Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown etiology that is characterized by inflammation, fibrosis, and stricturing of medium and large ducts in the intrahepatic and/or extrahepatic biliary tree (picture 1) [1-3].

This topic will review the clinical manifestations and diagnosis of PSC. The treatment of PSC is discussed separately. (See "Primary sclerosing cholangitis in adults: Management".)

The approach to patients with PSC was reviewed in a 2015 guideline from the American College of Gastroenterology [4] and in a 2010 guideline from by the American Association for the Study of Liver diseases [5]. The discussion that follows is generally consistent with these guidelines.

EPIDEMIOLOGY

Incidence and prevalence — Estimates of the incidence of primary sclerosing cholangitis (PSC) vary in Europe and North America. In a systematic review of population-based studies, the incidence of PSC was highest in studies performed in Northern Europe and North America as compared with the Mediterranean basin (Finland 1.6 per 100,000, United States 1.5 per 100,000 and Italy 0.1 per 100,000) [6]. In the studies that evaluated temporal trends, an increase in

prevalence of PSC was noted over time. Median transplant-free survival ranged from 9.7 years in the United States to 20.6 years in the Netherlands.

In a study performed in the United Kingdom, the incidence of PSC was 0.68 (95% CI 0.45-0.99) per 100,000 person-years and the age-standardized prevalence was 5.58 (95% CI 4.82-7.35) per 100,000 person-years [7]. PSC patients were more likely to have a history of inflammatory bowel disease (54 versus 2 percent). The mortality rate per 1000 person-years was threefold higher in PSC than population controls (49.5 versus 16.1; incidence rate ratio 3.1, 95% CI 2.2-4.2) [7].

Association with inflammatory bowel disease — The majority of patients with PSC have underlying ulcerative colitis (UC); the prevalence of ulcerative colitis may be as high as 90 percent when rectal and sigmoid biopsies are routinely obtained [8]. Because of this strong association, we evaluate patients diagnosed with PSC for inflammatory bowel disease (IBD). (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Evaluation'.)

Conversely, among patients with UC it has been estimated that PSC occurs in approximately 5 percent and perhaps less often in those with Crohn disease [9]. As a result, we do not routinely screen patients with IBD for PSC. However, patients with IBD who have abnormal liver tests should be evaluated for PSC. (See "Primary sclerosing cholangitis: Epidemiology and pathogenesis", section on 'PSC and inflammatory bowel disease'.)

Patients with IBD and PSC may have a different phenotype than patients with IBD alone. Studies suggest that among patients with UC, pancolitis is more common in patients who also have PSC [10,11]. In addition, colon biopsies from patients with IBD and PSC may show active histologic activity despite minimal endoscopic activity [12].

CLINICAL MANIFESTATIONS

PSC may be asymptomatic and diagnosed as part of the evaluation of abnormal laboratory tests, or they may have symptoms such as fatigue and pruritus. Physical examination may reveal jaundice, hepatomegaly, splenomegaly, and excoriations, though it is often normal. Liver biochemical tests usually demonstrate a cholestatic pattern, with elevation of the serum alkaline phosphatase predominating in most patients. Radiographic findings include abnormal-appearing bile ducts with wall thickening, dilations, and strictures.

Patients may also have findings related to inflammatory bowel disease. (See "Primary sclerosing cholangitis: Epidemiology and pathogenesis", section on 'PSC and inflammatory bowel disease' and "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on

'Clinical manifestations' and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Clinical features'.)

Symptoms — Approximately half of the patients with PSC are asymptomatic at the time of diagnosis [13,14], despite some already having advanced disease. PSC is often detected as part of the evaluation of abnormal liver tests in patients with inflammatory bowel disease [15]. Among patients who have symptoms, fatigue and pruritus are common. Little is known about the pathogenesis of fatigue; nevertheless, it may become quite debilitating.

Pruritus is a common symptom of PSC that can be extremely disabling, leading to severe excoriations and a decreased quality of life. The pathogenesis of pruritus in PSC, as in other disorders which cause cholestasis, is not clear. Several hypotheses have been proposed, including bile acid accumulation and endogenous opioids [16-18]. Intractable pruritus is an indication for liver transplantation in patients with PSC. Patients with pruritus associated with cholestasis often have a normal bilirubin. (See "Pruritus associated with cholestasis" and "Primary sclerosing cholangitis in adults: Management", section on 'Liver transplantation'.)

Fevers, chills, night sweats, and right upper quadrant pain can also be present. These features may represent episodic bacterial cholangitis from biliary obstruction rather than advanced disease. Liver biochemical tests may worsen during these episodes, but persistent jaundice usually reflects advanced disease.

Examination findings — Approximately half of patients with PSC will have a normal physical examination at the time of diagnosis. Abnormalities that may be detected on physical examination include jaundice, hepatomegaly, splenomegaly, and excoriations [5].

Laboratory tests — Liver biochemical tests usually demonstrate a cholestatic pattern, with elevation of the serum alkaline phosphatase predominating in most patients. The serum alkaline phosphatase and bilirubin may fluctuate substantially, possibly indicating transient blockage of strictured bile ducts by biliary sludge or small stones. The serum aminotransferases are typically less than 300 international unit/L. The serum albumin concentration is normal in patients with early stage disease, although those with active inflammatory bowel disease may have hypoalbuminemia. (See "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)".)

