

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis: an Update on MR Imaging Findings with Recent Developments

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ABSTRACT

Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are the most common immune-mediated chronic cholestatic liver diseases leading to cirrhosis and liver failure. Although magnetic resonance imaging (MRI) is not a necessary procedure for the diagnosis of PBC, MRI is recommended for monitoring disease progression and early detection of complications. Even though liver cirrhosis subtypes have similar MR imaging features, there are some findings which could indicate PBC, such as the periportal halo sign. Additionally, MRI using diffusion-weighted imaging with apparent diffusion coefficient measurements provides non-invasive assessment of the stage of liver fibrosis. The role of cholangiography is crucial for the diagnosis of PSC. Since endoscopic retrograde cholangiography is an invasive procedure with occasional post-procedural complications, the latest guidelines suggest magnetic resonance cholangiography as a reference procedure for evaluation of patients suspected with PSC. Characteristic magnetic resonance cholangiography findings include multiple segmental strictures with slightly dilated ducts among them, usually on both intrahepatic and extrahepatic bile ducts. Furthermore, magnetic resonance cholangiography is useful in the follow-up of these patients, allowing for timely diagnosis of complications such as cholangiocellular carcinoma. With the exception of ursodeoxycholic acid, which slows the progression of PBC, the only curative treatment for both PSC and PBC is still liver transplantation. However, recurrent disease occurs in some patients indicating the need for development of new more effective therapies.

Key words: cholestatic liver diseases – primary biliary cirrhosis – primary sclerosing cholangitis – magnetic resonance imaging – magnetic resonance cholangiopancreatography.

Abbreviations: AMA: anti-mitochondrial antibodies; ADC: apparent diffusion coefficient; CA 19-9: cancer antigen 19-9; CCC : cholangiocellular carcinoma; DWI: diffusion-weighted imaging; HCC: hepatocellular carcinoma; HLA: human leukocyte antigen; MRI: magnetic resonance imaging; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; TE: transient elastography; UDCA: ursodeoxycholic acid.

INTRODUCTION

Cholestatic liver diseases encompass a wide variety of entities, characterized by impaired hepatobiliary production and excretion of bile, with consecutive cholestasis. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the two most common chronic cholestatic disorders in adults, caused by immune-mediated cholangiocyte injury through

a complex interaction with environmental factors [1]. Each disease has distinguishing features and variable progression, but both ultimately result in biliary fibrosis, cirrhosis and hepatic failure. While PBC is characterized by small bile duct lymphocytic cholangitis, affecting mainly women and has a good response to ursodeoxycholic acid (UDCA), classic PSC involves large bile ducts mostly in young men and still without effective therapy [2]. A strong association with human leukocyte antigen (HLA), the presence of high circulating autoantibody titers, and increased frequency of other autoimmune diseases in affected individuals suggest the autoimmune nature of both PBC and PSC [2, 3]. Even though they represent relatively rare diseases, recent reports have shown an increasing incidence and prevalence globally [4]. Primary biliary cirrhosis and PSC account for approximately

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25% of all first liver transplantations in the Western world, indicating the importance of better understanding of their pathogenesis, earlier diagnosis, and development of treatment options [5]. We provide an overview of cholestatic diseases, PBC and PSC, and focus on their magnetic resonance imaging (MRI) features and the recent developments of MRI techniques that are used for establishing the diagnosis, monitoring disease progression, and for detecting complications.

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis is a slow progressive disease with immune-mediated inflammatory destruction of small intrahepatic bile ducts leading to chronic cholestasis and cirrhosis [6]. It occurs mainly in middle-aged women with prevalence up to approximately 40 per 100,000 people [7]. The prevalence rates have increased over time, but it is still unknown whether this increase reflects earlier diagnosis or new environmental exposures. In short, PBC is often referred to as a "model autoimmune disease" being one of the first conditions in which specific autoantibodies were recognized. It is associated with high titer of circulating anti-mitochondrial antibodies (AMA) in the majority of patients, and coexistence with other autoimmune diseases in 33% of patients [8]. Primary biliary cirrhosis is characterized by chronic, non-suppurative lymphocytic cholangitis that predominantly affects small, interlobular bile ducts in the portal triads leading to vanishing bile duct syndrome [9]. Histopathologically, PBC is divided into four stages. In stage 1 there is only periportal inflammation, while in stage 2 the inflammation extends towards neighboring hepatic parenchyma with a focal destruction of small septal and interlobular bile ducts leading to ductopenia. The typical sign of the stage 3 is the fibrous septa formation connecting the adjacent portal triads (bridging fibrosis). Micro- or macro-nodular cirrhosis is apparent in stage 4 [10].

