



## Secondary sclerosing cholangitis: mimics of primary sclerosing cholangitis

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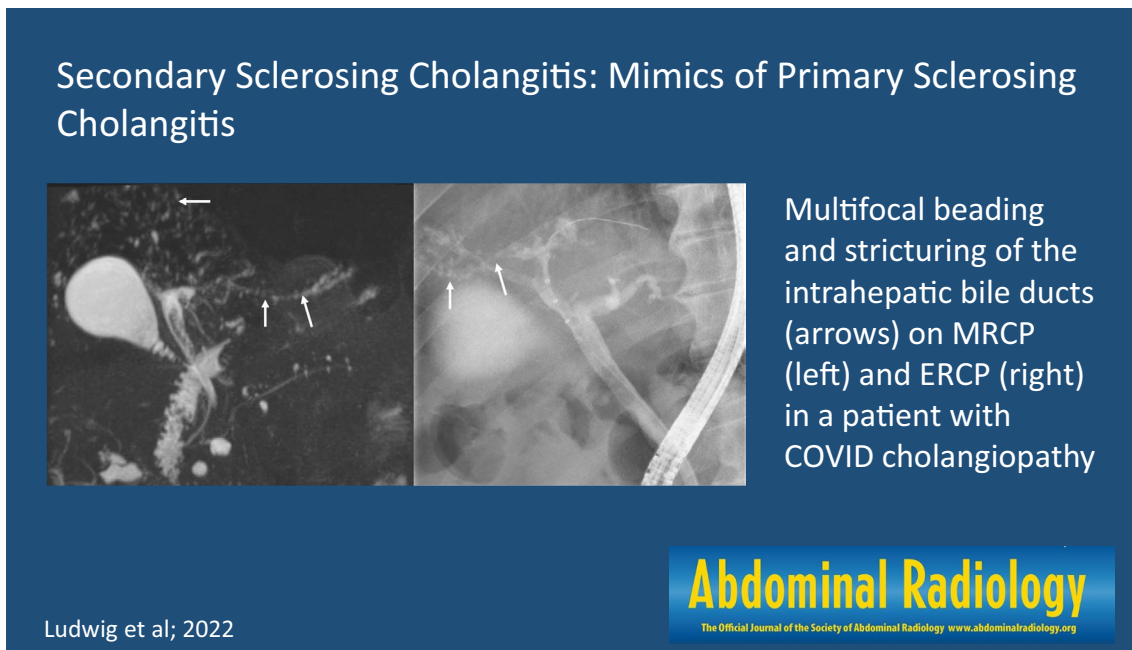
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### Abstract

Sclerosing cholangitis is a chronic cholestatic disease characterized by stricturing, beading, and oblitative fibrosis of the bile ducts. Sclerosing cholangitis is considered primary (PSC) if no underlying etiology is identified or secondary (SSC) if related to another identifiable cause. In this article, we will review the clinical features, pathogenesis, diagnosis, and imaging findings of PSC and SSC, with an emphasis on features that may aid in the distinction of these entities. We will also discuss various etiologies of SSC including recurrent pyogenic cholangitis, other infectious etiologies, ischemic damage, toxic insults, and immunologic, congenital, and miscellaneous causes, highlighting the unique imaging findings and clinical context of each diagnosis.

### Graphical abstract



**Keywords** Secondary sclerosing cholangitis · Recurrent pyogenic cholangitis · AIDS cholangiopathy · Ischemic cholangiopathy · Toxic cholangiopathy · IgG4-related sclerosing cholangitis

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## Introduction

Sclerosing cholangitis is a chronic cholestatic disease of biliary tree characterized by stricturing, beading, and obliterative fibrosis of the intrahepatic and extrahepatic bile ducts. If no underlying etiology is identified, sclerosing cholangitis is considered primary (i.e., primary sclerosing cholangitis; PSC). However, a broad range of insults to the bile ducts may lead to sclerosing cholangitis that can mimic the clinical presentation and imaging appearance of PSC. Indeed, if another infectious, ischemic, toxic, or inflammatory cause of bile duct stricturing is identified, then the diagnosis would be secondary sclerosing cholangitis (SSC) [1, 2]. In this article, we will review the clinical features, pathogenesis, diagnosis, and imaging findings of PSC and SSC, with an emphasis on features that may aid in the distinction of these entities. We will also cover the various etiologies of SSC, highlighting the unique imaging findings and clinical context that may allow the radiologist to suggest a more specific diagnosis.

## Primary sclerosing cholangitis

There are multiple postulated etiologies of PSC, though the disease is still considered idiopathic. However, the association between PSC and inflammatory bowel disease (IBD) makes an autoimmune etiology plausible [2]. There are also well known genotypic associations, suggesting that PSC occurs as a sequela of immunologic priming in a genetically-susceptible individual [3]. PSC has a mean age at diagnosis of 40 years, and is more common in men and individuals in northern Europe and the USA [4]. A significant majority of patients with PSC develop progressive hepatic fibrosis and biliary cirrhosis within 10–15 years of diagnosis [5]. At present, there is no effective medical therapy for delaying the progression of disease; however, liver transplantation is often curative [6]. Patients may present with asymptomatic laboratory abnormalities, active cholangitis with right upper quadrant pain and fever, or biliary obstruction with pruritis, jaundice, and fatigue. Other presenting symptoms related to PSC include abdominal distension from ascites, gastrointestinal (GI) bleeding from varices in the setting of portal hypertension, or enteritis or colitis if there is associated IBD [2].

The diagnosis of PSC is made by a combination of chronic cholestatic laboratory abnormalities such as elevated alkaline phosphatase, gamma glutamyl transferase, and modest transaminitis with multifocal stricturing of intrahepatic and/or extrahepatic bile ducts on magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiogram (ERCP) in the absence of another causative etiology [2]. Percutaneous biopsy, though not required to

diagnose large-duct PSC, may show the classic pathologic findings of periductal ‘onion-skin’ fibrosis [3]. MRCP is the preferred initial cholangiographic technique over ERCP since it is less invasive, less costly, avoids contamination of a potentially sterile biliary tree, and is not associated with procedural complications such as pancreatitis [7, 8]; however, MRCP lacks the ability to intervene on a stricture for purposes of cytologic diagnosis or stenting. Furthermore, MRCP can evaluate the entire biliary tree peripheral to a dominant stricture (DS), which is defined by a luminal diameter less than 1.5 mm within the common hepatic duct or common bile duct, or less than 1.0 mm within the left or right hepatic duct [9]. The biliary tree peripheral to a DS may not be evaluated by ERCP due to incomplete contrast opacification.

Imaging features of PSC include hallmark multifocal bile duct stricturing with beaded appearance from intervening mildly dilated or normal segments between sites of narrowing that can be intrahepatic, extrahepatic, or most commonly intrahepatic and extrahepatic (Table 1; Fig. 1). In chronic disease, peripheral bile ducts become fibrosed and may become pruned or invisible. With chronic cholestasis, the liver demonstrates morphologic changes of cirrhosis with relative hypertrophy of the caudate lobe, and atrophy of the left lateral and right lobes producing a box-like, macrolobulated shape with areas of confluent fibrosis. Sites of active cholangitis show bile duct wall thickening, hyperenhancement, and peribiliary edema. Bile duct stones, webs, diverticula, and hepatic abscesses can occur with chronic obstruction, stasis, and inflammation. Patients with PSC have an increased risk for cholangiocarcinoma (CCA), with a cumulative incidence of 10–20% [10–12]. CCA may present as a DS, a polypoid intraluminal bile duct mass, or a focal intrahepatic lesion.