Additional serologic findings in patients with PSC include [1] (see "Primary sclerosing cholangitis: Epidemiology and pathogenesis"):

- Hypergammaglobulinemia – 30 percent.
- Increased serum immunoglobulin M (IgM) levels – 40 to 50 percent.

- Atypical perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) – 30 to 80 percent.
- Human leukocyte antigen DRw52a – 0 to 100 percent in various reports [19,20].

A number of other autoantibodies, including antinuclear, antismooth muscle, anticardiolipin, thyroperoxidase, and rheumatoid factor, may also be present but are of uncertain clinical significance [21]. Antimitochondrial antibodies, which are characteristic of primary biliary cholangitis, are usually absent in PSC. In one study, 71 of 73 (97 percent) patients with PSC were positive for at least one autoantibody, while 59 (81 percent) were positive for ≥3 [21]. The presence of autoantibodies did not correlate with disease severity, with the exception of anticardiolipin antibodies, which correlated with the Mayo risk score. (See 'Prognosis' below.)

Elevated serum immunoglobulin G4 (IgG4) (a characteristic marker of autoimmune pancreatitis that is seen at lower levels in several other diseases) has been described in patients with PSC [22,23]. In a report of 127 patients with PSC, 12 (9 percent) had values above the upper limit of normal [22]. Patients with elevated IgG4 may have a distinct entity, IgG4-associated cholangitis. (See 'IgG4-associated cholangitis' below and "Autoimmune pancreatitis: Clinical manifestations and diagnosis", section on 'Serum IgG4'.)

Hepatic and urinary copper levels are increased, and serum ceruloplasmin is reduced in most patients with PSC. However, these findings are not specific, being commonly found in patients who have other forms of chronic cholestatic liver disease. Copper accumulation worsens as the disease progresses.

Radiographic findings — Patients with PSC who undergo radiographic imaging with ultrasound may have evidence of abnormal bile ducts (image 1A-B), although the findings are usually not diagnostic and the examination may be normal. Ultrasound findings in patients with PSC include bile duct wall thickening and focal bile duct dilations [5]. In addition, gallbladder abnormalities such as wall thickening, enlargement, gallstones, cholecystitis, and mass lesions may also be seen in those who have developed complications. (See 'Complications of primary sclerosing cholangitis' below.)

Computed tomography may reveal thickening and inflammation of the bile ducts, saccular dilations of the intrahepatic duct, heterogenous bile duct dilation, evidence of portal hypertension (eg, varices), and mass lesions.

Magnetic resonance cholangiopancreatography findings in patients with PSC include multifocal, short, annular strictures that alternate with normal or mildly dilated segments. This results in a "beaded" appearance of the bile duct. Long strictures may also be seen and are concerning for cholangiocarcinoma. (See 'Cholangiography' below.)

DIAGNOSIS

General diagnostic approach — PSC should be considered in patients with a cholestatic pattern of liver test abnormalities (particularly an elevated alkaline phosphatase), especially those with underlying inflammatory bowel disease. The diagnosis is then made by showing cholangiographic evidence of characteristic bile duct changes (multifocal strictures, segmental dilations) and excluding secondary causes of sclerosing cholangitis. A percutaneous liver biopsy may support the diagnosis of PSC but is rarely diagnostic. In patients with characteristic findings on cholangiography, a liver biopsy is typically not required. However, a liver biopsy is required for patients with suspected small duct PSC. (See 'Differential diagnosis' below.)

In addition to performing imaging to confirm a diagnosis of PSC, we also obtain an antimitochondrial antibody to help exclude primary biliary cholangitis and an immunoglobulin G4 (IgG4) level [4]. (See 'IgG4-associated cholangitis' below.)

Cholangiography — The diagnosis of PSC is typically established by the demonstration of characteristic multifocal stricturing and dilation of intrahepatic and/or extrahepatic bile ducts on cholangiography (image 2). A cholangiogram may be obtained using magnetic resonance cholangiopancreatography (MRCP) (image 3), endoscopic retrograde cholangiopancreatography (ERCP) (image 2), or percutaneous transhepatic cholangiography (PTC). Because it is noninvasive with comparable diagnostic accuracy to ERCP, MRCP is typically the first test of choice [4,5,24]. In a meta-analysis of six studies, the sensitivity and specificity of MRCP for diagnosing PSC were 86 and 94 percent, respectively. PTC is the most invasive approach and is reserved for patients who are unable to undergo ERCP. (See "Percutaneous transhepatic cholangiography in adults".)

ERCP may be required in patients who are unable to undergo MRCP (eg, those with implanted metal devices) and in patients with early PSC since early changes may be missed by MRCP [5]. Finally, ERCP may be better than MRCP at detecting large-duct PSC.

Classic PSC — The biliary strictures in patients with PSC may be focal, with normal intervening areas, or diffuse, involving long segments. Strictures can occur in any part of the biliary tree. In one report of 100 patients, strictures were present in the following distribution [1]:

- Intrahepatic and extrahepatic bile ducts – 87 percent
- Intrahepatic bile ducts alone – 11 percent
- Extrahepatic bile ducts alone – 2 percent

The gallbladder and cystic duct may also be involved. A study of 286 patients with PSC found one or more gallbladder abnormalities in 41 percent of patients [25]. Gallbladder findings were more common in those with extrahepatic PSC. A gallbladder mass lesion was found in 18 patients (6 percent), 10 of which represented gallbladder carcinoma, suggesting that cholecystectomy should be performed when such lesions are detected. Similar results have been reported by others [26]. (See "Gallbladder polyps", section on 'Primary sclerosing cholangitis'.)