Diagnosis and imaging findings

The diagnosis of PBC is usually based on combination of clinical findings, cholestatic biochemical pattern persisting for more than six months, and the presence of detectable AMA in

serum [11]. Liver biopsy is not routinely required for diagnosis except in AMA negative patients [12], but it enables assessment of necroinflammatory activity and grading of liver fibrosis. Due to the many limitations of liver biopsy, the new non-invasive procedures for the assessment of liver fibrosis, such as, for instance, transient elastography (TE) and MRI techniques, are gaining attention, as they allow for whole liver examination, as well as repetitive measurements for monitoring disease progression and treatment response. Transient elastography provides immediate evaluation of liver fibrosis severity measuring a hundred times bigger volume of liver parenchyma than liver biopsy, with the highest diagnostic accuracy among all non-invasive procedures [13]. However, it also has some limitations as it cannot be performed accurately in patients with ascites and in obese patients plus it is not still widely available and it cannot enable multisegmental analysis of liver fibrosis [14]. Diffusion-weighted MRI (DWI) is a technique based on altered diffusion of water protons in fibrotic tissue [15] which provides insight into liver fibrosis distribution, with apparent diffusion coefficient (ADC) measurements in each liver segment. Regarding previous studies which demonstrated high sensitivity and high specificity of DWI in liver fibrosis staging in cholestatic liver diseases, this sequence should be part of the standard MRI protocol in the evaluation of PBC patients [13]. Conventional MRI sequences are used for long term follow-up and monitoring disease progression with early detection of complications such as hepatocellular carcinoma (HCC) and portal hypertension [16].

Although the end stage of all chronic liver diseases is cirrhosis, there are some MRI features which favor the diagnosis of PBC. Thus, perivascular cuffing, which represents periportal edema, inflammatory cell infiltration and dilatation of lymph vessels in portal triads seen as T2-weighted periportal hyperintensity is frequently seen in PBC (Fig. 1). The incidence of this finding was reported to be 87% in early stage and 66.7% in advanced stages, suggesting that inflammation in periportal spaces persists with disease progression [16, 17]. A characteristic MRI feature for PBC is the "periportal halo sign" which was first described by Wenzel et al. [18] as a rounded lesion, 5mm-1cm in size, centered on portal venous

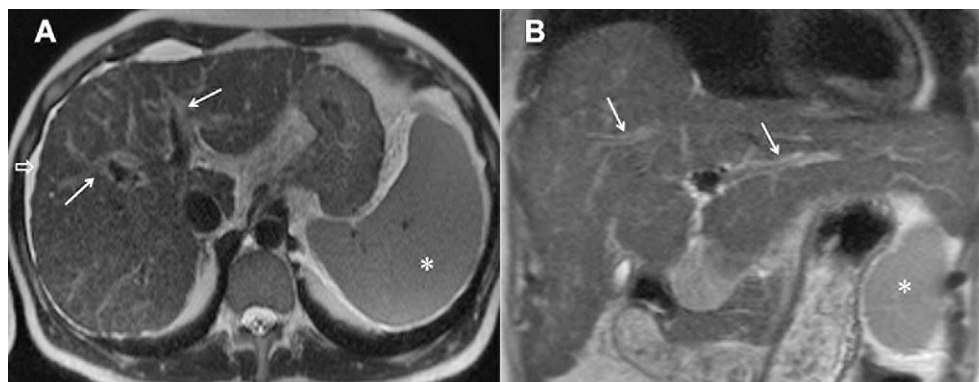


Fig. 1. Periportal hyperintensity in primary biliary cirrhosis. Axial T2-weighted image depicts periportal hyperintensity around medium-sized portal triads (arrows) in a 55-year old female patient with micronodular cirrhosis (lace-like fibrosis) (open arrow). Note also splenomegaly (asterisk) and small amount of free fluid around spleen (A). Coronal T2-weighted MR image in another 47-year old PBC patient shows periportal hyperintensity (arrows) and diffuse hepatomegaly as the most common morphological liver change in PBC. Note also the "kissing sign" (asterisk on the spleen)(B).