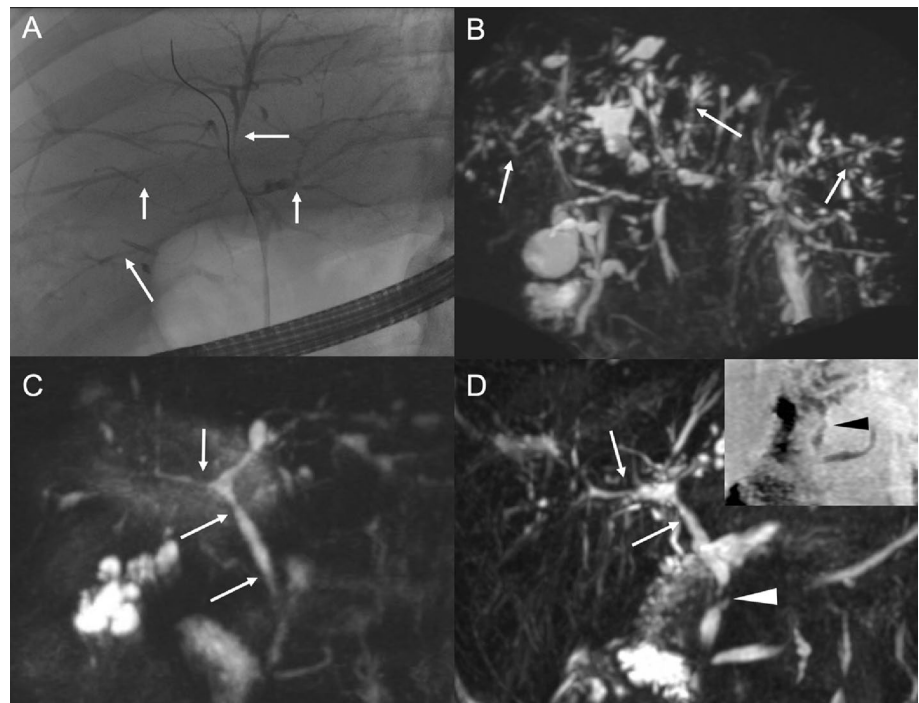
## Secondary sclerosing cholangitis (SSC)

Compared to PSC, SSC is relatively uncommon although the prevalence and demographics of SSC are not well understood due to the lack of relevant studies [13, 14]. In general,

**Table 1** Typical imaging findings of PSC

Multifocal bile duct stricturing with beaded appearance
May be intrahepatic, extrahepatic, or intra- and extrahepatic
Bile duct wall thickening and enhancement
Dominant stricture (DS) involving the extrahepatic or central ducts
Peripheral bile ducts may be pruned or invisible in chronic disease

**Fig. 1** Typical imaging findings on ERCP and MRCP in different patients with PSC. **A**, **B** Beading and stricturing in two different patients with PSC on ERCP (**A**) and MRCP (**B**) with predominant involvement of the peripheral intrahepatic ducts (arrows). **C**, **D** Periductal tissue thickening predominantly involving the central intrahepatic ducts and extrahepatic duct in two different patients with PSC on MRCP (arrows). **D** A dominant stricture is evident the distal common bile duct (arrowhead), with enhancing periductal soft tissue on post-contrast coronal T1-weighted image (inset, **D**). Bile duct resection was performed due to suspicious findings on brushings during ERCP, with final pathology showing an inflammatory stricture



the prognosis of SSC is usually worse than PSC, but the propensity for disease progression is heavily dependent on the underlying etiology of SSC and whether it can be effectively addressed [15]. For instance, SSC related to IgG4 disease is highly responsive to steroid therapy [16], whereas SSC occurring in the setting of critical illness is often irreversible and rapidly progressive [17]. Similar to PSC, end-stage SSC results in biliary cirrhosis which is only curable with liver transplantation [18]. Unlike PSC, however, most etiologies of SSC are not associated with an increased risk of CCA [17].

The presentations of SSC may be similar to PSC, and include asymptomatic laboratory abnormalities, symptoms of biliary obstruction such as jaundice and pruritus, and/or features of active cholangitis including right upper quadrant pain and fever. MRCP is the imaging modality of choice and depicts multifocal beading and stricturing of the intrahepatic and/or extrahepatic bile ducts. Although the clinical presentation and imaging findings in SSC may mimic PSC, the distribution of disease, associated findings, and clinical context may provide for a more specific diagnosis. Even if a specific diagnosis cannot be rendered based on imaging alone, the etiology of SSC can usually be identified clinically [13]. There are numerous identifiable causes of SSC, which can be broadly categorized as related to infections, ischemic damage, toxic insults, and immunologic, congenital, and miscellaneous causes (Table 2). Key features of the selected entities will be discussed in the following sections.

### Recurrent pyogenic cholangitis

Recurrent episodes of cholangitis may lead to SSC, with recurrent pyogenic cholangitis (RPC) being a prototypical example. RPC is most common in patients of Asian descent but can occur in other populations including in the USA in association with rural environment and low socioeconomic status [19, 20]. Parasitic infections such as *Clonorchis sinensis* and *Ascaris lumbricoides* have been implicated in RPC, and may be present in some cases, although the association is relatively weak [21]. In RPC, repeated infection results in biliary strictures, stasis, and intraductal stone formation (i.e., hepatolithiasis). Accordingly, the disease manifests clinically with repeated episodes of bacterial cholangitis and laboratory evidence of cholestasis [22].

On cholangiography, RPC is characterized by central-predominant intrahepatic and extrahepatic biliary strictures with dilated ducts often packed with intraductal stones (Fig. 2). The majority of hepatoliths in RPC are pigmented (i.e., composed of calcium bilirubinate) which are hyperdense on non-contrast CT relative to background liver parenchyma and intrinsically hyperintense on T1-weighted MRI sequences [23]. A reported imaging sign in RPC is the “arrowhead sign,” in which there is reduced arborization or acute tapering of the peripheral intrahepatic bile ducts [19]. In the setting of an acute exacerbation, peribiliary enhancement and hyperemia are often evident, and complications of acute disease include intrahepatic bilomas, hepatic abscesses, and thrombophlebitis