In contrast to the characteristic strictures, shallow ulcerations of the bile ducts may be the only cholangiographic finding in patients with early stage disease. ERCP is typically required to detect such changes.

Small duct PSC — Cholangiography is normal in a small percentage of patients who have a variant of PSC known as "small duct primary sclerosing cholangitis." This variant (sometimes referred to as "pericholangitis") is probably a form of PSC involving small caliber bile ducts [27]. It has similar biochemical and histologic features to classic PSC. It appears to have a significantly better prognosis than classic PSC [28-30], although it may evolve into classic PSC [29,31]. Classic PSC developed in 4 of 27 patients in one series of patients with small duct PSC who underwent repeat cholangiographic examinations after a median of 72 months [28]. (See 'Complications of primary sclerosing cholangitis' below.)

Liver biopsy — A percutaneous liver biopsy may support the diagnosis of PSC, but is rarely diagnostic [32]. We reserve liver biopsy for patients with suspected small duct PSC or if other conditions such as an overlap syndrome with autoimmune hepatitis are suspected. We give antibiotics (eg, ciprofloxacin) prior to the procedure to minimize the risk of subsequent cholangitis, though this approach has not been studied.

The most specific histologic finding in PSC is fibrous obliteration of small bile ducts, with concentric replacement by connective tissue in an "onion skin" pattern (picture 1), although this histological finding is seen in less than 25 percent of liver biopsies. More often, histologic abnormalities in PSC are nonspecific and are similar to those in primary biliary cholangitis. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis", section on 'Liver biopsy'.)

The histologic findings initially involve the portal triads but expand into the hepatic parenchyma as the disease progresses. As a result, liver biopsy is helpful for staging the disease and determining prognosis. The staging system used most commonly in PSC is similar to that used in primary biliary cholangitis [33]:

- Stage I – Enlargement, edema, and scarring of the portal triads, and mononuclear cell infiltration with some piecemeal necrosis and damage to isolated bile ducts. Proliferation of interlobular bile ducts with mononuclear and polymorphonuclear cells may also be present, although the inflammation is usually less dense than in primary biliary cholangitis.
- Stage II – Expansion of portal triads with fibrosis extending into the surrounding parenchyma.
- Stage III – Bridging fibrosis.
- Stage IV – Cirrhosis.

Transient elastography — Transient elastography measures liver stiffness and is a technique for noninvasively assessing hepatic fibrosis. Studies suggest that it can be used to estimate the degree of hepatic fibrosis in patients with cholestatic liver disease, including PSC. In one study, the area under the receiver operating characteristic curve for transient elastography predicting cirrhosis in patients with cholestatic liver disease was 0.96 when a cutoff of 17.3 kPa was used [34]. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography", section on 'Transient elastography'.)

DIFFERENTIAL DIAGNOSIS

PSC needs to be differentiated from secondary causes of sclerosing cholangitis and IgG4-associated cholangitis/autoimmune pancreatitis. In addition, PSC-autoimmune hepatitis overlap syndrome should be considered.

Secondary sclerosing cholangitis — Secondary causes of the cholangiographic findings seen in PSC need to be excluded prior to making a diagnosis of PSC. Secondary causes of PSC include [5]:

- Chronic bacterial cholangitis
- Infectious or ischemic cholangiopathy
- Cholangiocarcinoma
- Choledocholithiasis
- Diffuse intrahepatic metastases
- Eosinophilic cholangitis
- Intra-arterial chemotherapy
- Mast cell cholangiopathy

- Portal hypertensive biliopathy
- Recurrent pancreatitis
- Recurrent pyogenic cholangitis
- Surgical biliary trauma

In most cases, secondary causes of sclerosing cholangitis can be excluded based on the patient's history and imaging studies (eg, to rule out cholangiocarcinoma).

IgG4-associated cholangitis — A form of glucocorticoid-responsive sclerosing cholangitis that shares clinical and radiographic features with PSC may occur as part of the immunoglobulin G4 (IgG4)-related diseases. IgG4-associated cholangitis is the most frequent extrapancreatic manifestation of type 1 autoimmune pancreatitis (IgG4-related), present in over 70 percent of such patients [35]. It also rarely occurs in the absence of pancreatitis. Whether IgG4-associated cholangitis, autoimmune pancreatitis, and PSC are separate entities or are different manifestations of one disease is unclear. Serum IgG4 should be measured in all newly diagnosed patients with PSC, since treatment of IgG4-associated cholangitis/autoimmune pancreatitis includes glucocorticoids [5]. (See "Autoimmune pancreatitis: Management", section on 'Induction of remission' and "Autoimmune pancreatitis: Clinical manifestations and diagnosis", section on 'Type 1 AIP'.)

PSC-autoimmune hepatitis overlap syndrome — PSC has been associated with autoimmune hepatitis (AIH). PSC-AIH overlap syndrome is typically seen in children and young adults. It is characterized by clinical, biochemical, and histologic findings of AIH with the addition of cholangiographic findings of PSC. (See "Overview of autoimmune hepatitis" and "Autoimmune hepatitis variants: Definitions and treatment", section on 'Autoimmune hepatitis-PSC overlaps' and "Autoimmune hepatitis variants: Definitions and treatment", section on 'Autoimmune hepatitis-PSC overlap'.)

