therapy for PSC

UDCA at doses of 13-21 mg/kg may reduce cholestasis

via cholehepatic shunting.²⁶⁻²⁹ A norUDCA phase II trial demonstrated a dose-dependent reduction of alkaline phosphatase in patients receiving 500–1500 mg of norUDCA compared with placebo.³⁰ Additionally, research following the same logic has expanded knowledge on a broad range of nuclear receptors that respond to cholestasis and are involved in normal bile acid homeostasis (e.g. farnesoid X receptor (FXR,) retinoid X receptor (RXR), peroxisome proliferator-activated receptor alpha (PPARalpha) and pregnane X receptor (PXR). (31) These receptors are currently being evaluated as therapeutic targets in early phase clinical trials (e.g. trials of the FXR agonist, obeticholic acid). The majority of clinical trials are focused on cholestatic and fibrotic targets (e.g. norUDCA, anti-LOXL2, obeticholic acid and other FXR agonists, ASBT inhibition), with some emerging interest in therapeutic targeting of the gut microbiota (e.g. faecal transplantation, long-term non-absorbable antibiotics) and T-lymphocyte homing (e.g. anti-VAP1, vedolizumab).

Endoscopic Therapy

Dominant biliary strictures are seen in approximately 50% of patients.³² A dominant stricture has been

defined as a stenosis with a diameter of less than or equal to 1.5 mm in the common bile duct or less than or equal to 1 mm in the hepatic duct. The presence of a dominant stricture is associated with a significantly reduced transplantation-free survival. Endoscopic therapy (balloon dilatation and/or stenting) has shown biochemical and clinical improvement and improved survival compared to that expected by the Mayo risk model.³³ However, in a study comparing balloon dilatation alone with dilatation followed by stent placement, stent therapy did not give additional benefit and resulted in more complications.³⁴ Short-term stenting of up to three weeks has been shown to be safe and effective.³⁵ Both the EASL and AASLD guidelines recommend prophylactic antibiotic therapy for endoscopic interventions and treatment with biliary dilatation of dominant strictures with significant cholestasis in PSC.

Liver Transplantation

PSC patients with recurrent bacterial cholangitis, intractable pruritus and/or a severely impaired quality of life due to fatigue, are considered for transplantation as per the EASL and AASLD guidelines.^{5,6} Liver transplantation in PSC is

Key Points: PSC and Liver Transplantation

Indicated for patients with high MELD scores

Indicated for patients with with recurrent bacterial cholangitis, intractable pruritus and/or a severely impaired quality of life due to fatigue

85% 5-year survival

20-25% PSC recurrence following transplantation

IBD may present de novo at any time after liver transplantation

Key Points: Endoscopic Therapy

Dominant biliary strictures are seen in 50% of patients

Balloon dilatation and /or stenting has shown biochemical and clinical improvement

Prophylactic antibiotics for endoscopic interventions is recommended

indicated based on model for end-stage liver disease (MELD) score as in cirrhosis.³⁶ The indication for liver transplantation in patients with colonic dysplasia and no signs of cholangiocarcinoma remains controversial.⁵ In Scandinavian countries, liver transplantation is offered to patients with cholangiocellular dysplasia. In the United States, only a few centres undertake liver transplantation for patients with hilar cholangiocarcinoma. An analysis of United Network for Organ Sharing (UNOS) outcomes demonstrated that patients with PSC had a lower waitlist mortality and were less likely to be removed from the list than patients listed for other indications despite similar MELD scores.³⁷ These findings suggest that MELD scoring may overestimate the severity of liver dysfunction in patients with PSC. Conversely, it has been argued that whilst MELD predicts waitlist mortality; in patients with PSC, MELD introduces a systematic disadvantage.^{37,38} PSC patients frequently experience a poor quality of life and increased risk of disease-specific adverse outcomes, including recurrent or intractable cholangitis and the development of biliary malignancies, all poorly reflected by MELD-score based risk prediction.³⁸

The outcome of transplantation is very good with an approximately 85% 5-year survival.³⁹ However, a recurrence of PSC is seen in ~20–25% of transplanted PSC patients, and the effect of recurrence on graft survival is currently undetermined.⁴⁰ IBD may present de novo at any time after liver transplantation for PSC.

PSC still remains a clinical challenge despite the many scientific advances made over recent years. While no medical therapies for PSC have been FDA approved, there is currently significant being performed to hopefully facilitate the development of new, effective therapies. Treatment of PSC is used for symptomatic disease. Therapeutic endoscopy, ERCP and liver transplantation remain the mainstays of management. A better understanding of the pathogenetic mechanisms involved in the development of PSC is required in order to be able to develop clinically meaningful serum disease state markers, new medical therapies for the treatment of PSC and improved markers and treatments for cholangiocarcinoma. ■

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