**Table 2** Causes of secondary sclerosing cholangitis

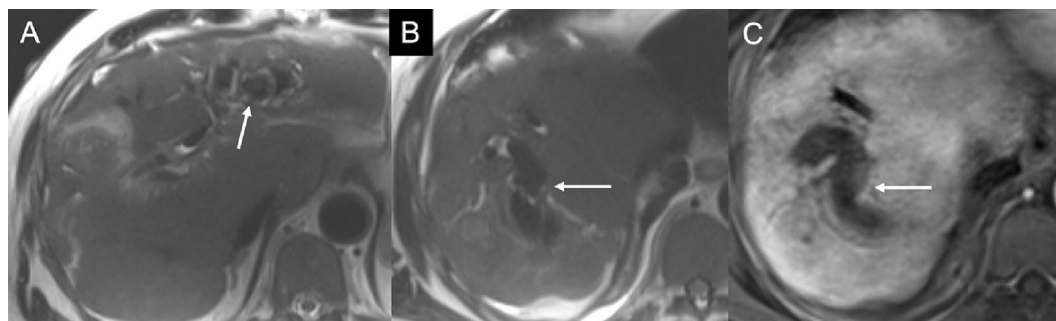
Infectious
Recurrent pyogenic cholangitis (RPC)
Repeated episodes of bacterial cholangitis
AIDS cholangiopathy
COVID-associated cholangiopathy
Ischemic
Hepatic arterial thrombosis
Ischemic-type biliary lesions (liver transplant recipients)
Critical illness (e.g., hypoperfusion/shock, cardiac arrest, severe trauma)
Systemic vasculitis
Hematologic disorders (e.g., sickle cell disease and paroxysmal nocturnal hemoglobinuria)
Radiation therapy
Toxic
Liver-directed arterial therapy
Hepatic arterial infusion pump
Direct exposure to caustic agents
ERCP
Immunologic
IgG4-related
Inflammatory pseudotumor
Eosinophilic
Immune checkpoint inhibitors
Congenital
Caroli's disease
Cystic fibrosis
Miscellaneous
Portal biliopathy
Choledocholithiasis
Chronic pancreatitis
Sarcoidosis
Amyloidosis
Metastatic disease

of the portal or hepatic veins [24]. RPC is one of the few etiologies of SSC which is associated with CCA, occurring in up to 6% of patients, which may be a mucinous subtype [25–28]. ERCP or percutaneous techniques are often employed for intraductal stone extraction and management of underlying strictures, with partial hepatectomy reserved for advanced or refractory disease [29].

### Other infectious etiologies

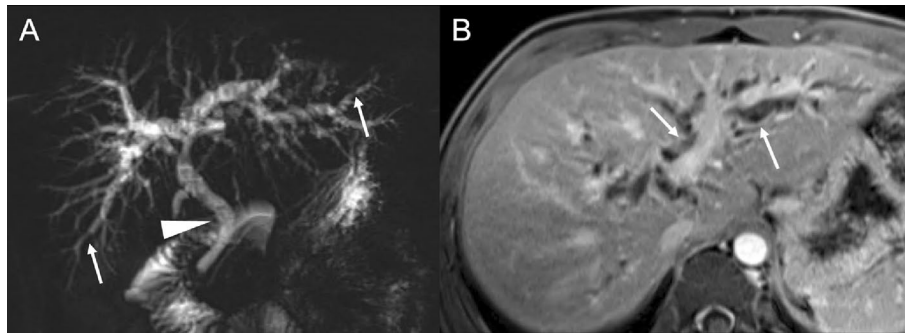
Chronic nonpyogenic infections of the biliary tree may cause SSC, most likely due to chronic inflammation [13]. AIDS cholangiopathy is a form of SSC occurring in the setting of human immunodeficiency virus (HIV) infection with severe immunocompromise (i.e., CD4 count less than 100/mm<sup>3</sup>) [30]. Several pathogens have been implicated in the pathogenesis of AIDS cholangiopathy including the parasitic organisms *Cryptosporidium* and *Microsporidium* as well as viral infection with cytomegalovirus [19]. Interestingly, antimicrobial therapy is ineffective at halting the progression and successful treatment relies on correction of the underlying immunodeficiency [13]. The majority of patients present with severe right upper quadrant or epigastric pain and abnormal liver chemistries [30]. Infection with HIV may or may not be known at the time of presentation.

Cholangiographic findings in AIDS cholangiopathy overlap with those of PSC and often show beading and stricturing of the intrahepatic and extrahepatic bile ducts with periductal soft tissue thickening (Fig. 3). Long segment extrahepatic strictures and a predilection for left-sided biliary involvement are common features [19]. An additional finding which is seen in AIDS cholangiopathy but is not typical of PSC is that of papillary stenosis, often occurring in conjunction with additional biliary stricturing but occasionally found in isolation [31]. The diagnosis of AIDS cholangiopathy may be made based on duodenal or papillary biopsy if the typical imaging features are not present and/or



**Fig. 2** Recurrent pyogenic cholangitis (RPC) in a 68-year-old man presenting with acute cholangitis. Axial T2-weighted images at two different levels (**A** and **B**) and axial post-contrast T1-weighted image in the portal venous phase (**C**, same level as **B**) shows multifocal

areas of marked intrahepatic duct dilation most pronounced in the left lateral and right posterior sections (arrows). There is associated hepatolithiasis with numerous T2-hypointense stones filling the dilated intrahepatic ducts



**Fig. 3** AIDS cholangiopathy in 24-year-old man with longstanding HIV/AIDS and a CD4 count of 0. MRCP image **A** shows mild multifocal stricturing of the peripheral intrahepatic ducts and moderate diffuse dilation of the intrahepatic and extrahepatic bile duct with abrupt

narrowing near the ampulla (arrowhead), compatible with papillary stenosis. Axial T1-weighted post-contrast image **B** shows mild diffuse periductal enhancement (arrows)

the clinical context uncertain [19]. Endoscopic sphincterotomy generally results in symptomatic relief and normalization of liver chemistries if papillary stenosis is present [32].

A recently described form of SSC related to an infectious etiology is COVID-associated cholangiopathy which occurs after severe COVID-19 infection [33]. The pathogenesis is unclear, but may be related to microvascular ischemia, immune-mediated damage, or direct viral infection of the biliary epithelium [34, 35]. Imaging findings are similar to PSC and include beading and stricturing of the intrahepatic and extrahepatic bile ducts with periductal soft tissue thickening (Fig. 4). Liver transplantation is a viable treatment option in patients with severe cholestasis or progressive disease [36].

