Primary sclerosing cholangitis

Definition: Chronic cholestatic liver disease of unknown cause. It is characterized by ongoing inflammation, destruction, and fibrosis of intrahepatic and extrahepatic bile ducts.

Epidemiology: 70 percent of patients with PSC are men. Mean age of diagnosis is 39. Prevalence: occurs in 1-6 cases per 100,000. It is the fourth leading indication of liver transplantation in the United States although it is 1% as common as alcoholic liver disease. 75% of patients with PSC have inflammatory disease—87% have UC, 13% have Crohn's disease. However, 2.5-7.5 percent of people with UC have PSC.

Pathology (or what I forgot after 2nd year of med school): Fibrous obliteration of small bile ducts. Histology is used for confirmation and determines the stage of disease. Usually the diagnosis is made on cholangiography. There are four histologic stages of PSC. Initially, the portal triads are involved but expand into the hepatic parenchyma as the disease progresses:
I. Initial lesion-degeneration of epithelial cells in the bile ducts. Occasional infiltration of lymphocytes and/or neutrophils. Portal triad inflammation, scarring, and enlargement occur—not seen outside of the portal triad.
II. The lesion is more widespread, inflaming the periportal parenchyma and eventually leads to piecemeal necrosis in the periportal hepatocytes.
III. Bridging fibrosis as bile ducts either disappear or undergo severe degenerative changes. Cholestasis occurs especially in periportal and paraseptal hepatocytes.
IV. Frank cirrhosis occurs with changes of the large ducts. Onion skinning (concentric replacement of small bile ducts with connective fibrous tissue) is rarely seen on percutaneous liver biopsy of the liver.

Pathogenesis: Unknown cause, although it is thought that a number of factors that cause recurring damage to the bile ducts could lead to the development of the disease. Chronic portal bacteremia, toxic bile acid metabolites produced by enteric flora, chronic viral infections, ischemic vascular damage, are just some of these factors, although none have been linked definitively with PSC.

Clinical manifestations: Often, patients are asymptomatic at the time of diagnosis, even with advanced disease. The earliest symptoms are fatigue and pruritus. Ten to 15% of patients can have fevers, chills, night sweats, and right upper quadrant pain at the time of presentation. The episodes of fevers and chills can be accompanied by transient worsening of LFTs, which could be a result of the underlying inflammatory response.

Laboratory tests: Abnormal biochemical tests of liver function, especially alkaline phosphatase and gamma-glutamyltransferase, can be seen and can persist. The serum bilirubin level is usually normal in early stages of PSC, but eventually, it may begin to increase. The serum albumin level may also begin to decrease. Hypergammaglobulinemia is found in 30 percent of patients, especially IgM (in 40-50%). Anti-smooth muscle antibodies are
Copper, which is normally excreted primarily in bile, increases in 11 percent of patients, and ANA in 6 to 35 percent, but antimitochondrial antibodies are almost never seen. As with other chronic cholestatic diseases, hepatic and urinary copper levels are increased. Copper, which is normally excreted primarily in bile, increases as cholestasis worsens.

**Diagnosis:** Disorders causing secondary sclerosing cholangitis must be ruled out, such as chronic bacterial cholangitis, infectious cholangiopathy associated with AIDS, previous biliary surgery, congenital biliary-tree abnormalities, and bile duct neoplasms. Usually these are ruled out with patient histories, blood test results, cholangiographic or ultrasound findings, or path results from bile duct scrapings and biopsies. Visualization of the bile duct is essential for making the diagnosis. ERCP is the method of choice; transhepatic cholangiography is done if ERCP is unsuccessful. Characteristic findings of PSC are multifocal strictures and dilatations usually involving the intrahepatic and extrahepatic biliary tree. Percutaneous liver biopsy is rarely definitive although it is useful for staging and determining the prognosis.

**Prognosis:** The median length of survival from diagnosis is 9 to 12 years in varying studies. Patients who are asymptomatic at diagnosis lived longer than those who were symptomatic. There have been multivariate analysis models to try to predict the progression of PSC. Variables used were age, serum bilirubin and hemoglobin levels, hepatic histologic stage, and the presence of splenomegaly. Ninety percent of those with stage II disease can be expected to progress to stages III and IV, while 50 percent of those with stage III disease can be expected to go on to stage IV. The Mayo model below uses age, serum bilirubin, serum albumin, serum AST, and history of variceal bleeding. This risk score correlates well with observed survival and is useful in determining timing for liver transplantation (see below).

**Mayo Model for Predicted Survival in Primary Sclerosing Cholangitis**

\[
R = 0.03 \text{ (age [yrs])} + 0.54 \log_{10} \text{bilirubin [mg/dL]} + 0.54 \log_{10} \text{AST [IU/L]} + 1.24 \\
\text{(various bleeding [0=mo/1=yes] - 0.64 (albumin [g/dL])}
\]

**Survival function coefficient \([S_0(t)]\)**

- 1 year = 0.963
- 2 years = 0.919
- 3 years = 0.878
- 4 years = 0.833

**Calculated patient survival**

Probability of survival at time \(t\) years is calculated as \(S(t) = S_0(t^{0.824 \text{(R-1.00)}})\)


**Complications:** Common to chronic cholestatic liver diseases like PSC, including fatigue, pruritus, steatorrhea, fat-soluble vitamin deficiencies, and metabolic bone disease.

