

Sclerosing Cholangitis: A Focus On Secondary Causes

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Secondary sclerosing cholangitis (SSC) is a disease that is morphologically similar to primary sclerosing cholangitis (PSC) but that originates from a known pathological process. Its clinical and cholangiographic features may mimic PSC, yet its natural history may be more favorable if recognition is prompt and appropriate therapy is introduced. Thus, the diagnosis of PSC requires the exclusion of secondary causes of sclerosing cholangitis and recognition of associated conditions that may potentially imitate its classic cholangiographic features. Well-described causes of SSC include intraductal stone disease, surgical or blunt abdominal trauma, intra-arterial chemotherapy, and recurrent pancreatitis. However, a wide variety of other associations have been reported recently, including autoimmune pancreatitis, portal biliopathy, eosinophilic and/or mast cell cholangitis, hepatic inflammatory pseudotumor, recurrent pyogenic cholangitis, primary immune deficiency, and AIDS-related cholangiopathy. This article offers a comprehensive review of SSC. (HEPATOLOGY 2006; 44:1063-1074.)

Sclerosing cholangitis (SC) represents a spectrum of chronic, variably progressive cholestatic diseases of the intrahepatic and/or extrahepatic biliary system characterized by patchy inflammation, fibrosis, and stricture. The hallmarks of its natural history are progressive involvement of the bile ducts complicated by cholangiocarcinoma even in early disease and the often insidious onset of portal hypertension, cirrhosis, and subsequent hepatic failure.¹ It is an indication for liver transplantation worldwide.² Primary sclerosing cholangitis (PSC), the most common form, is an idiopathic entity that can occur independently or in association with other conditions. The diagnosis of PSC has evolved in recent years to a comprehensive characterization that is based on clinical, biochemical, histological, and, most importantly, radiological features. The classical findings on cholangiography—such as multifocal strictures, segmental dilatation, diverticulum-like outpouchings, and irregular beading of

large and/or peripheral smaller bile ducts—may also be seen in association with a broad array of local and systemic diseases. Diagnosis requires the exclusion of secondary causes of sclerosing cholangitis and an appreciation for those conditions that may potentially mimic its classic cholangiographic features. These entities should not be missed, because they may respond favorably—at times dramatically—to the institution of early medical and/or interventional therapy. The causes of secondary sclerosing cholangitis (SSC) and its reported “associations” are outlined in Table 1.

Studies comparing patients with SSC and PSC are limited. A recent retrospective review from the Mayo Clinic³ over a 10-year period (1992-2002) identified 31 patients with SSC. Documented etiologies in their series included surgical trauma from cholecystectomy, intraductal stones, recurrent pancreatitis, and abdominal injury. Nine of their patients with SSC ultimately required liver transplantation, and 4 died. In this series, when compared with matched controls with PSC, transplant-free survival was significantly shorter. Because the literature on SSC is widely scattered, a focused review is timely.

Pathogenesis of SSC: Insight Into the Mechanisms of PSC

The pathogenesis of PSC remains unknown. Insight into the possible mechanisms could be achieved by examining the pathogenesis of SSC. In SSC, the pathogenesis is linked to a known cause. The heterogeneity of conditions that lead to biliary tract changes no different than those seen in PSC suggests that widely different insults may give rise to a similar pattern of biliary disease.

Abbreviations: SSC, secondary sclerosing cholangitis; PSC, primary sclerosing cholangitis; SC, sclerosing cholangitis; IgG4, immunoglobulin G4; AIP, autoimmune pancreatitis; MR, magnetic resonance; ERCP, endoscopic retrograde cholangiopancreatography; IPT, inflammatory pseudotumor; RPC, recurrent pyogenic cholangitis.

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Table 1. Sclerosing Cholangitis: Reported Disease Associations

Idiopathic	Secondary etiology Cholelithiasis/Cholelithiasis
Inflammatory bowel disease	
Crohn's disease	Infection
Ulcerative colitis	Bacterial cholangitis Recurrent pyogenic cholangitis
Idiopathic fibrosis	
Retroperitoneal fibrosis	Immunodeficiency-related
Mediastinal fibrosis	Congenital immunodeficiency
Peyronie's disease	Acquired immunodeficiency
Idiopathic lobular panniculitis	Combined immunodeficiency
	Angioimmunoblastic lymphadenopathy
Reidel's thyroiditis	
Pseudotumour of the orbit	
Autoimmune & connective tissue disorders	Congenital
Systemic lupus erythematosus	Caroli's disease
Rheumatoid arthritis	Cystic fibrosis
Systemic sclerosis	
Sjögren's syndrome	Pancreatic disorder
Celiac disease	Autoimmune pancreatitis
Type 1 diabetes mellitus	Chronic pancreatitis
Autoimmune hemolytic anemia	
Immune thrombocytopenic purpura	Toxic
	Intraductal formaldehyde or hypertonic saline
Lupus nephritis	Intra-arterial chemotherapy
Membranous nephropathy	
Rapidly progressive glomerulonephritis	Ischemic
Chronic sclerosing sialadenitis	Vascular trauma
	Hepatic allograft arterial occlusion
Primary biliary cirrhosis	Paroxysmal nocturnal hemoglobinuria
	Posttraumatic sclerosing cholangitis
Allimmune disorders	Others
Hepatic allograft rejection	Hepatic inflammatory pseudotumor
Graft-versus-host disease	Neoplastic/Metastatic disease
Infiltrative disorders	Eosinophilic cholangitis
Amyloidosis	Portal biliopathy
Sarcoidosis	Langerhans cell histiocytosis
Systemic mastocytosis	
Hypereosinophilic syndrome	
Hodgkin's disease	
Cholangitis glandularis proliferans	