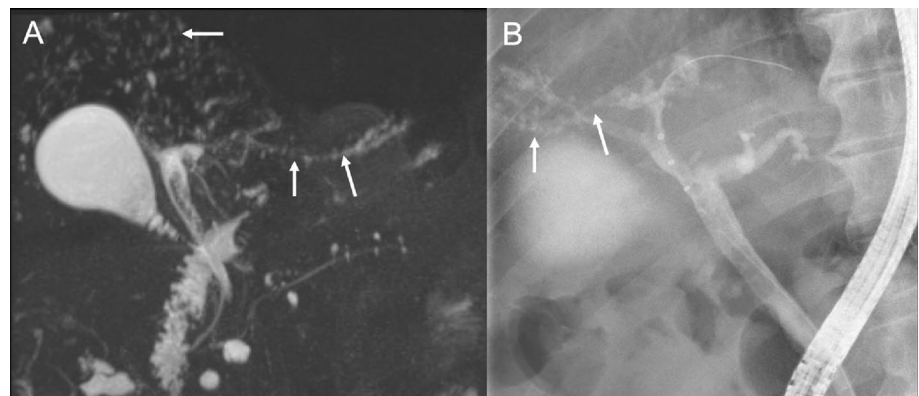
### Ischemic cholangiopathy

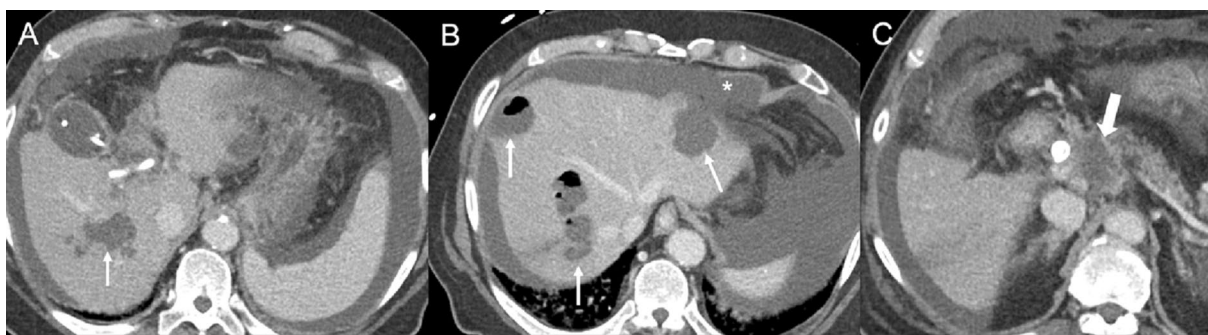
Under normal circumstances, the liver has dual blood supply with 70–80% from the portal vein and the remainder from the arterial system. The bile ducts, on the other hand, rely almost entirely on the arterial circulation; the intrahepatic ducts are supplied primarily by branches of the right and left hepatic arteries (HAs) whereas the extrahepatic

ducts are supplied by a well-collateralized peribiliary arterial plexus on their surface [37]. The reliance on arterial supply makes the bile ducts especially prone to ischemic damage in the setting of arterial compromise. Accordingly, ischemic cholangiopathy is a form of SSC that occurs due to impaired arterial blood supply to the bile duct walls, resulting in biliary ischemia and in some cases biliary necrosis. Early complications include the development of bile leaks, intrahepatic bilomas, abscess formation, and sepsis (Fig. 5), whereas late findings include multifocal structuring of the intrahepatic and extrahepatic ducts and eventually secondary biliary cirrhosis. The cholangiographic findings of ischemic cholangiopathy are not specific, though the clinical context and associated vascular findings often provide for a more specific diagnosis.

In the setting of liver transplantation, the extrahepatic donor ducts rely entirely on the hepatic arterial supply due to severing of the extrahepatic collaterals that typically provide flow to the peribiliary arterial plexus in the native liver [38]. HA thrombosis is the most common vascular complication after liver transplant occurring in 5–9% of adult recipients, and often results in ischemic cholangiopathy (Fig. 6) [39]. Ischemic-type biliary lesions (IBL) are also encountered in

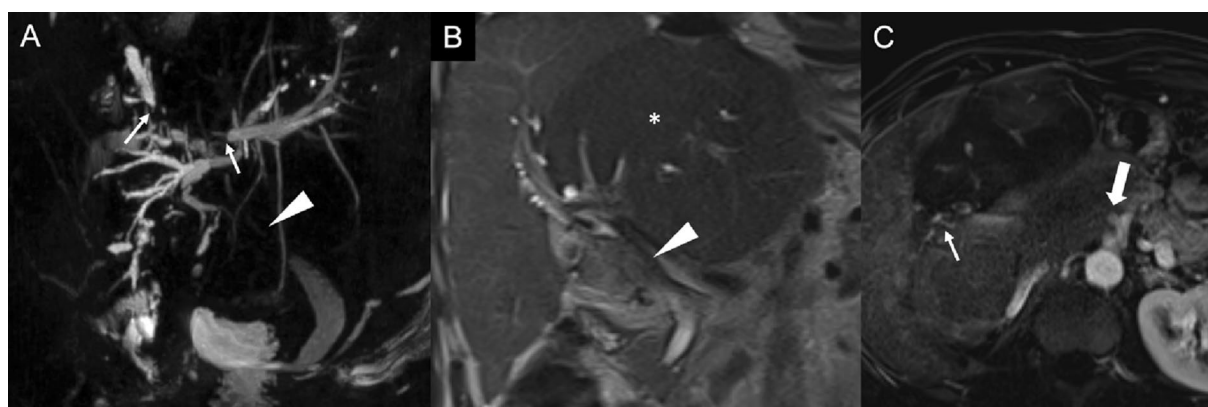
**Fig. 4** COVID cholangiopathy in a 69-year-old man with elevated liver function tests and recent SARS-CoV-2 infection. MRCP image (**A**) and contemporaneous ERCP image (**B**) shows diffuse beading and stricturing of the intrahepatic bile ducts (arrows). The patient underwent liver transplantation, with explant pathology showing a biliary pattern of injury with scattered bile duct injury and loss with advanced fibrosis





**Fig. 5** Biliary necrosis as a manifestation of ischemic cholangiopathy in a 75-year-old man with pancreatic adenocarcinoma and hepatic arterial and portal venous thrombosis. Axial contrast-enhanced CT images at three levels **A–C** show multiple collections in the liver which have a peribiliary distribution and several of which contain gas (arrows), indicative of communication with the biliary tree in this patient with an indwelling common bile duct stent. The collec-

tion in the left lateral section is ruptured, resulting in bilious ascites (asterisk, **B**). There is occlusion of the main portal vein and common hepatic artery at the site of the hypoechoic pancreatic head mass (thick arrow, **C**). Rather than representing ischemic injury to the central ducts, biliary necrosis represents ischemic necrosis of the peripheral branch bile ducts

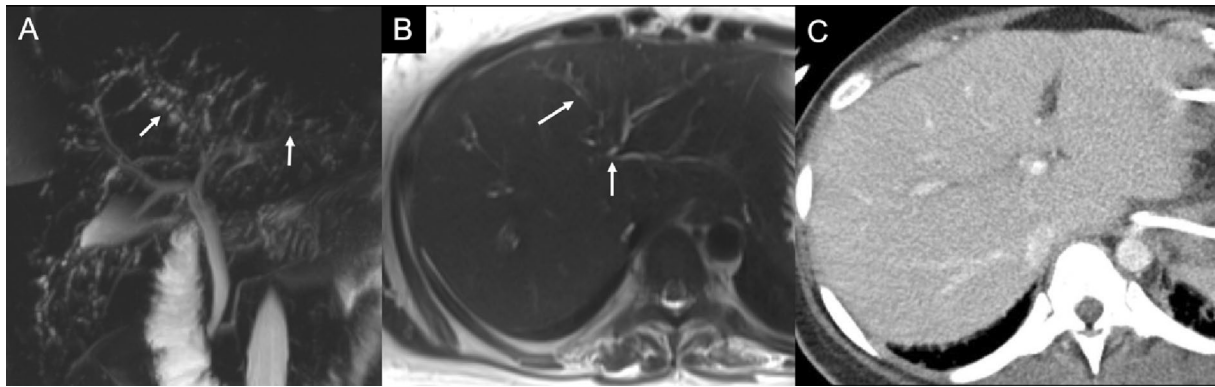


**Fig. 6** Ischemic cholangiopathy in the setting of chronic hepatic artery thrombosis in a 35-year-old man who underwent liver transplant several years prior for metastatic neuroendocrine tumor. MRCP and coronal T2-weighted image shows severe central-predominant intrahepatic stricturing (thin arrows) and a long segment high-grade stricture of the proximal extrahepatic duct (arrowhead). Note the

presence of marked caudate hypertrophy (asterisk, **B**). Axial post-contrast subtraction images in the arterial phase **C** show abrupt occlusion of the proximal common hepatic artery (thick arrow). The branch hepatic arteries were reconstituted in the porta hepatitis by multiple small collaterals (thin arrow, **C**)

liver transplant recipients with a patent hepatic artery, and are favored to be multifactorial with most likely culprits, in addition to ischemic injury, being immunologic (e.g., from allograft rejection) and cytotoxic (e.g., from bile salts) [40]. Additionally, a liver donated after cardiac death may have ischemic cholangiopathy even before it is transplanted into the recipient [41]. Nonetheless, identification of SSC in a liver transplant recipient should prompt a thorough evaluation of the HA with Doppler ultrasound or CT or MR angiography, as prompt revascularization improves graft survival and overall outcomes in patients with HA thrombosis [42].

