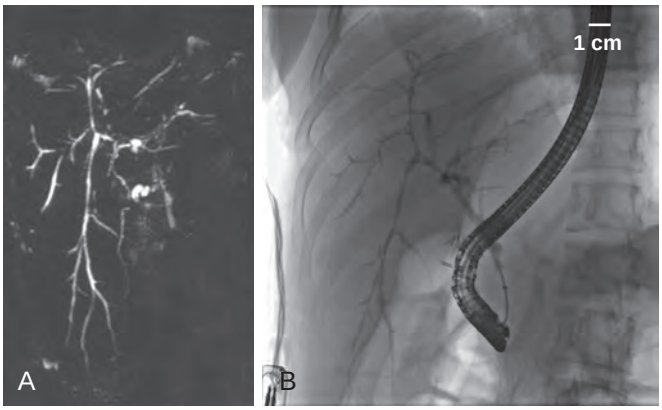

Figure 18-38 Imaging studies of a patient with primary sclerosing cholangitis. **A,** Magnetic resonance cholangiography shows focal dilatation in some bile ducts (bright, broad areas) and stricturing of others (thinning or absence). **B,** Endoscopic retrograde cholangiography of the same patient shows nearly identical features as in **A.** The endoscope is visible, giving a sense of scale. (Courtesy Dr. M. Edwyn Harrison, MD, Mayo Clinic, Scottsdale, Ariz.)

Pathogenesis. Several features of PSC suggest immunologically mediated injury to bile ducts, even though environmental triggers presumably also play a role. First degree relatives of patients with PSC have an increased risk of developing the disease suggesting a genetic component. T cells in the periductal stroma, the presence of circulating autoantibodies, association with HLA-B8 and other MHC antigens, and linkage to ulcerative colitis all support an inherent immunologic process.

It has been proposed that T cells activated in the damaged mucosa of patients with ulcerative colitis migrate to the liver where they recognize a cross-reacting bile duct antigen. Autoantibody profiles in PSC are not as characteristic as they are in PBC, although atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) targeting a nuclear envelope protein are found in approximately 65% of patients; however, the pathogenic relationship of pANCA to PSC is unknown.

MORPHOLOGY

Morphologic changes differ between the large ducts (intrahepatic and extrahepatic) and the smaller intrahepatic ducts. **Large duct inflammation** is similar to that seen in ulcerative colitis: acute, neutrophilic infiltration of the epithelium superimposed on a chronic inflammatory background. Inflamed areas develop strictures because edema and inflammation narrows the lumen or because of subsequent scarring. The **smaller ducts,** however, often have little inflammation and show a striking **circumferential "onion skin" fibrosis** around an increasingly atrophic duct lumen (Fig. 18-39), eventually leading to obliteration by a "tombstone" scar. Because the likelihood of sampling smaller duct lesions on a random needle biopsy is miniscule, diagnosis depends on radiologic imaging of the extrahepatic and larger intrahepatic ducts. As the disease progresses the liver becomes markedly cholestatic, culminating in biliary cirrhosis much like that seen with chronic obstruction and primary biliary cirrhosis. Biliary intraepithelial neoplasia may develop and cholangiocarcinoma appears usually with a fatal outcomes.

Clinical Features. **Asymptomatic patients may come to attention only because of persistent elevation of serum alkaline phosphatase, particularly in patients with ulcerative colitis who are being routinely screened.** Alternatively, progressive fatigue, pruritus, and jaundice may develop. Acute bouts of ascending cholangitis may also signal the development of PSC. The disease follows a protracted course of 5 to 17 years, and the severely afflicted patients have the usual symptoms of chronic cholestatic liver disease including steatorrhea. Approximately 25 % of the patients develop cholelithiasis in the dilated ducts. The annual risk of developing cholangiocarcinoma is 0.6 to 1.5 % with a lifetime risk of 20%.

Chronic pancreatitis and chronic cholecystitis from involvement of pancreatic ducts and gallbladder are also seen. A distinctive type of sclerosing cholangitis, with elevated IgG4 levels in association with autoimmune pancreatitis, has been recognized recently. There is no specific medical therapy for PSC. Cholestyramine has been used for pruritus and endoscopic dilation with sphincterotomy or stenting is used for relieving symptoms. Ursodeoxycholic acid has not yet been shown to be effective. Liver transplantation is the definitive treatment for persons with end-stage liver disease.

KEY CONCEPTS

Cholestatic Diseases

- **Cholestasis** occurs with impaired bile flow, leading to accumulation of bile pigment in the hepatic parenchyma. Causes include mechanical or inflammatory obstruction or destruction of the bile ducts or by metabolic defects in hepatocyte bile secretion.
- **Large bile duct obstruction** is most commonly associated with gallstones and malignancies involving the head of the pancreas. Chronic obstruction can lead to cirrhosis. Ascending cholangitis may develop.
- **Cholestasis in sepsis** may arise through direct effects of intrahepatic bacterial infection, ischemia relating to hypotension caused by sepsis, or in response to circulating microbial products.
- **Primary hepatolithiasis** is a disorder of *intrahepatic* gallstone formation, most common in East Asia, that

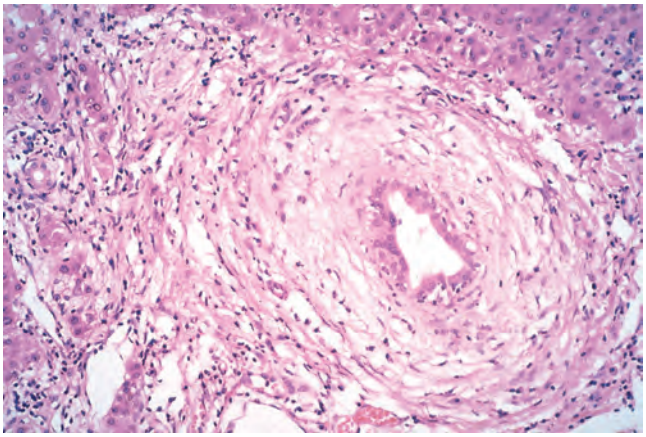

Figure 18-39 Primary sclerosing cholangitis. A degenerating bile duct is entrapped in a dense, "onion-skin" concentric scar.