The association of PSC with autoimmune diseases suggests a role for specific autoantigens and effector mechanisms leading to fibrosis causing an obliterative cholangitis.⁴ In autoimmune pancreatitis and hepatic inflammatory pseudotumor, the presence of hypergammaglobulinemia, high immunoglobulin G4 (IgG4) serum levels, and dense lymphoplasmacytic periductal infiltration indicates an immunomediated disease process in the causation of SC. The dramatic response to treatment with corticosteroids seen in this condition confirms this hy-

pothesis.^{5,6} The multiplicity of associations with other autoimmune disorders, including scleroderma,⁷ polyarteritis nodosa,⁸ giant cell arteritis,⁸ and connective tissue disorders also supports an autoimmune basis for SC.

There are several situations in which it appears that a bacterial infection (either opportunistic or classical) may contribute to the pathogenesis of biliary tract sclerosis. Bacterial or viral infections of the biliary tree have also been implicated as causes of PSC; however, there is no direct evidence to support this. The intimate connection between PSC and inflammatory bowel disease (IBD) has led to speculations of a complex interplay between adaptive and innate immune responses that result in sustained tissue-specific inflammatory infiltrates and production of injurious proinflammatory cytokines such as tumor necrosis factor α .⁹ In a mouse knockout model of SSC from *Cryptosporidium parvum* chronic infection, production of tumor necrosis factor α and signaling through tumor necrosis factor receptors was required for the development of cholangitis.¹⁰ Pathogenesis of duct injury may be related to activation of the innate immune response mediated through special pattern recognition receptors that detect conserved microbial structures known as *pathogen-associated molecular patterns*.¹¹ Toll-like receptors are examples of such recognition tools that help discriminate between self and nonself antigens and are believed to play a role in the pathogenesis of PSC.¹² Toll-like receptor stimulation via microbial products activates the innate immune response, which is mediated by activated macrophages, dendritic cells, natural killer cells, and natural killer T cells. The subsequent peribiliary recruitment of gut-primed T cells may mediate further bile duct injury.¹¹ An overlapping expression of various identified endothelial adhesion molecules and tissue-specific chemokines between the liver and the gut further support this theory.^{13,14} The recent observation of SSC in severely septic patients in the intensive care unit, as well as in individuals with primary or acquired immunodeficiency states, also suggests that bacterial infection of the biliary tree in a susceptible host may cause biliary strictures and beading as seen in PSC.¹⁵ Systematic attempts to culture culprit pathogens in cohorts of patients with fully established PSC—often from explanted livers—have failed, but perhaps end-stage disease is the wrong place to look.¹⁶

The immunomediated/infectious theory does not exclude the effect of primary or superimposed ischemic injury in the pathogenesis of SC. This has been best exemplified by animal models in which direct injury of hepatic arteries or peribiliary capillary plexi produces ischemic secondary sclerosing cholangitis.⁸ In humans, post-transplantation hepatic artery thrombosis gives rise to biliary tree findings typical of PSC.¹⁷ Focal strictures as-

sociated with intra-arterial infusion of floxuridine,¹⁸ polyarteritis nodosa of the branches of the hepatic artery,⁸ or paroxysmal nocturnal hemoglobinuria¹⁹ further support an ischemic etiology of duct injury. Thus, it may be that immune-based vascular endothelitis is a plausible cause of PSC, although several studies have documented intact hepatic arteries, arterioles, and capillary plexi.²⁰ A theory of microcirculatory ischemia secondary to aberrant responses of the renin-angiotensin system within intrahepatic portal vessels is another possible mechanism.¹¹

The recently described *mdr2* knockout model²¹ of PSC and the *NOD.c3c4* congenic mouse model of primary biliary cirrhosis²² suggest a different pathogenesis of SC. The *mdr2* knockout mouse, which lacks expression of the specific phospholipid translocator on the canalicular membrane, develops SC with both macroscopic and microscopic features similar to human PSC.²¹ The model for primary biliary cirrhosis, the *NOD.c3c4* congenic mouse, also exhibits changes in large and small bile ducts.²² Evidence of normal bile acid transporter haplotypes for MDR3 and various other biliary transporters in PSC argues against this susceptibility association.²³ In addition, biliary epithelial cells exhibit a high endogenous expression of cystic fibrosis transmembrane conductance regulator²⁴ and thus become a target of injury in children with cystic fibrosis. However, reports of cystic fibrosis transmembrane conductance regulator gene mutations in PSC are discordant.^{24,25}