Ischemic cholangiopathy may also occur in the native liver secondary to hypoperfusion/shock, cardiac arrest, severe trauma, or critical illness in general, usually in setting of a patient HA [43]. The pathogenesis is likely multifactorial and may be mediated by ischemia, systemic inflammatory response, medications, and/or massive transfusions. Clinically, ischemic cholangiopathy is often considered in an intensive care patient who has laboratory evidence of cholestasis, especially if abnormalities in liver chemistries persist despite recovery from the critical event. Cholangiographic findings of multifocal beading and stricturing usually appear rapidly and are irreversible (Fig. 7) [17]. Other less common causes of ischemic cholangiopathy in the native liver include systemic vasculitis,



**Fig. 7** Ischemic cholangiopathy in a 41-year-old woman who suffered cardiac arrest in the setting of pulmonary embolism. On the MRCP (A) and axial T2-weighted image (B) there is extensive beading and structuring of the intrahepatic bile ducts (arrows). Axial con-

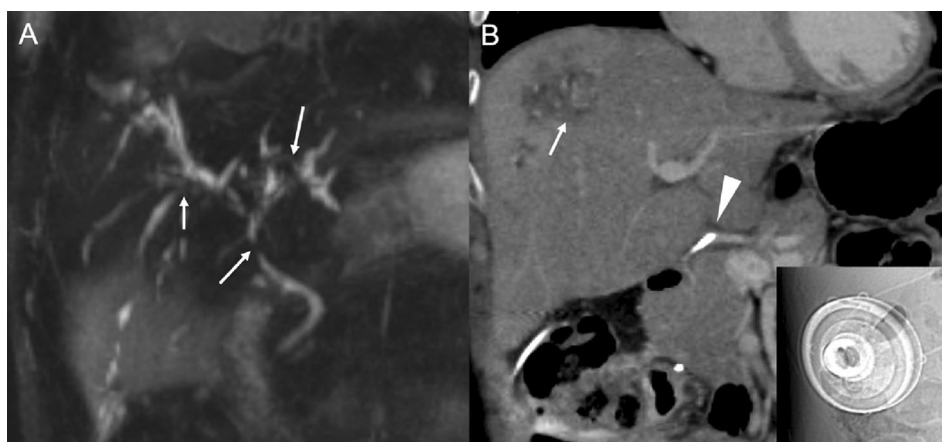
trast-enhanced CT image performed three weeks earlier (C) shows no intrahepatic bile duct dilation, highlighting the rapid interval development

hematologic disorders such as sickle cell disease and paroxysmal nocturnal hemoglobinuria, hereditary hemorrhagic telangiectasia, and HA thrombosis, embolization, or ligation [44]. Radiation to the liver may cause SSC which can be classified as ischemic cholangiopathy due to the resultant obliterative and sclerosing arterial damage [44].

### Toxic causes

Cytotoxic damage to the biliary epithelium may be a sole or a compounding factor in cases of SSC. Cytotoxic injury can result from static bile salts during prolonged preservation times of liver explants, or from direct injection of toxic agents into the hepatic arterial system such as liver directed arterial therapy. Repeated delivery of intra-arterial

chemotherapy such as in the setting of a hepatic arterial infusion (HAI) pump may result in a SSC, likely due to a combination of direct biliary and small vessel injury which has mixed features of toxic and ischemic cholangiopathy (Fig. 8) [45, 46]. Toxic SSC can occur secondary to drug or chemical-induced injury which is associated with certain medications and systemic chemotherapy, and may be immune-mediated [47, 48]. Additionally, toxic SSC may result from direct exposure to caustic agents when a liver cyst undergoing sclerosis has direct communication with the bile ducts [49]. Rarely, toxic SSC may occur following ERCP, which may be immunologic or sequela of post-ERCP cholangitis [50]. In toxic cholangiopathy, imaging features generally resemble those of PSC, with multifocal stricturing of the intrahepatic and extrahepatic bile ducts. A regional



**Fig. 8** Hepatic arterial infusion (HAI) chemotherapy-related cholangiopathy in a 42-year-old man with colorectal cancer and hepatic metastatic disease. MRCP (A) and coronal contrast-enhanced CT image (B) show multifocal central-predominant stricturing of the intrahepatic and proximal extrahepatic bile duct (arrows). The cath-

eter of the HAI pump is located within the gastroduodenal artery with tip at the origin of the proper hepatic artery (arrowhead). The Codman 3000 pump is visualized on the corresponding tomogram (inset, B)

or segmental distribution or stricturing may be encountered depending on the specific location of prior treatment or toxic injury [47, 51].

### Immunologic causes

IgG4-related sclerosing cholangitis (IgG4-SC) is a biliary manifestation of IgG4-related disease (IgG4-RD) resulting from immune-mediated fibro-inflammation [52]. Although the pathogenesis is likely multifactorial, most authors consider it as an autoimmune disorder, which is supported by the histopathologic findings of IgG4-enriched lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis, and variable presence of eosinophils [53]. IgG4-SC is relatively uncommon and most frequently encountered in males in their fifth and sixth decades of life [54]. Abdominal pain and jaundice are the common clinical symptoms, and the diagnosis is made based on the HISORt (histology, imaging, serology, other organ involvement, and response to therapy) criteria from the Mayo Clinic or the Japanese Clinical Diagnostic Criteria, both of which take into consideration the elevated serum IgG4 levels, typical cholangiographic appearance, systemic organ involvement, biopsy findings, and response to corticosteroids [55, 56].

Typical cholangiographic findings of IgG4-SC include long segment continuous strictures of the extrahepatic bile duct with circumferential ductal wall thickening, most commonly involving the intrapancreatic portion of the common bile duct (i.e., type 1) [57]. Findings of autoimmune pancreatitis are often coexistent and are found in 90% of patients with type 1 IgG4-SC (Fig. 9). Less common manifestations of IgG4-SC include diffuse intrahepatic and