COMPLICATIONS OF PRIMARY SCLEROSING CHOLANGITIS

Continued destruction of bile ducts in primary sclerosing cholangitis (PSC) leads to end-stage liver disease. Patients with PSC also may develop a number of other complications, including:

- Fat-soluble vitamin deficiencies (A, D, E, and K)
- Metabolic bone disease
- Dominant biliary strictures
- Cholangitis and cholelithiasis
- Cholangiocarcinoma

- Gallbladder cancer
- Hepatocellular carcinoma (in patients with cirrhosis)
- Colon cancer (in patients with concomitant ulcerative colitis) (see "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer")

Patients with small duct PSC (ie, histologic findings consistent with PSC but normal findings on cholangiography) may have a better prognosis than patients with classic PSC. One study compared 18 patients with small duct PSC with 36 matched controls with classic PSC who were seen over a four-year period [29]. None of the patients with small duct PSC developed hepatobiliary malignancy, compared with four of the patients (11 percent) with classic PSC. In addition, patients with small duct PSC had higher transplant-free survival rates (83 versus 58 percent).

Cirrhosis and portal hypertension — As PSC progresses, patients develop progressive hepatic fibrosis, ultimately resulting in cirrhosis. Once cirrhosis has developed, patients may also develop complications of cirrhosis, such as varices, ascites, and hepatic encephalopathy. The approaches to the diagnosis of cirrhosis and its complications are discussed elsewhere. (See 'Prognosis' below and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

Steatorrhea and vitamin deficiency — Steatorrhea with concomitant fat-soluble vitamin deficiency may be seen in patients with advanced PSC, but it is rare in early disease. It is generally thought to be due to decreased secretion of conjugated bile acids into the small intestine [36,37]. However, associated conditions that may coexist with PSC, such as chronic pancreatitis and celiac disease, may also contribute to the genesis of steatorrhea [38-40]; these disorders should be considered in the differential diagnosis of steatorrhea in a patient with PSC who has no jaundice or evidence of cirrhosis by histology [41]. (See "Overview of vitamin A", section on 'Deficiency' and "Overview of vitamin D", section on 'Deficiency and resistance' and "Overview of vitamin E", section on 'Deficiency' and "Overview of vitamin K", section on 'Vitamin K deficiency'.)

Vitamin A deficiency has been reported in up to 82 percent of patients with advanced PSC, occasionally accompanied by night blindness [42]. In addition, vitamin D and vitamin E deficiencies occur in approximately one-half of those with advanced disease [42]. Thus, patients with PSC should be screened for fat-soluble vitamin deficiencies by determination of the prothrombin time (vitamin K) and serum levels of vitamins A, D, and E. Supplemental therapy should be administered as necessary. (See "Evaluating nutritional status in adults with cirrhosis", section on 'Nutritional assessment'.)

Metabolic bone disease — Metabolic bone disease, in particular osteoporosis, is a complication of advanced PSC, with radiologic and histologic evidence of osteopenia in the lumbar spine, iliac crest, and femur [43-45]. The axial skeleton (eg, trabecular bone of the lumbar spine) is affected more commonly than the appendicular skeleton (cortical bone) [46]. Radiologic techniques such as dual photon absorptiometry are superior to traditional serum and urinary markers of bone loss for diagnosing osteopenia in patients with PSC. We agree with a 2010 guideline from the AASLD that recommends bone density examinations at diagnosis and every two to three years thereafter [5]. (See "Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women", section on 'Diagnosis'.)

The pathogenesis of bone disease in PSC and other chronic cholestatic liver diseases (eg, primary biliary cholangitis) is unknown. Bone disease in patients with PSC is due to osteopenia/osteoporosis rather than osteomalacia, and thus, malabsorption of vitamin D or low serum vitamin D concentration is not the cause in most cases. Furthermore, vitamin repletion in the minority of cases with low serum vitamin D levels does not reduce either the presence or severity of osteoporosis [47]. The vast majority of patients with PSC suffer from inflammatory bowel disease, which increases the risk of bone disease. In addition, treatment with glucocorticoids increases the rate of bone loss and the risk of fractures. Patients with PSC are also prone to develop fractures after liver transplantation, even in the absence of metabolic bone disease, due to immobilization and concomitant therapy with glucocorticoids [48]. (See "Metabolic bone disease in inflammatory bowel disease" and "Prevention and treatment of osteoporosis after solid organ or stem cell transplantation".)

It has also been proposed that a toxin or toxins retained because of cholestasis prevents the osteoblast from functioning normally, resulting in decreased bone formation; unconjugated bilirubin [49], copper [46], and bile salts [46] have all been implicated as potential toxins [49]. (See "Evaluation and treatment of low bone mass in primary biliary cholangitis (primary biliary cirrhosis)".)

The prevalence of metabolic bone disease was examined in an illustrative study that included 237 patients who underwent bone density testing every year for 10 years [50]. Osteoporosis (defined as a T-score less than -2.5) was detected in 15 percent of patients (24 times more commonly than expected in an age-, sex-, and ethnicity-matched general population). Risk factors included age older than 54 years, body mass index ≤24 kg/m^2, and the presence of inflammatory bowel disease for ≥19 years. Osteoporosis was present in 75 percent of patients with all three risk factors compared with only 3 percent of those without any risk factors. In another report, bone density was measured in 30 patients with advanced PSC (group 1) and 18 patients with newly diagnosed disease (group 2) [43]. Mean bone mineral density was

significantly reduced in group 1 compared with age-matched and sex-matched controls (0.97 versus 1.25 gm/cm^2); in 15 of the 30 patients, bone density was below the fracture threshold. By contrast, bone mineral density in group 2 was not significantly different from controls, and no patient was below the fracture threshold.