Causes of SSC

Autoimmune Pancreatitis. In 1961, Sarles et al.²⁶ introduced the notion of an immune pathogenesis in chronic pancreatitis and reported a case of pancreatitis with hypergammaglobulinemia. Autoimmune pancreatitis (AIP) as a distinct primary pancreatic disorder was first proposed much later by Yoshida et al.²⁷ Since then, many case reports have been published in Eastern Asia under different nomenclatures.^{28,29} The pathogenesis of AIP is uncertain, and no gold standard exists for its diagnosis. It is more common in middle-aged men (average reported age, 59–61 years³⁰), an age at which pancreatic carcinoma occurs.³¹ Whether AIP is a primary pancreatic disorder or part of a systemic autoimmune disease with more extensive organ involvement is not fully understood. Immunohistochemical studies demonstrating that IgG4-plasma cells, which are markers of AIP, are found in various other organs (*e.g.*, bile duct, gallbladder, gastric mucosa, colon, salivary glands, ureters, kidneys, lymph nodes, and bone marrow)^{32,33} support the latter concept.

The clinical manifestations of AIP at presentation vary. They may include symptoms related to acute or chronic

pancreatitis,²⁸ biliary or pancreatic strictures,³⁴ and/or pancreatic lesions.^{35,36} Obstructive jaundice was observed in 40% of patients in one series.³⁰ Symptoms related to other autoimmune manifestations may also be present. An obstructive pattern of liver enzyme abnormalities, hypergammaglobulinemia, and an elevated serum IgG4 level are the hallmarks of the biochemical changes seen in AIP.^{36,37} Using a cutoff of 135 mg/dL, the sensitivity and specificity of serum IgG4 for distinguishing AIP from pancreatic cancer were 95% and 97%, respectively.³⁷ Histologically, AIP is characterized by diffuse lymphoplasmacytic infiltration with marked interstitial fibrosis, acinar atrophy, and obliterative phlebitis within the pancreas.³⁸

The typical magnetic resonance (MR) characteristics of AIP include focal or diffuse enlargement of the pancreas (mass-forming type), absence of parenchymal atrophy or dilation proximal to the site of stenosis, absence of peripancreatic spread, clear demarcation of the culprit lesion and the presence of a peripancreatic rim.³⁹ In addition, diffuse pancreatic hypointensity on T1-weighted MR images and delayed enhancement on dynamic CT and MR studies are other features of this disorder.⁴⁰ A diffusely hypoechoic, enlarged pancreas on endoscopic sonography, together with chronic inflammatory cells in cytological specimens from fine needle aspirates, was also supportive of the diagnosis in a small study of 14 patients.⁴¹ The predominant feature on endoscopic retrograde cholangiopancreatography (ERCP) may be that of a diffusely or segmentally irregular and narrow main pancreatic duct (*i.e.*, the duct-stenotic type). In addition, strictures of the distal bile ducts are evident in nearly all cases.⁴² All investigators have demonstrated significant improvement of both the pancreatic and biliary lesions with orally administered corticosteroids, a phenomenon not observed in patients with PSC or pancreatic malignancies.

Hepatic Inflammatory Pseudotumor. Inflammatory pseudotumor (IPT) is a relatively rare and benign lesion characterized histologically by a heterogeneous population of inflammatory cells—particularly plasma cells, eosinophils, macrophages, and fibroblasts—as well as areas of fibrosis and/or necrosis.⁴³ The first description of IPT of the liver was made by Pack and Baker⁴⁴ in 1953. There are neither specific signs on imaging, nor conclusive diagnostic biochemical tests. The etiology of IPT remains obscure to date. Some associations with phlebitis⁴⁵ and Crohn's disease⁴⁶ have been made. In addition, there are several case reports of hepatic IPT associated with SC, in which SC is considered either as the condition preceding or associated with hepatic IPT.^{47–49} The histological findings are quite similar to AIP and feature many IgG4-

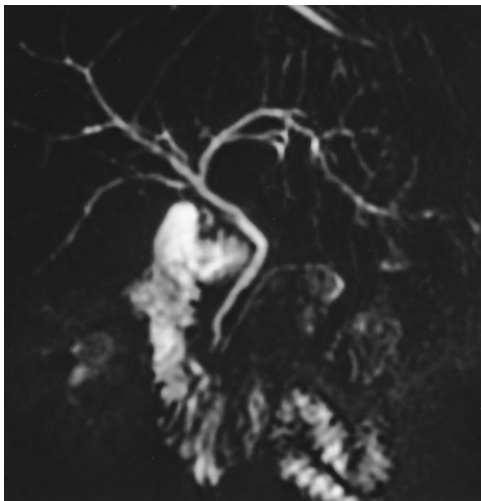


Fig. 1. Eosinophilic cholangitis in a 42-year-old woman with jaundice and eosinophilia. Coronal MR cholangiopancreatography image shows subtle intrahepatic ductal irregularity. Note the peripheral ducts intersecting at right angles, which suggest an inflammatory process. (Copyright Vitellas et al. *Radiographics* 2000;20:959-975.)