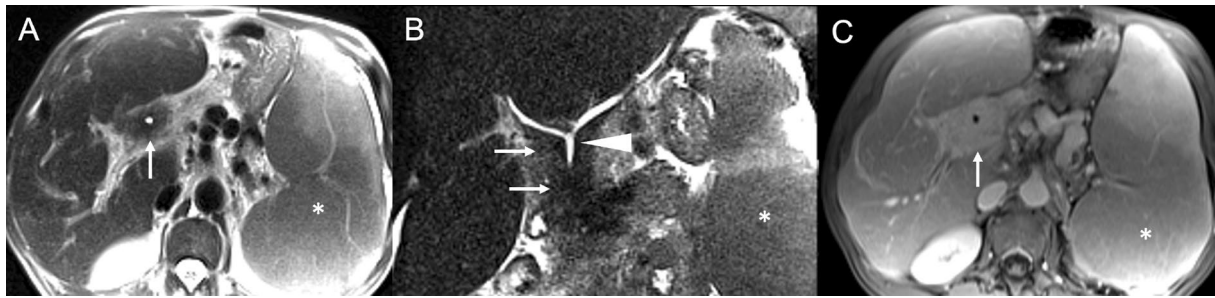
extrahepatic involvement (i.e., type 2), hilar along with distal intrapancreatic common duct involvement (i.e., type 3), and isolated hilar involvement (i.e., type 4). IgG4-SC with diffuse intrahepatic and extrahepatic involvement has the greatest propensity to mimic PSC, though the strictures in PSC are typically shorter with normal intervening segments. Accordingly, the Association for the Study of Liver Diseases (AASLD) recommends measuring serum IgG4 levels for all patients with suspected PSC, to exclude IgG4-SC (based on level 2C evidence) [58]. On the other hand, hilar involvement especially in the absence of intrapancreatic common duct involvement is more likely mimic cholangiocarcinoma. A related manifestation of IgG4-RD is the hepatobiliary inflammatory pseudotumor, specifically the lymphoplasmacytic variant, which is commonly found in the hepatic hilum and often resembles hilar cholangiocarcinoma (Fig. 10) [59]. In such cases, raising the possibility of IgG4-RD when the appearance is typical or in the setting of other organ involvement may avoid treatment related morbidity when malignancy is misdiagnosed.

MRCP is preferred over ERCP due its ability to depict periductal soft tissue thickening and associated pancreatic and other organ involvement such as renal, retroperitoneal, and mesenteric IgG4-RD findings, though ERCP also allows for biliary stenting in patients with symptomatic biliary obstruction and concomitant tissue sampling either with brush cytology or in conjunction with endoscopic ultrasound-guided sampling [54, 60]. Corticosteroids are the mainstay of treatment and the majority patients with IgG4-SC experience a dramatic response to therapy [61]. When diagnosed and treated early, IgG4-SC has a very good prognosis, while delayed treatment may lead to development of

**Fig. 9** IgG4-related sclerosing cholangitis in a 59-year-old man with autoimmune pancreatitis and elevated liver function tests. MRCP (A) and coronal T2-weighted image (B) show T2-hypointense periductal soft tissue thickening with high-grade stricturing of the central intrahepatic ducts (thin arrows). Coronal T1-weighted post-contrast image (C) shows long segment soft tissue thickening with enhancement involving the extrahepatic duct (arrowhead), with areas of mild stricturing evident on the MRCP image (arrowhead, A). On the axial contrast-enhanced T1-weighted image (D) there is sausage like enlargement of the pancreas and loss of normal T1 hyperintensity (thick arrow), in keeping with autoimmune pancreatitis







**Fig. 10** Inflammatory pseudotumor which had four years of imaging stability. Axial (A) and coronal (B) T2-weighted images show a T2-hypointense soft tissue mass surrounding the central intrahepatic and extrahepatic duct (arrows) and a high-grade stricture of the mid common bile duct and mild upstream biliary duct dilation (arrow-

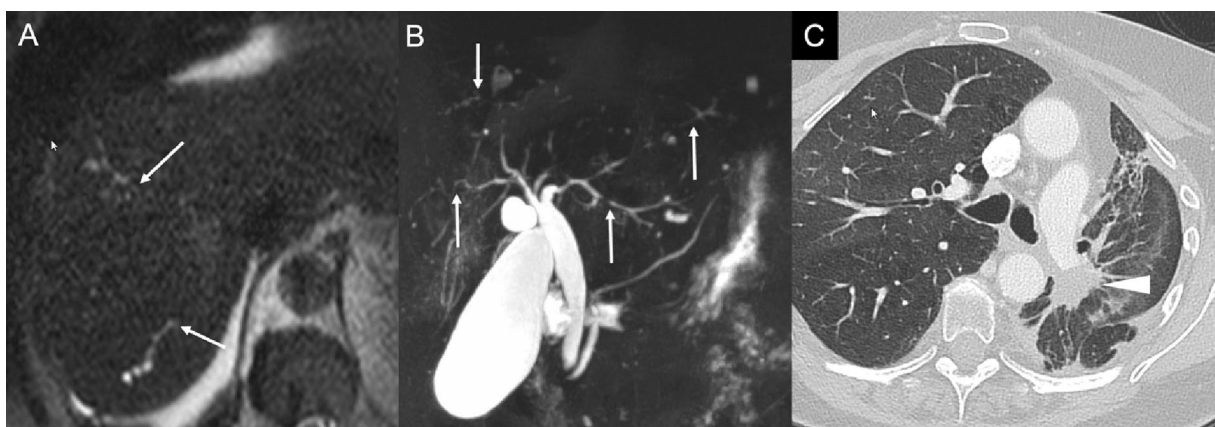
head). Axial post-contrast T1-weighted images in the portal venous phase show confluent homogenous enhancement within the mass (arrow). There were morphologic features of advanced fibrosis or cirrhosis with marked splenomegaly (asterisk) secondary to portal hypertension

complications such as biliary cirrhosis and portal hypertension [62]. In contradistinction to PSC, these patients are not at increased risk for the development of cholangiocarcinoma [63].

Another rare immunologic cause of SSC is eosinophilic cholangitis (EC), which is characterized by dense eosinophilic infiltration of the bile ducts and biliary stricturing [64, 65]. EC is associated with hypereosinophilic syndrome, allergic conditions, and parasitic infections, and may be coexistent with eosinophilic involvement of the luminal gastrointestinal tract. Imaging findings include segmental or diffuse peribiliary soft tissue thickening associated with multifocal stricturing, similar in appearance to PSC [66]. However, unlike PSC, EC may be reversible with steroid therapy [67].

A newly recognized immunologic cause of sclerosing cholangitis is that due to immune checkpoint inhibitor (ICI) therapy, which is increasingly used to treat a variety of malignancies. Histopathologically, ICI-related sclerosing

cholangitis is characterized by cytotoxic CD8+ lymphocytes infiltrating the bile ducts, presumably due to disruption in the balance between regulatory and effector T cells [68]. The small ducts, large ducts, or both may be involved, in a similar manner to PSC [69]. Imaging findings are dependent on the pattern of involvement, but cases affecting the large ducts typically manifest cholangiographically as periductal soft tissue thickening and multifocal stricturing of the intrahepatic and extrahepatic ducts (Fig. 11). ICI-related sclerosing cholangitis may occur early or late in the course of therapy, and should be considered in the differential for cholestatic liver injury and multifocal stricturing in a patient receiving ICI therapy regardless of when it was initiated [70]. Treatment is generally with corticosteroids, though the low overall response rate indicates that the biliary injury is irreversible in many patients [69, 70].



**Fig. 11** Secondary sclerosing cholangitis in a patient receiving pembrolizumab for adenocarcinoma of the lung. Axial T2-weighted (A) and coronal MRCP image (B) show multiple areas of peripheral bil-

iary duct dilatation consistent with multifocal peripheral stricturing (arrows). Axial CT image of the chest (C) shows the left hilar malignancy (arrowhead)

## Congenital causes

Congenital causes of SSC include Caroli's disease and cystic fibrosis (CF). Caroli's disease is an autosomal recessive disorder characterized by multifocal saccular dilation of the intrahepatic bile ducts due to an alteration in embryonic remodeling which results in duct destruction and dilation [71]. Characteristically, the extrahepatic bile duct is spared. A specific imaging finding of Caroli's disease is the "central dot" sign, which occurs when a dilated bile duct surrounds the adjacent hepatic artery and portal vein, producing a focus in the center of a dilated duct [72]. SSC, though uncommon in Caroli's disease, likely occurs due to intrahepatic cholestasis, intraductal stone formation, and repeated episodes of cholangitis [73]. However, SSC occurring in the setting Caroli's disease is unlikely to mimic PSC due to the characteristics findings that accompany it (Fig. 12).