Although few studies have specifically addressed the treatment of bone disease in PSC, management principles are similar to those in primary biliary cholangitis. Calcium supplementation and measurement of vitamin D levels are generally recommended. For patients with more significant loss of bone density, bisphosphonate therapy may also be beneficial [51]. (See "Evaluation and treatment of low bone mass in primary biliary cholangitis (primary biliary cirrhosis)", section on 'Management'.)

Dominant biliary strictures — Up to 60 percent of patients with PSC develop a dominant stricture in the intrahepatic or extrahepatic biliary tree [13,41,52-54]. One definition of a dominant stricture is a stenosis with a diameter of ≤1.5 mm in the common bile duct or ≤1 mm in the hepatic ducts [53,55]. Strictures can occur at the biliary hilum or anywhere along the common hepatic or common bile ducts [56]. Patients typically present with evidence of mechanical biliary obstruction manifested by jaundice, pruritus, ascending cholangitis, and malabsorption. This presentation is difficult to distinguish from that of cholangiocarcinoma. Thus, if a dominant stricture is identified, cytologic brushings of the stricture should be performed to exclude malignancy [57]. (See 'Cholangiocarcinoma' below.)

Cholangitis and cholelithiasis — Choledocholithiasis and cholelithiasis due to cholesterol and/or pigment stones may be present in up to a third of patients with PSC [58]. Ultrasonography can identify biliary obstruction but has a low sensitivity for determining its cause (eg, stricture, stone, or neoplasm). Thus, cholangiography should be used to detect reversible causes of biliary obstruction [41,59].

Gallstones in patients with PSC are treated the same way as in other patients. Attempts are made to remove gallstones only if they are causing obstruction of the major bile ducts; incidental gallstones in the gallbladder are not treated unless the clinical scenario dictates that they need to be removed. (See "Approach to the management of gallstones" and "Overview of gallstone disease in adults" and "Choledocholithiasis: Clinical manifestations, diagnosis, and management".)

Bacterial cholangitis can occur in patients with PSC. The risk is greatest after endoscopic or surgical manipulation (including liver biopsy), but cholangitis can also develop spontaneously, particularly in patients with bile duct stones or obstructing strictures [59-61]. Biliary candida

infections have also been described [62]. (See "Acute cholangitis: Clinical manifestations, diagnosis, and management".)

Hepatobiliary cancer — Patients with PSC are at increased risk for cholangiocarcinoma, gallbladder cancer, and in patients with cirrhosis, hepatocellular carcinoma.

Cholangiocarcinoma — Patients with PSC have a 10 to 15 percent lifetime risk of developing cholangiocarcinoma [1,63]. The annual incidence in the setting of PSC has been estimated to be 1.5 percent [64]. In a series of 161 patients seen at the Mayo clinic, 7 percent developed cholangiocarcinoma during a mean follow-up of 11.5 years [65]. Patients with normalization or near normalization of their alkaline phosphatase may be at decreased risk for developing cholangiocarcinoma [66,67]. Studies have failed to show a benefit of screening for cholangiocarcinoma in patients with PSC. However, given the high incidence, our approach is to screen annually for cholangiocarcinoma with either ultrasound or MRCP, plus measurement of a serum CA 19-9.

Risk factors that have been identified in one or more studies include the presence of inflammatory bowel disease, cirrhosis, variceal bleeding, a dominant stricture (in patients who also have inflammatory bowel disease), and regular alcohol consumption [65,68-70]. However, the strength of these associations remains uncertain.

The development of cholangiocarcinoma is often heralded by rapid clinical deterioration with jaundice, weight loss, and abdominal discomfort [63]. The presence of progressive biliary dilatation in the setting of a dominant stricture should also raise a strong suspicion of cholangiocarcinoma. (See "Clinical manifestations and diagnosis of cholangiocarcinoma".)

The diagnosis of cholangiocarcinoma can be extremely difficult in patients with PSC. In an illustrative study, 10 percent of patients with PSC undergoing liver transplantation had an unsuspected cholangiocarcinoma [71]. Delayed diagnosis often results in the discovery of tumors at an advanced stage when they cannot be resected for cure. It is also difficult to distinguish a dominant stricture from a cholangiocarcinoma, even with imaging, endoscopic biopsy, and cytology.

The tests used to make the diagnosis include biliary brush cytology, endobiliary biopsy, computed tomography or magnetic resonance cholangiopancreatography (MRCP) scanning, and serum tumor markers such as CEA or CA 19-9 [72-74]. All of these studies have limitations, and none has been shown to be beneficial for screening. However, because of the high incidence of cholangiocarcinoma in patients with PSC, some have argued for annual screening with imaging studies and a serum CA 19-9 [75]. (See "Clinical manifestations and diagnosis of cholangiocarcinoma".)

The presence of cholangiocarcinoma portends a poor prognosis in patients with advanced PSC; only 10 percent of patients survived two years in one report [41]. Liver transplantation has been a disappointment in the treatment of cholangiocarcinoma, with significantly lower patient survival due to recurrent disease [71,76,77]. Thus, most transplant centers are not transplanting these patients outside of study protocols. The poor prognosis has led to the suggestion for earlier liver transplantation in patients with PSC before cholangiocarcinoma has a chance to develop.