positive plasma cells, thereby suggesting a shared pathogenic mechanism.⁵⁰

To date, several treatment approaches, including antibiotics,⁵¹ nonsteroidal anti-inflammatory drugs,⁵² and corticosteroids,⁴³ have been prescribed for hepatic IPT. Spontaneous resolution after a few months may also occur.⁵³ The prognosis is considered favorable in most cases. A few reports of surgical resection and liver transplantation have been described.^{54,55}

Eosinophilic Cholangitis. Eosinophilic infiltrates of the portal triads with or without peripheral eosinophilia is usually suggestive of a parasitic, fungal, or drug-induced disease. However, similar infiltrates may also be found in association with primary biliary cirrhosis,⁵⁶ hepatic allograft rejection,⁵⁷ autoimmune cholangitis, and PSC.⁵⁸⁻⁶¹ In 1985, Butler et al.⁵⁸ reported a case of obstructive jaundice, lymphadenopathy, and peripheral eosinophilia in which marked eosinophilic infiltration of the gallbladder, cystic duct, and liver was observed. Rosengart et al. reported a case of eosinophilic cholecystitis with radiologically documented biliary tract obstruction.⁵⁹ The dense eosinophilic infiltration of the porta hepatis introduced the notion of eosinophilic cholangitis (Fig. 1). Watanabe et al.⁶² described a 16-year-old boy who, at the age of 5 years, had been found to have massive eosinophilic infiltration in the liver that, on follow-up 11 years later, had disappeared, leaving extensive portal fibrosis with a cholangiographic pattern compatible with PSC. Hartleb et al.⁶³ reported a case of a 24-year-old man whose liver biopsy revealed a portal infiltrate comprised almost exclusively of eosinophils; parasitic causes were ruled out, and

cholangiography performed 2 months later demonstrated classical features of PSC. Eosinophilic colitis and SC in a 17-year-old female with atypical celiac disease has also been reported.⁶⁴ Most patients respond rapidly to corticosteroids.

The diagnostic significance of eosinophilic infiltrates in SC is not yet clear. Activated eosinophils may contribute to the process of hepatocyte and/or cholangiocyte injury mediated perhaps through host defense mechanisms targeted at an unidentified pathogen. It is unknown whether eosinophil infiltration is an initial step in the pathogenesis of SC or whether it constitutes a subtype of the disease in the context of hypereosinophilic syndrome. Longitudinal studies among patients with SC may help answer this question.

Mast Cell Cholangiopathy. The link between mast cells and cholangiopathy stems from the finding of heavy mast cell infiltrates in patients with SSC from gallstones.⁶⁵ The role of mast cells in fibrogenesis, epithelial cell proliferation, metaplasia, and inflammatory cell recruitment has been well characterized in other diseases.⁶⁶ Mast cells mediate collagen synthesis and promote organization of connective tissue elements by producing and secreting bioactive mediators that lead to fibrosis.⁶⁷ Mast cells are present in the human liver, and their distribution in normal and diseased states has been investigated by Farrell et al.,⁶⁸ who studied the hepatic distribution of these cells in normal subjects and in 2 subjects with chronic progressive liver disorders (primary biliary cirrhosis and alcoholic liver disease). Recently, mast cells were implicated in the progression of hepatic fibrosis in patients with PSC.⁶⁹

Only one case report of mast cell cholangiopathy causing SC exists in the literature.⁷⁰ In this case, a 75-year-old woman with known systemic mastocytosis presented with abdominal pain, ascites, and bile duct thickening on CT and sonography. A liver biopsy showed heavy infiltration with mast cells. ERCP revealed ductal changes classical for PSC. Brush cytology of the intrahepatic bile ducts confirmed extensive mast cell infiltration. It was proposed that systemic mastocytosis had infiltrated the biliary tree, producing a cholangiopathy radiographically similar to PSC.

Portal Biliopathy. Bile duct and gallbladder wall anomalies seen in patients with portal hypertension are collectively referred to as *portal biliopathy*.^{71,72} Meredith et al.⁷³ and others^{74,75} have reported several cases of common bile duct obstruction caused by extrinsic compression of the ducts from large venous collaterals at the porta hepatis. Such changes have mostly been observed in patients with extrahepatic portal vein obstruction, although it has been reported in patients with cirrhosis, portal fibrosis without cirrhosis, and congenital hepatic fibrosis.⁷¹



Fig. 2. Portal biliopathy in a 41-year-old man with extrahepatic portal vein obstruction. Coronal MR cholangiopancreatography image shows stricture of the distal common bile and common hepatic ducts, as well as mild intrahepatic duct irregularities.

Following thrombosis of the portal vein, extensive collaterals develop in an attempt to bypass the obstruction. *Cavernous transformation* of the portal vein is a term that is used often.⁷³ Mechanical protrusion of the paracholedochal veins (venous plexus of Petren) in the lumen of the bile duct and a secondary ischemic vascular bile duct injury is believed to lead to the development of significant strictures.