In CF, alterations in the CFTR protein, which regulates chloride channel activity and fluid and ion concentrations, results in hyperviscous pulmonary secretions and repeated pulmonary infections. The CFTR protein is also highly expressed in the biliary tree, and loss of CFTR function may cause biliary pH dysregulation, increased sensitivity of the biliary epithelial cells to inflammation from bacterial products in the intestine, and impaired bile acid synthesis, all of which may contribute to biliary damage and SSC [74]. Biliary tract abnormalities are common in CF, occurring in approximately 65% of patients including in those without known liver disease [75]. Cholangiographic findings in CF resemble PSC and commonly appear as beading and stricturing of the intrahepatic and/or extrahepatic bile ducts (Fig. 13). Abnormalities of the gallbladder such as a microgallbladder and cholelithiasis are often coexistent, and complete fatty replacement of the pancreas is invariably present.

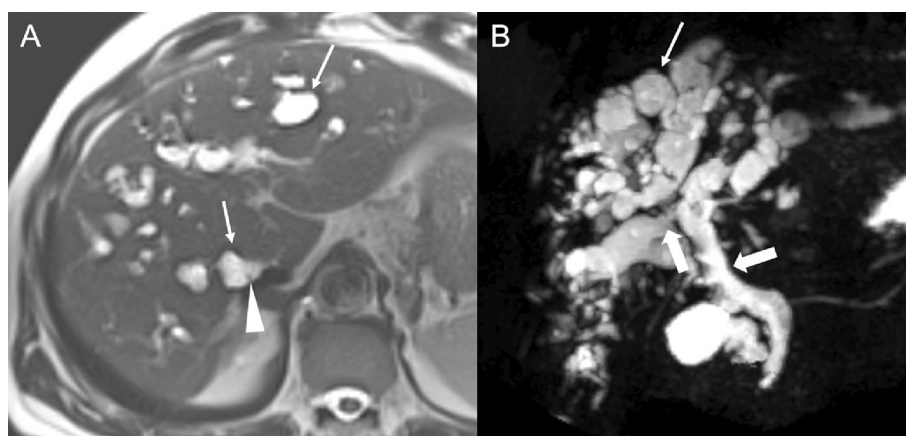
## Miscellaneous causes

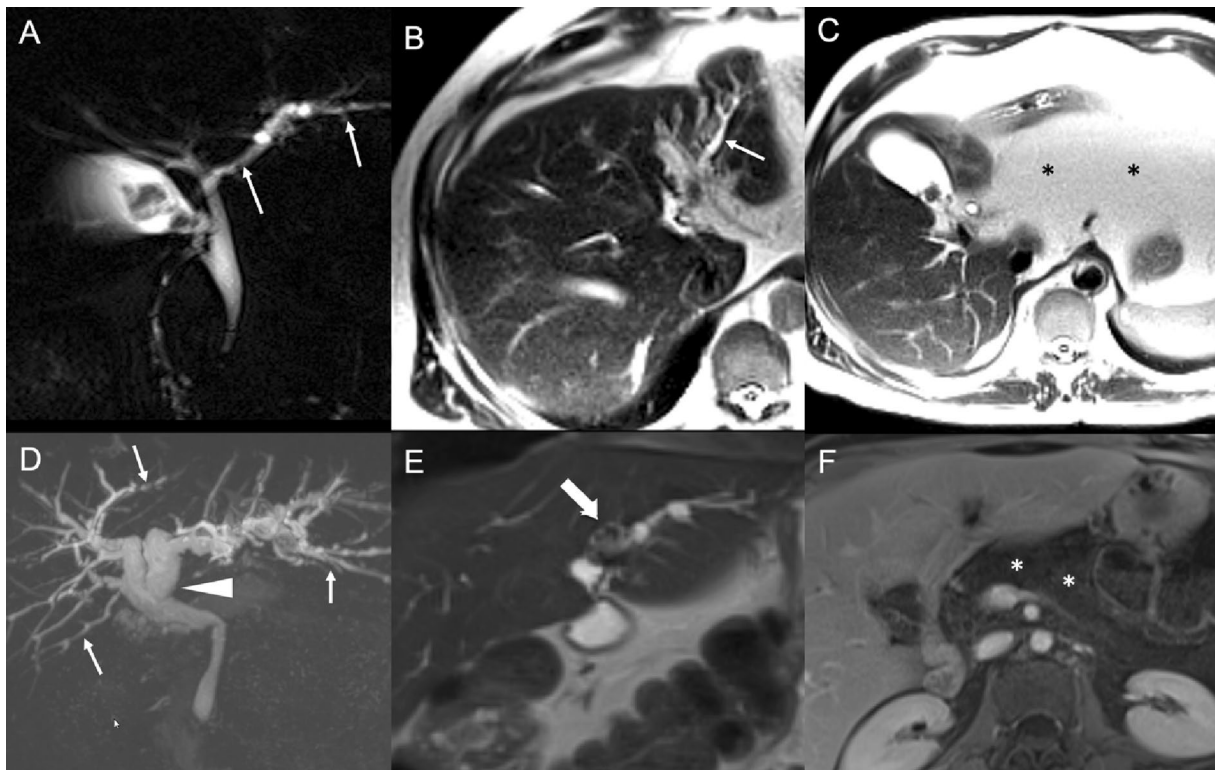
Portal biliopathy refers to biliary abnormalities occurring due to extrinsic compression of the bile ducts by cavernous collaterals in setting of portal vein thrombosis [76]. The common bile duct is drained by an epicholedochal and paracholedochal venous plexus which run along the surface of bile ducts, which in turn communicate with the intramural and subepithelial plexuses in the wall of the common bile duct by perforator veins [77]. Cavernous transformation leads to varicose dilation of paracholedochal and epicholedochal venous collaterals, protruding and compressing the pliable ductal wall, resulting in biliary wall thickening and luminal narrowing [78]. Prolonged compression may compromise the ductal arterial supply leading ductal fibrosis and strictures [79]. Although the majority of patients with cavernous transformation have some degree of biliary compression, only a minority develop symptomatic or functionally significant stricturing, which in turn may lead to jaundice, choledocholithiasis, and cholangitis [80].

Cholangiographic findings of the portal biliopathy included smooth extrinsic extrahepatic ductal compression or indentations, biliary ductal irregularity, and ductal displacement and angulation [81]. These findings occur exclusively in the setting of portal vein thrombosis with cavernous transformation, and serpiginous peribiliary collaterals are readily evident on cross sectional imaging using MRI and CT (Fig. 14). Fibrotic strictures and upstream biliary duct dilation may be present, especially in cases of chronic portal biliopathy [82]. Endoscopic management with biliary stenting is performed for those with symptomatic biliary obstruction, choledocholithiasis, or cholangitis [78]. Portosystemic shunting, when feasible, serves to reduce portal venous pressure and relieve compression from dilated collaterals, with biliary bypass procedures reserved for refractory cases [83].