**Pruritus** can be extremely debilitating (the cause is not clear; it could be due to bile acid accumulation and endogenous opioids). It may be treated with warm baths, antihistamines, and cholestyramine. Some patients respond, at least temporarily, to naloxone, rifampin, or phototherapy. If the pruritus is severe and refractory, liver transplantation may be considered.
Steatorrhea and subsequent vitamin deficiency is probably due to decreased secretion of conjugated bile acids into the small intestine. Vitamin A deficiency is seen in up to 82 percent of patients; one-half of patients can also experience vitamin E and D deficiency. Patients can be screened by serum levels and prothrombin time and treated with supplemental therapy.

Osteoporosis is a complication of advanced PSC, particularly affecting the lumbar spine, iliac crest, and femur. This may result from toxin/toxinics retained due to cholestasis that prevents osteoblasts from working normally and thus can lead to decreased bone formation. Some suspected culprits have been unconjugated bilirubin, copper, and bile salts. No effective therapy has been shown to prevent or manage osteopenia. Calcium supplementation is safe but not proven to be effective.

Dominant biliary strictures in the intra/extrahepatic biliary tree, whose presentation can be confused with that of cholangiocarcinoma. These can be managed successfully by balloon dilatation or stenting. Many patients have improvement in both biochemical tests and symptoms, but restenosis is common (30 to 50%), and patients may require repeated treatments.

Cholangitis and choledolithiasis occur in up to one-third of patients with PSC. Cholangitis risk is greatest after endoscopy and surgical manipulation (which includes liver biopsy). Therefore, prophylactic treatment with ciprofloxacin is indicated before such procedures (alternative meds used are amoxicillin and Bactrim). Gallstones in patients with PSC are not treated unless they obstruct the major bile ducts.

Cholangiocarcinoma. Patients with PSC have a ten to 15 percent lifetime risk of developing this disease. The annual incidence has been estimated to be 1.5 percent. Rapid clinical deterioration with jaundice, weight loss, and abdominal discomfort often herald its development. The risk was increased in one trial by alcohol consumption. Ultrasound or CT-guided biopsy gives the best yield, as serum tumor markers such as CEA and CA may be elevated in those with cholangitis without malignancy. Only ten percent of patients with cholangiocarcinoma survived two years in one study. Patients with cholangiocarcinoma do poorly after liver transplant and thus many centers do not consider them for transplantation outside of study protocols.

Colon cancer is increased in those with PSC and ulcerative colitis. In these patients, surveillance colonoscopy is recommended.

Medical therapies: At this time, no drug has been shown to alter the natural history of this disorder. Penicillamine was considered due to the elevated serum copper levels, but, as the elevated stores seem to be due to cholestasis and not a primary event, the drug has not been shown to be efficacious. Steroids only seem to worsen osteoporosis and also do not change the Mayo risk score significantly. Neither cyclosporine nor methotrexate showed any improvement in much more than a decrease in alkaline phosphatase levels. Azathioprine, used to treat concomitant inflammatory bowel disease, has not been shown to improve the course of the disease. Ursodeoxycholic acid (UDCA), which is a hydrophilic bile acid, does help with some symptom relief but has not delayed the need for liver transplant or survival benefit. High dose UDCA (20-30 mg/kg versus 13-15 mg/kg per day), however, showed an improvement in liver biochemistries and the Mayo risk score, but more studies are underway. Tacrolimus has been shown to improve pruritus and decrease serum bilirubin and alkaline phosphatase levels but did not favorably alter ERCP findings or histology.
Surgical therapies: Biliary reconstitution was once considered but due to the risk of post op infection and scarring in the porta hepatis (which might interfere with later transplantation), it has seen waning enthusiasm. It also has been found to be inferior to liver transplantation in terms of survival. Liver transplantation is the treatment of choice for those with advanced PSC. The five-year survival rate is as high as 85%. Some indications are hemorrhage from esophageal varices or portal gastropathy, intractable ascites, recurrent bacterial cholangitis, and hepatic encephalopathy. The Mayo risk score suggest that transplantation be done when the estimated 6-month survival is less than 80%. The Mayo score is a more accurate predictor of survival than the Child-Pugh score, especially in early stage disease. A place you can check it on the web is http://www.mayo.edu/int-med/gi/model/mayomodl-3.htm.

References: UpToDate Version 10.2 “Primary sclerosing cholangitis.”
Another recommended article, once it gets back from the bindery in Indiana, is Lee, YM, Kaplan, MM. Management of primary sclerosing cholangitis. Am J Gastroenterol 2002; 97: 528.