The predominant symptoms of portal biliopathy are related to partial or complete bile duct obstruction, thus patients are more likely to be symptomatic at diagnosis.^{76,77} Choledocholithiasis is observed in 17% of patients,⁷³ and cholangitis seems to be a late manifestation. Symptomatic patients are usually adults, indicating that portal biliopathy is a slowly progressive disease, because most are thought to have acquired their portal vein thrombosis in early childhood. Liver histology is usually normal, at times revealing nonspecific portal inflammation and, occasionally, bile duct lesions similar to those of PSC. Transabdominal sonography is very helpful in the diagnosis of portal cavernoma and in the detection of venous collaterals.^{78,79} Endoscopic sonography with Doppler flow was essential for documentation of the dilated venous collateral vessels in one case in which noninvasive imaging modalities had failed.⁸⁰ Findings included serpiginous anechoic vascular channels within or surrounding the extrahepatic bile ducts.

Cholangiographic studies are essential for the diagnosis and establishment of the full spectrum of changes seen with portal biliopathy. Most abnormalities are noted in the common bile duct and include wall irregularities, localized saccular dilatation, and filling defects that may be interpreted as common bile duct calculi^{73,76,77} (Fig. 2). In patients with associated cirrhosis and portal fibrosis with-

out cirrhosis, pruning of the intrahepatic biliary radicles can be seen. Chandra et al.⁸¹ have proposed a classification scheme of portal biliopathy based on the location and extent of cholangiographic abnormalities. ERCP has been the method of imaging and diagnosis in published reports to date. However, the one study of MR cholangiography combined with MR portography in patients with portal cavernoma revealed stenosis of the common bile duct and/or hepatic ducts from a mass effect of the cavernoma in 21 of 25 patients.⁸²

Therapeutic strategies for the management of portal biliopathy have to date been targeted only for symptomatic patients who have developed choledocholithiasis and obstructive jaundice. Stones can be extracted by the use of endoscopic sphincterotomy,^{83,84} but this usually simple procedure can be risky in the presence of extensive venous collaterals juxtaposed to the ampulla. Obstructive jaundice can arise from a dominant stricture or other anatomic bile duct defects in the absence of common bile duct stones but not due to varices alone. Biliary balloon dilatation—preferably without stenting of the strictured segment—has been recommended.⁸¹ If endoscopic therapy fails or is considered to be too risky, a distal portosystemic shunt has been shown to induce partial or complete regression of bile duct abnormalities.^{85–88} Smooth strictures and areas of proximal dilations and/or caliber irregularities may disappear after shunt surgery, whereas angulations and ectasias of biliary ducts tend to be irreversible.⁸⁸ If obstruction persists, a hepatico-jejunostomy may be indicated.⁸⁷ Liver transplantation has been reported to be successful in one published case.⁸⁹

AIDS Cholangiopathy. A cholangiopathy in association with AIDS that mimics PSC was first described in 1986⁹⁰ and remains problematic in the developing world. However, with the advent of antiretroviral therapy, this condition has become quite rare.⁹¹ The current incidence is not known but remains significant in areas where access to antiretroviral therapy is limited. Several pathogens have been isolated from endoscopic biliary biopsy specimens, including cytomegalovirus, *Cryptosporidium parvum*, *Microsporidium*, *Cyclospora cayetanensis*, and *Mycobacterium avium complex*.^{91,92} The large intrahepatic ducts are most frequently involved.⁹³

Patients typically present in the advanced stages of the HIV spectrum, particularly when their CD4 counts are below 135/mm³.⁹⁴ The majority of patients present with epigastric and/or right upper quadrant abdominal pain. More severe pain may be caused by papillary stenosis⁹⁵ Almost all patients exhibit an elevated ALP generally five to seven times above normal limits⁹² However, up to 20% of patients have normal serum biochemistry despite documented cholangiographic abnormalities⁹⁶ (Fig. 3). Four

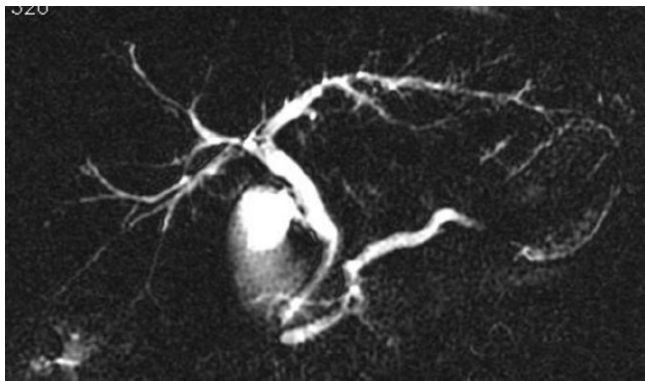


Fig. 3. AIDS-related cholangiopathy in a 59-year-old HIV-positive man with cholestasis. Coronal MR cholangiopancreatography image demonstrates dilatation of the pancreatic duct and its side branches down to the ampulla. There is also dilation of the common bile duct measuring up to 9 mm, with an abrupt cutoff more distally.

distinct changes on ERCP have been described⁹⁵: SC and papillary stenosis (50%), papillary stenosis alone (15%), intrahepatic SC alone (20%), and long extrahepatic bile duct strictures with or without intrahepatic disease (15%). The combined occurrence of intrahepatic duct disease with papillary stenosis appears relatively unique to AIDS cholangiopathy and has not been reported in PSC.