A variety of infiltrative hepatic processes can produce SSC, with sarcoidosis one such example. Although hepatic involvement is evident histologically in up to 70%

**Fig. 12** Sclerosing cholangitis occurring in the setting of Caroli's disease. Axial T2-weighted image (A) and coronal MRCP image (B) shows multifocal saccular dilation of the intrahepatic bile ducts (thin arrows), some of which show the "central dot" sign (arrowhead, A). There is mild beading of the central intrahepatic bile and extrahepatic ducts (thick arrows, B)





**Fig. 13** Secondary sclerosing cholangitis in two patients with cystic fibrosis. **A–C** Coronal MRCP image (**A**) and axial T2-weighted image (**B**) show mild biliary duct dilation within the left liver with multifocal stricturing (thin arrows). Axial T2-weighted image more inferiorly (**C**) shows complete fatty replacement of the pancreas (asterisks). **D–F** Coronal MRCP image (**D**) shows diffuse stricturing

of the intrahepatic bile ducts (thin arrows) with moderate diffuse biliary duct dilation (arrowhead). Coronal T2-weighted image (**E**) shows hepatolithiasis within the left lateral section duct (thick arrow). Diffuse fatty replacement of the pancreas is evident on the axial post-contrast T1-weighted image (**F**, asterisks)

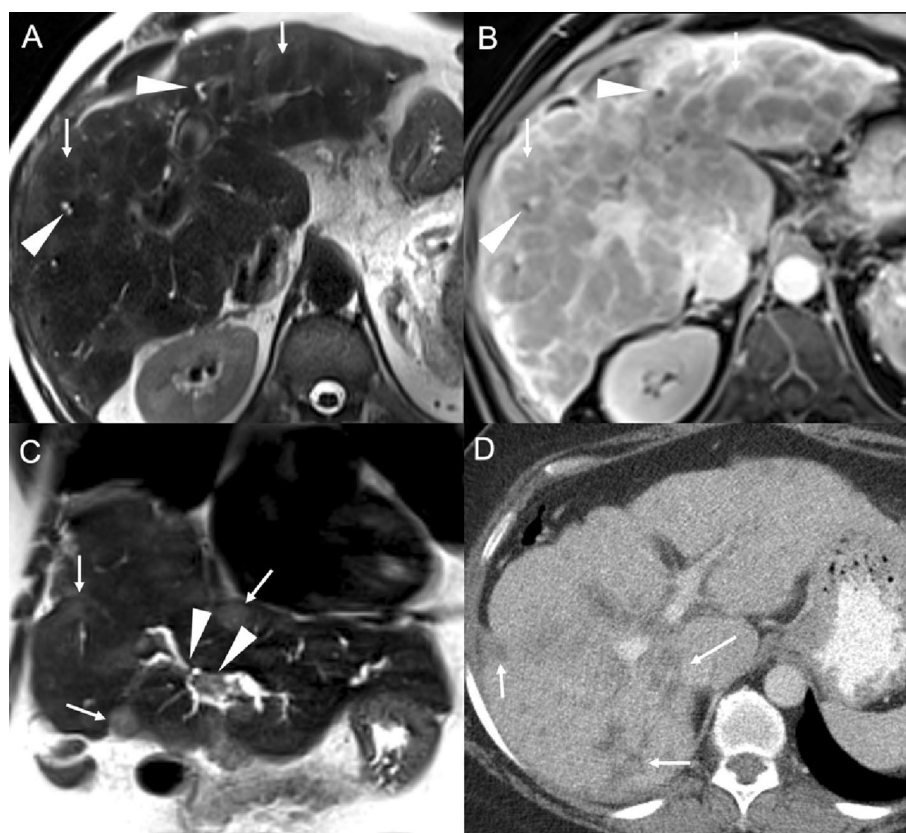


**Fig. 14** Portal biliopathy in a 63-year-old man with chronic portal vein occlusion in the setting of myeloproliferative disorder with essential thrombocytosis. MRCP image (**A**) shows intrahepatic biliary duct dilation with multiple strictures involving the central intrahepatic and proximal extrahepatic ducts (arrows, **A**). Axial T2-weighted

(**B**) and post-contrast T1-weighted (**C**) images show T2-hypointense flow voids with peribiliary enhancement in a serpiginous configuration (arrows, **B–C**), consistent with cavernous peribiliary collaterals. Note the lack of a normal portal vein, in keeping with chronic portal venous occlusion

of patients with sarcoidosis, clinically significant hepatic involvement is less common, and isolated hepatic involvement is rare [84]. Granulomatous periportal inflammation and fibrosis with secondary biliary stricturing and primary granulomatous cholangitis represent two potential mechanisms of SSC [85, 86]. Strictureing more commonly

involves the intrahepatic ducts but may also involve the extrahepatic duct [87]. The T2 “halo sign”, though not specific to sarcoidosis, is often seen due to confluent granulomas surrounding the portal tracts, and in advanced cases a cirrhotic morphology to the liver may be evident (Fig. 15A–B). Extrahepatic manifestations are common



**Fig. 15** Other miscellaneous causes of SSC in two different patients. **A, B** Hepatic sarcoidosis with resultant cirrhosis and underlying SSC. Axial T2-weighted (**A**) and post-contrast T1-weighted images in a delayed imaging phase (**B**) show numerous confluent areas of T2 hypointensity and associated hypoenhancement surrounding the portal tracts (i.e., halo sign) consistent with coalescent granulomas (arrows). Scattered areas of peripheral biliary duct dilation (arrowheads) represented multifocal peripheral intrahepatic stricturing,

in keeping with SSC. **C, D** Treated neuroendocrine tumor metastasis with pseudocirrhosis and associated SSC. Coronal T2-weighted image and contemporaneous contrast-enhanced CT image show numerous ill-defined lesions with intermediate signal intensity and relative hypoenhancement (arrows) which corresponded to treated lesions. Central-predominant intrahepatic stricturing was best appreciated on MRI (arrowheads, **C**)

and include upper abdominal and symmetric hilar and mediastinal lymphadenopathy, splenic lesions, and pulmonary micronodules in a perilymphatic distribution, which often allow the radiologist to suggest a specific diagnosis [88]. Other infiltrative processes that are associated with SSC include amyloidosis and metastatic disease (Fig. 15C–D) [89–91].

## Conclusion

Sclerosing cholangitis can be characterized as primary or secondary to another infectious, ischemic, toxic, or inflammatory cause. PSC is strongly associated with IBD but considered idiopathic. Most patients progress to cirrhosis within 10–15 years of diagnosis and there is no effective medical therapy available. SSC is relatively uncommon

and less well understood, but the propensity for disease progression is dependent on the underlying etiology of SSC and whether it can be effectively addressed. There are multiple identifiable causes of SSC, which can be categorized into recurrent pyogenic cholangitis, other infectious etiologies, ischemic damage, toxic insults, and immunologic, congenital, and miscellaneous causes. Although some etiologies of SSC may mimic PSC in clinical presentation and on imaging, unique imaging findings and the distinct clinical contexts of these entities may allow the radiologist to suggest a more specific diagnosis.

**Author contributions** All authors approve the final version to be published and agree to be accountable for all aspects of the work.

## Declarations

**Conflict of interest** The authors declare no conflict of interest.

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