Gallbladder cancer — The prevalence of gallbladder cancer among patients with PSC is estimated to be 3 to 14 percent [75]. We agree with the American Association for the Study of Liver Diseases [5] and the European Association for the Study of the Liver [78], which recommend annual screening for gallbladder cancer using ultrasound. However, MRCP may permit screening for both gallbladder cancer and cholangiocarcinoma [75]. (See "Gallbladder polyps", section on 'Primary sclerosing cholangitis'.)

Hepatocellular carcinoma — Patients with PSC and cirrhosis are at increased risk for hepatocellular carcinoma and should undergo screening. (See "Surveillance for hepatocellular carcinoma in adults", section on 'Patients with cirrhosis'.)

Colon cancer — Patients with both PSC and ulcerative colitis have an increased risk of colon cancer and progression of neoplastic transformation and require screening with periodic colonoscopy. (See "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer", section on 'Management'.)

PROGNOSIS

Primary sclerosing cholangitis (PSC) is usually a progressive disorder that ultimately leads to complications of cholestasis and hepatic failure. Median survival without liver transplantation after diagnosis is 10 to 21 years [6,13,14,79,80]. Survival is significantly worse for patients who are symptomatic at the time of diagnosis [14]. (See 'Complications of primary sclerosing cholangitis' above.)

Variables associated with prognosis in primary sclerosing cholangitis (PSC) have been incorporated in a well-validated statistical model (the Mayo risk score [81]) (table 1). The components of the Mayo risk score include age, serum bilirubin, serum albumin, serum AST, and history of variceal bleeding. The calculation of this risk score correlates well with observed survival and is useful in assessing prognosis and determining timing for liver transplantation,

although prioritization for transplantation is based upon the MELD score. (See "Model for End-stage Liver Disease (MELD)".)

Several groups have studied variables that appear to predict prognosis in PSC. These include age, histological stage, hepatomegaly, splenomegaly, serum alkaline phosphatase, serum bilirubin, the presence of a dominant bile duct stricture, concurrent inflammatory bowel disease (IBD), and Candida in bile [13,14,80,82-85]. One study, for example, found that approximately 90 percent of those with stage II disease would be expected to progress to bridging fibrosis or cirrhosis, while approximately one-half of those who had already developed bridging fibrosis were expected to develop cirrhosis within five years [86].

Concurrent IBD may also be associated with a poorer prognosis. In a study that compared 60 patients with PSC and IBD with 19 patients with PSC but without IBD, the presence of IBD was associated with a lower median age at presentation (46 versus 64 years), the development of serious malignant complications (23 versus 0 percent), and lower liver transplant-free survival (57 versus 84 percent) [83]. A second study of 222 patients with PSC (167 with ulcerative colitis [UC] and 55 without UC) also found that patients with PSC associated with UC were diagnosed at a younger age than those without UC (median age at presentation 38 versus 47 years) [87]. It also found higher rates of dysplasia and/or colon cancer among patients with UC (33 versus 2 percent). However, the presence of UC was not associated with death or liver transplantation after adjusting for sex, Mayo risk score, and year of diagnosis.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Primary sclerosing cholangitis".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown etiology that is characterized by inflammation, fibrosis, and stricturing of medium and large ducts in the intrahepatic and/or extrahepatic biliary tree. PSC is usually a progressive disorder that ultimately leads to complications of cholestasis and hepatic failure. Median survival without liver transplantation after diagnosis is 10 to 12 years. The majority of patients with PSC have underlying ulcerative colitis (UC). (See 'Epidemiology' above.)

- **Clinical features** – Patients with PSC may be asymptomatic and diagnosed as part of the evaluation of abnormal laboratory tests, or they may have symptoms such as fatigue and pruritus. Physical examination may reveal jaundice, hepatomegaly, splenomegaly, and excoriations, though it is often normal. Liver biochemical tests usually demonstrate a cholestatic pattern, with elevation of the serum alkaline phosphatase predominating in most patients. Radiographic findings include abnormal appearing bile ducts with wall thickening, dilations, and strictures. (See 'Clinical manifestations' above.)

- **Diagnosis** – PSC should be considered in patients with a cholestatic pattern of liver test abnormalities (particularly an elevated alkaline phosphatase), especially those with underlying inflammatory bowel disease. The diagnosis is then made by showing cholangiographic evidence of characteristic bile duct changes (multifocal strictures, segmental dilations) and excluding secondary causes of sclerosing cholangitis. A percutaneous liver biopsy may support the diagnosis of PSC, but it is rarely diagnostic. In patients with characteristic findings on cholangiography, a liver biopsy is typically not required. However, liver biopsy is required for patients with suspected small duct PSC or if other conditions such as an overlap syndrome with autoimmune hepatitis are suspected. (See 'Diagnosis' above.)

- **Differential diagnosis** – PSC needs to be differentiated from secondary causes of sclerosing cholangitis and IgG4-associated cholangitis/autoimmune pancreatitis. In addition, PSC autoimmune hepatitis overlap syndrome should be considered. (See 'Differential diagnosis' above.)