For overt symptomatic disease, endoscopic sphincterotomy can provide prompt and lasting pain relief if papillary stenosis is the cause,⁹⁷ but liver enzyme abnormalities tend to persist despite this intervention.⁹⁵ Isolated or dominant common bile duct strictures can be treated with endoscopic stenting as a last resort. On the whole, treatment options are limited. Targeted treatment against *C. parvum*, *Microsporidium*, or cytomegalovirus does not alter cholangiographic abnormalities, nor does it improve symptoms.^{96,98} For abdominal pain refractory to endoscopic therapy, a CT-guided celiac plexus block may be effective.⁹⁹ Treatment with ursodeoxycholic acid is associated with improved liver biochemistry, and a small percentage of patients experience symptomatic relief.¹⁰⁰

The overall prognosis of patients with AIDS cholangiopathy is poor, because the disease itself is believed to be a manifestation of advanced HIV. The survival of patients is not affected by endoscopic therapy.⁹⁵ One-year and 2-year survival rates were as low as 14%-41% and 8%, respectively, with a mean reported survival of 7-12 months.^{92,95} An association with cholangiocarcinoma has also been reported.¹⁰¹

It is worthwhile to note that *C. parvum* has been implicated in the development of SC in other immunocompromised patients,¹⁰²⁻¹⁰⁴ particularly those with X-linked hyper-IgM syndrome.¹⁰³ The most common diagnosis in a screen of hepatobiliary disease in 35 children with various primary immunodeficiency syndromes was SC.¹⁰⁴

Recurrent Pyogenic Cholangitis. Recurrent pyogenic cholangitis (RPC), previously called "oriental" cholangiohepatitis, is a disease characterized by recurrent episodes of bacterial cholangitis that occur in association with biliary obstruction from strictures and pigmented stones.¹⁰⁵ Digby¹⁰⁶ first described this condition in the Chinese in 1930. RPC seems to be endemic to Southeast Asia.¹⁰⁷ Its worldwide prevalence is largely undetermined, however, because there is a paucity of disease statistics in most regions where RPC is prevalent. It peaks in the third and fifth decades of life, occurs equally in both sexes, and seems more prevalent in rural and low socioeconomic classes.¹⁰⁸

The mechanisms underlying the initiation of biliary sepsis are unknown. *Ascaris lumbricoides*, *Clonorchis sinensis*, *Opisthorchis viverrini*, *Opisthorchis felinus*, and *Fasciola hepatica* are pathogens that lead to the initial epithelial damage.^{105,109,110} Chronic recurrent infection promotes the formation of pigment biliary stones and/or inflammatory strictures. Recurrent biliary obstruction causes biliary stasis and suppurative cholangitis. Patients may present with an acute attack of cholangitis (44%), abdominal pain (32%), and pancreatitis (17%).¹¹¹ Related complications include gram-negative sepsis and shock,¹¹¹ rupture of an infected duct into the peritoneum,¹¹² portal vein thrombosis,¹¹² acute or chronic pancreatitis,¹¹³ secondary biliary cirrhosis, and cholangiocarcinoma.

As initial screening, ultrasound may identify ductal stones, duct dilatation, or a hepatic abscess in up to 90% of cases.¹¹⁴ A contrast-enhanced CT scan may show dilated central intrahepatic ducts with acute tapering of the more peripheral ducts¹¹⁵ (Fig. 4). MRI may help identify



Fig. 4. Recurrent pyogenic cholangitis in a 27-year-old Vietnamese immigrant admitted with cholestasis and septic shock. Coronal ERCP image reveals dilatation of the intrahepatic ducts, intrahepatic "bile lakes," decreased branching pattern, and abrupt tapering of distal ducts.

noncalcific stones.¹¹⁶ Both ERCP and percutaneous cholangiography carry a significant risk of precipitating cholangitis in patients who are not yet septic. A variety of diagnostic abnormalities that mimic PSC can be seen.¹¹⁷ Some cholangiographic features of RPC do allow differentiation from PSC. The finding of a more generalized pattern of ductal narrowing and multifocal strictures favor a diagnosis of PSC. Diffuse extrahepatic ductal strictures are a rare occurrence in RPC.¹⁰⁵ However, multiple ductal stones are more likely associated with RPC.

Medical management entails adequate supportive care and prompt use of broad-spectrum antimicrobials. Conservative management fails in approximately 15% of patients.¹¹⁸ Surgery is indicated when symptoms persist and/or peritonitis develops, stone disease predominates, or overwhelming sepsis leads to multiorgan failure despite optimal medical care. Drainage is usually essential, and this may require common bile duct exploration with T tube placement and/or cholecystectomy. Intraoperative lithotripsy may aid in the surgical clearance of stones.¹¹⁸ Endoscopic stenting and/or stone extraction or percutaneous decompression may be offered to some.^{118,119} Long-term drainage is often needed, particularly in patients with extensive intrahepatic disease. A Roux-en-Y hepatico-jejunostomy is usually favored.¹²⁰ In patients with recurrent disease, a Hudson loop allowing access to the biliary system via an abdominal stoma may be created.

It has been observed that liver abscesses alone may extend to the biliary tree and produce irregularities in the intrahepatic duct walls.¹²¹ Patients in the intensive care unit are at particular risk for this condition. On cholangiography, a characteristic pattern of saccular and more peripheral duct dilatations may help distinguish multiple liver abscesses from PSC. Steinhart et al.¹²¹ reported a case of a 59-year-old man with multiple hepatic abscesses following a bout of diverticulitis whose percutaneous transhepatic cholangiography showed subsequently reversible radiographic changes reminiscent of SC. Multiple intrahepatic duct strictures on ERCP and MR cholangiography were reported in 3 patients with gram-positive infections and persistent cholestasis.¹²² SSC following *Escherichia coli* 0157:H7 in a 2-year-old boy with hemolytic uremic syndrome has also been reported.¹²³ Disseminated *Mycobacterium genavense* infection as a cause of pseudo-Whipple's disease, and SC exists in the German literature.¹²⁴ Systemic fungal infections may infiltrate the biliary tree and produce a PSC-like picture as well.¹²⁵

Ischemic Cholangitis. Unlike hepatic parenchyma, which depends on a dual blood supply from the hepatic artery and portal vein, the biliary system depends only on its arterial supply for viability. Ischemia-induced bile duct lesions have been collectively labeled as *ischemic cholangi-*



Fig. 5. Ischemic cholangitis in a 38-year-old man who developed jaundice 5 days after liver transplantation for PSC. Coronal MR cholangiopancreatography image shows random strictures throughout the biliary tree with minimal multifocal intrahepatic ductal dilatation. Doppler sonography showed a tardus-parvus waveform suggestive of proximal arterial stenosis (not shown), and a previous hepatic arteriogram showed high-grade stenosis of the hepatic artery (not shown). (Copyright Vitellas et al. Radiographics 2000;20:959-975.)

tis.⁸ Injury to the biliary epithelium occurs when the arterial supply is compromised either at the level of the main hepatic branches or at the peribiliary capillary plexus. Histologically, large ducts will demonstrate atrophy and erosion, and smaller interlobular ducts may show epithelial atrophy causing ductopenia. The affected arteries may show thrombotic occlusion, vasculitic changes, or foam cell arteriopathy as in chronic allograft rejection.¹²⁶ The clinical and radiological manifestations reflect cholestasis. Cholangiographic findings resemble those of PSC.¹²⁷ Ischemic cholangitis has been mostly described in the transplantation literature.¹²⁷⁻¹²⁹ Nonanastomotic strictures of ischemic origin in patients with hepatic allografts occur in 2%-19% of liver transplant recipients.¹²⁸ The classic cholangiographic appearance is that of multiple, segmental nonanastomotic strictures and dilatations⁸ (Fig. 5).

SSC following trauma (also termed *posttraumatic SC*) is a rare but probably underdiagnosed complication of severe trauma.^{15,130,131} It, too, is likely mediated through ischemic injury to the bile ducts. Several previous reports have illustrated how marked cholestasis may occur with severe trauma. Hypoxia, mass transfusions, inflammation and drugs were deemed the likely culprits.^{132,133} Unfortunately, cholangiographic studies were not performed in most of these earlier reports, because nearly all were published in the pre-ERCP era. Benninger et al.¹⁵ recently reported 5 patients with persistent jaundice following severe life-threatening trauma (1 burn injury, 3 accidents, and 1 power current injury). All patients required long-term treatment in intensive care. Other causes of liver

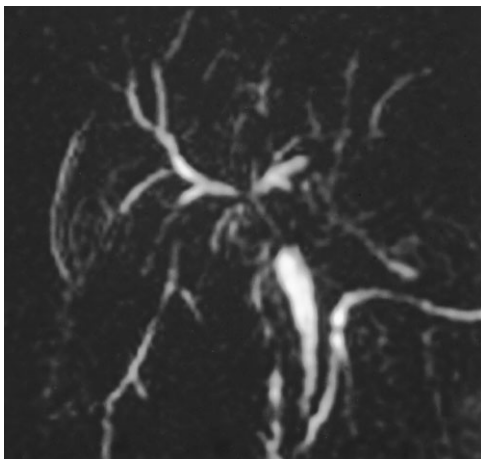


Fig. 6. Floxuridine-induced cholangitis in a 64-year-old woman with jaundice who was treated with intra-arterial floxuridine for metastatic colon cancer. Coronal MR cholangiopancreatography image shows common hepatic duct and hilar strictures with proximal ductal dilatation. (Copyright Vitellas et al. Radiographics 2000;20:959-975.)

disease were excluded. Diagnostic ERCP revealed a PSC-like pattern of beading of intrahepatic ducts in all patients. Hemodynamic instability, and systemic arterial hypotension (<70 mm Hg) occurred in 4 of the described cases, suggesting an ischemic etiology.