- **Complications** – Continued destruction of bile ducts in PSC leads to end-stage liver disease. Patients with PSC also may develop a number of other complications, including (see 'Complications of primary sclerosing cholangitis' above):

  - Fat-soluble vitamin deficiencies (see "Evaluating nutritional status in adults with cirrhosis", section on 'Nutritional assessment')
  - Metabolic bone disease (see 'Metabolic bone disease' above)
  - Cholangiocarcinoma (see 'Cholangiocarcinoma' above)
  - Gallbladder cancer (see 'Gallbladder cancer' above)
  - Hepatocellular carcinoma in patients with cirrhosis (see "Surveillance for hepatocellular carcinoma in adults", section on 'Patients with cirrhosis')
  - Colon cancer in patients with inflammatory bowel disease (see "Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer", section on 'Management')

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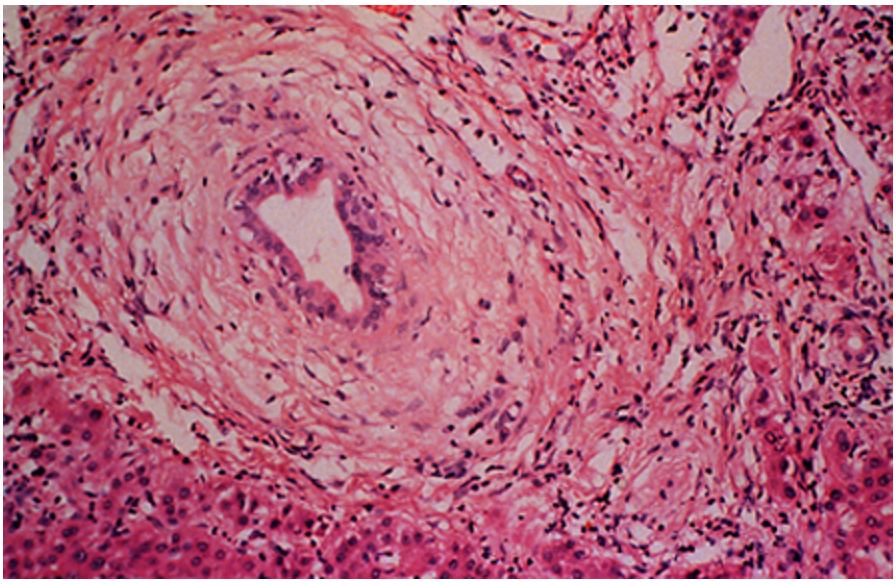
Topic 660 Version 38.0

GRAPHICS

Primary sclerosing cholangitis

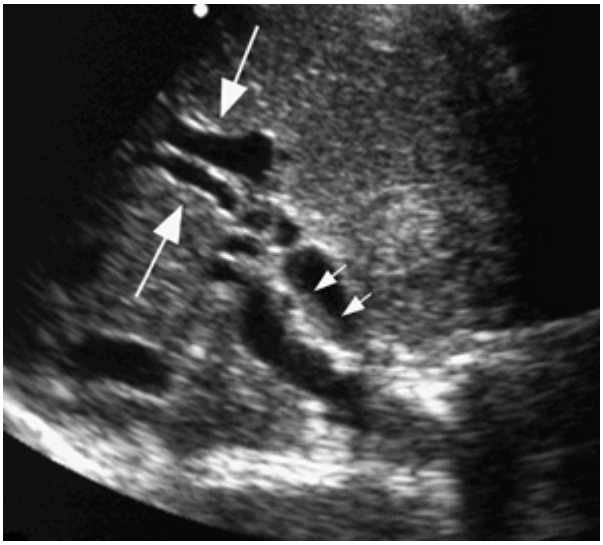


Medium power view of a liver biopsy from a patient with primary sclerosing cholangitis shows a portal bile duct with periductal sclerosis associated with degeneration of the bile duct epithelium.

Courtesy of Robert Odze, MD.

Graphic 70795 Version 1.0

Primary sclerosing cholangitis

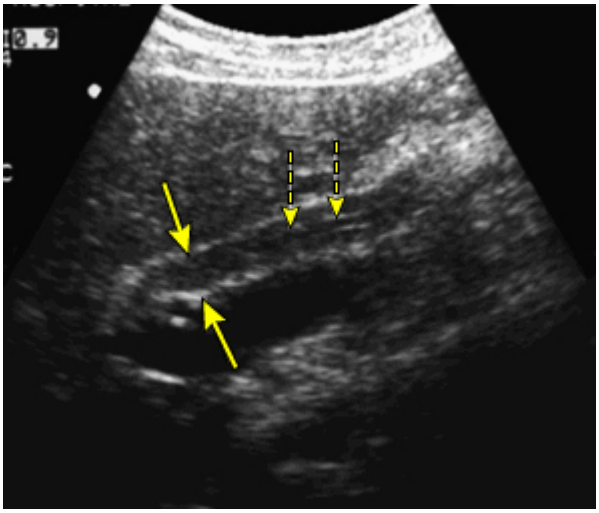


Ultrasound image in a patient with primary sclerosing cholangitis shows dilation of segmental ducts (large arrows) and debris within the lumen of intrahepatic ducts (small arrows).

Courtesy of Jonathan Kruskal, MD.

Graphic 81306 Version 2.0

Extrahepatic primary sclerosing cholangitis



Ultrasound image of the right upper quadrant in a patient with ulcerative colitis and primary sclerosing cholangitis shows marked thickening of the wall of the common bile duct (arrows) and narrowing of its lumen (dashed arrows).

Courtesy of Jonathan Kruskal, MD.