Hepatic artery infusion of chemotherapeutic agents has been implicated as a cause of ischemic cholangitis. The fluorinated antimetabolite floxuridine, employed in the palliative treatment of metastatic adenocarcinoma, is the best-studied agent¹³⁴ (Fig. 6). SC has been reported in as much as 56% of patients treated as such.¹⁸ Drug-induced intravascular thrombosis and toxic vasculitis have been implicated as possible mechanisms.¹³⁴ Additional cases of SC after intrahepatic instillation of 5-fluorouracil,¹³⁵ mitomycin C,¹³⁶ cis-diamminedichloroplatinum,¹³⁶ and formaldehyde (for the treatment of hydatid cyst)¹³⁷ have been reported.

Ischemic injury can also occur after trauma to the vascular supply during biliary surgery or blunt abdominal injury.¹³⁸ The few cases of SC described in children with sickle cell disease is likely attributable to an ischemic etiology.¹³⁹ Batts⁸ reported a few cases of presumed ischemic cholangitis related to vasculitis in patients with polyarteritis nodosa and giant cell arteritis occurring after self-cessation of oral corticosteroid therapy. A single case report of sclerosis of the biliary system in a patient with scleroderma has been described as well.⁷

Other Conditions. Additional entities should be included in the differential diagnosis of PSC. Cholangitis glandularis proliferans, also termed *proliferative cholangitis*, is a rare disorder that presents with jaundice.^{140,141} It predominantly occurs in females and lacks an association

with IBD. Its histology is characterized by florid intramural proliferation of glandular elements in association with dense inflammation. Lesions are typically confined to the extrahepatic biliary tree, which facilitates surgical intervention. The disease itself is nonprogressive. Infiltrative processes such as histiocytosis X,¹⁴² sarcoidosis,¹⁴³ chronic sialadenitis,¹⁴⁴ amyloidosis,¹⁴⁵ and metastatic liver disease¹⁴⁶ can also mimic the histological and/or cholangiographic findings of PSC. Diffuse biliary strictures can also occur in congenital biliary anomalies and cystic fibrosis.¹⁴⁷ Extrinsic biliary compression from primary biliary cirrhosis nodules¹⁴⁸ or extensive hepatic cysts in polycystic kidney disease has been reported (Fig. 7). A late complication of SC is the development of intraductal calcium bilirubinate stones and/or biliary sludge. Differentiation of such cases from primary hepatolithiasis, which can mimic PSC, may be difficult.

Risk of Cholangiocarcinoma

In the only retrospective review comparing the natural history of patients with SSC to a cohort with a diagnosis of PSC,³ no cases of either cholangiocarcinoma or hepatocellular cancer were identified among the 31 patients with SSC during the 10-year follow-up period. However, a 38-year-old HIV-positive man has been reported to have cholangiocarcinoma 3 years after a diagnosis of AIDS-related cholangiopathy.¹⁰¹ Mucinous cholangiocarcinoma as an unusual complication of hepatolithiasis and RPC has also been reported.¹⁴⁹ Cholangiocarcinoma is also a well-recognized complication of *Clonorchis sinensis*¹⁵⁰ or *Ascaris lumbricoides* infection.¹⁵¹ The rarity of cholangiocarcinoma in SSC is most likely because of the associated competing comorbidities as well as the lack of a



Fig. 7. Endoscopic retrograde cholangiography in a 57-year-old woman with polycystic kidney disease and asymptomatic persistent cholestasis. Multiple areas of extrinsic compression generates a picture that mimics intrahepatic PSC.

long asymptomatic phase as seen in PSC. As SSC becomes more frequently recognized due to the introduction of noninvasive imaging modalities of the biliary tree, malignant change may be more frequently detected.

In conclusion, the diagnosis of PSC remains a challenge. The issue of differentiating it from SC secondary to local and/or systemic processes is not widely recognized. Careful history-taking is key. Various clinical features, such as immunodeficiency, autoimmune disease, cholelithiasis, traumatic injury, hypercoagulability, past intra-arterial chemotherapy, and liver transplantation should prompt physicians to implicate secondary etiologies. Overwhelming sepsis itself may account for typical yet reversible cholangiographic findings in the intensive care unit patient. Elevated serum IgG4 levels should raise the suspicion for autoimmune pancreatitis. The distribution of disease on cholangiography may be helpful. Generally, the findings of a more diffuse pattern of ductal narrowing and multifocal strictures favors a diagnosis of PSC, whereas isolated peripheral disease favors secondary causes. The combined occurrence of intrahepatic disease with papillary stenosis is unique to AIDS cholangiopathy. The presence of multiple ductal stones, abrupt duct cutoff, and intrahepatic "bile lakes" suggest RPC. Involvement of the main pancreatic duct with or without diffuse enlargement of the pancreas suggests AIP. Isolated proximal biliary disease may suggest portal biliopathy. These secondary causes of SC need to be considered in all patients, because some cases are potentially reversible with appropriate therapy.

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