Graphic 81312 Version 3.0

Primary sclerosing cholangitis

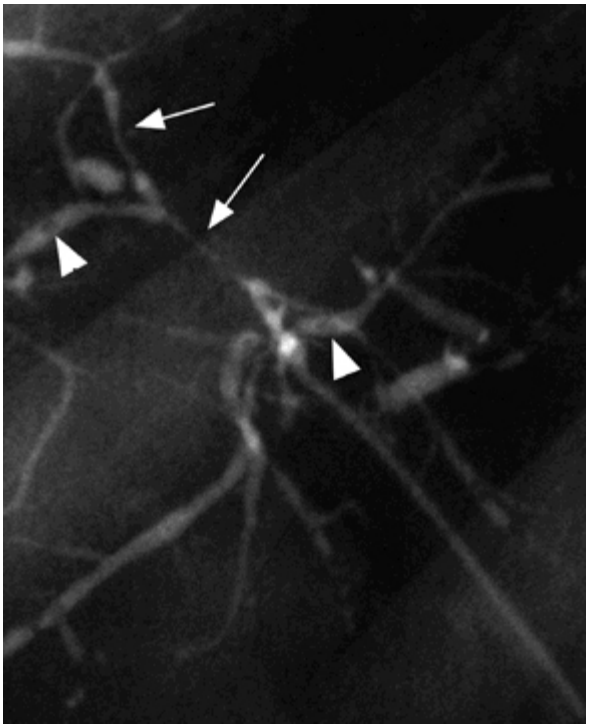
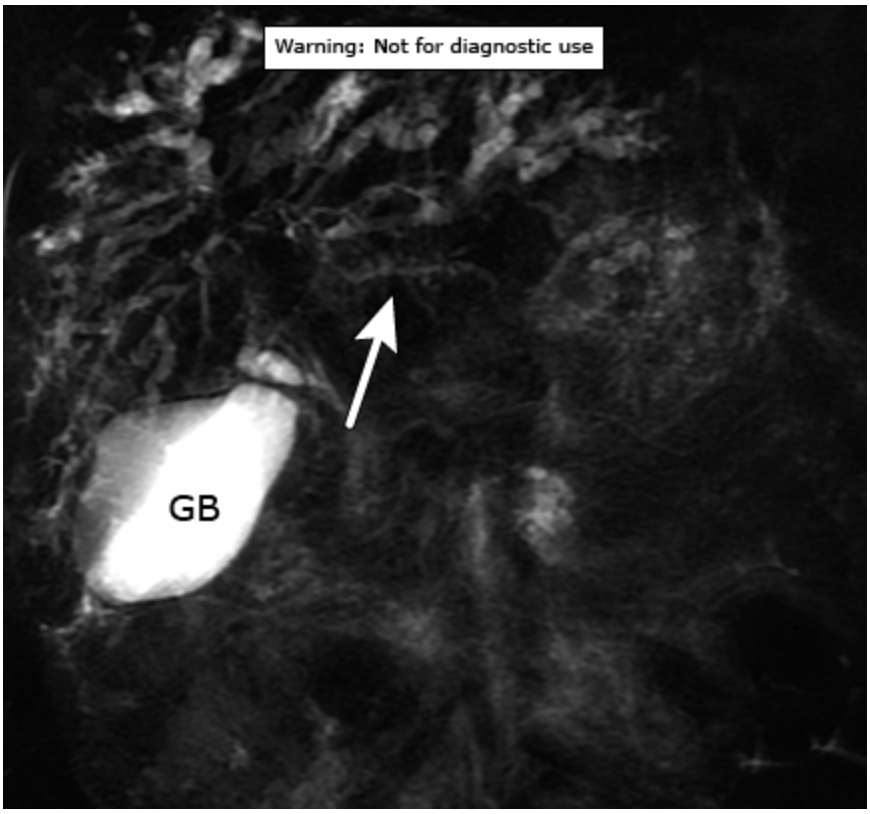


Image obtained during endoscopic retrograde cholangiopancreatography in a patient with primary sclerosing cholangitis demonstrates stenotic intrahepatic bile ducts (arrows) with several intraductal stones (arrowheads).

Courtesy of Jonathan Kruskal, MD.

Graphic 72605 Version 2.0

Magnetic resonance cholangiopancreatography in a patient with primary sclerosing cholangitis



A thick slab coronal magnetic resonance image of the liver in a patient with primary sclerosing cholangitis. The image sequence shows all bile ducts with a bright white signal. Note the beaded duct in the left lobe (arrow) as well as the many dilated intrahepatic ducts.

GB: gallbladder.

Graphic 69476 Version 3.0

Mayo model for predicted survival in primary sclerosing cholangitis

R = 0.03 (age [yrs]) + 0.54$_e$(bilirubin [mg/dL]) + 0.54 log$_e$(AST [IU/L]) + 1.24 (variceal bleeding [0=no/1=yes]) - 0.84 (albumin [g/dL]).]
Survival function coefficient [$S_0(t)$]
1 year = 0.963
2 years = 0.919
3 years = 0.873
4 years = 0.833
Calculated patient survival
Probability of survival at time t years is calculated as $S(t) = S_0(t)^{exp(R-1.00)}$

Adapted from: Kim WR, Therneau TM, Wiesner RH, et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clin Proc 2000; 75:688. Calculator for this model available at: http://www.mayoclinic.org/gi-rst/mayomodel3.html (Accessed on September 11, 2007).

Graphic 54210 Version 2.0

Contributor Disclosures

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