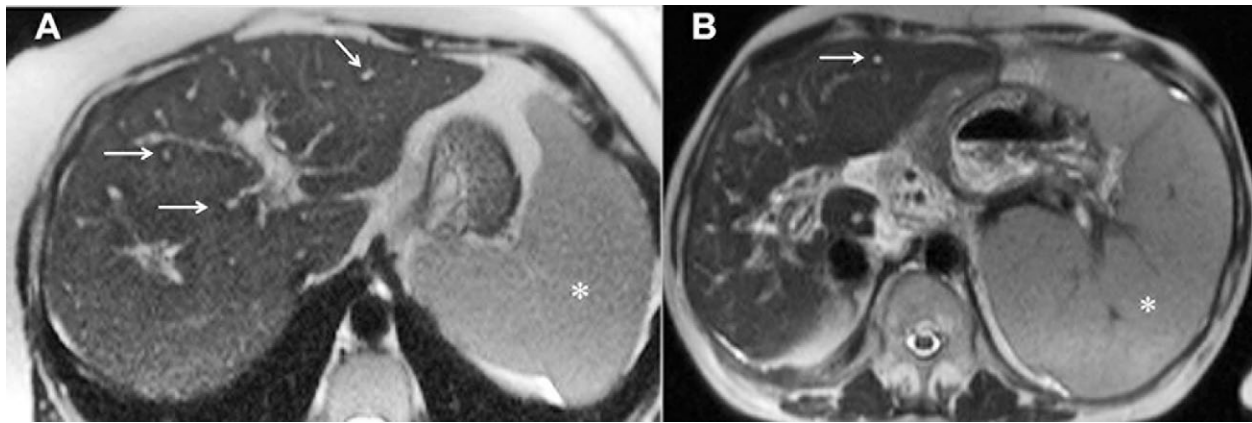


Fig. 2. Periportal halo sign in primary biliary cirrhosis. Axial T2-weighted image shows periportal halo sign as hypointense areas around portal veins (arrows) in a 63-year old woman at cirrhosis stage (A). Periportal halo sign (arrow) in a 58-year old PBC patient (B). Note also splenomegaly (asterisk) (A, B).

branches, without mass effect (Fig. 2). It results from deposition of fibrous tissue and hepatocellular parenchymal extinction around the portal triads, seen as an area of hypointensity on both T1- and T2-weighted MR images most commonly in advanced disease. Nevertheless, due to the inhomogeneous distribution of liver fibrosis, both periportal hyperintensity and periportal halo signs could be seen in the same patient [17]. Abdominal lymphadenopathy (enlarged lymph nodes in porta hepatis, gastrohepatic ligament and upper retroperitoneal space) is a frequent finding in PBC patients, observed in up to 88% of patients in all histological stages [19]. Concerning morphological liver changes, diffuse hepatomegaly (Fig. 1B) is the most common pattern, which can also be found in end-stage disease [20]. Patients with PBC usually develop micronodular or lacelike liver fibrosis (Fig. 1A), as was observed in the study by Ito et al. [21].

In the majority of the patients with PBC, cholangiograms may be normal especially in the early stages of the disease (Fig. 3A) [20]. With disease progression to cirrhosis, intrahepatic bile ducts become irregular with pruning, leading eventually to vanishing bile duct syndrome (Fig. 3B) [22]. On both endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiography (MRCP), most of the peripheral branches of the intrahepatic bile ducts cannot be visualized, while medium sized bile ducts present with decrease in caliber and irregularity. In the case of focal atrophy, the bile ducts in the atrophic segment will become crowded

[20]. These findings could be explained pathologically by destruction and disappearance mainly of small intrahepatic bile ducts in PBC. Although MRCP is not a necessary diagnostic imaging procedure for PBC, it has an important role in the differential diagnosis with PSC, since clinically both entities show chronic cholestatic features. While PSC is characterized by irregular stricturing and dilatation of the intrahepatic and extrahepatic biliary tree with “beaded” appearance, these segmental abnormalities are not seen in PBC.

Complications, therapy and prognosis

The signs of portal hypertension (ascites, splenomegaly, portosystemic collaterals and portal vein thrombosis) are common MRI findings in PBC patients [16] and occur early in the course of the disease. In addition, severe splenomegaly is present in patients with PBC, even in those noncirrhotic, probably due to immunological disorders and prolonged portal hypertension [23]. The incidence of HCC in PBC patients with end-stage disease is approximately 10%, with 4.1% in women and 20% in men. Even though HCC is not as frequent as in the cirrhosis caused by alcohol or viral hepatitis, all PBC patients should be under regular follow up especially if other risk factors for HCC are present [24].

Primary biliary cirrhosis is a slow progressive disease that advances variably in 10 to 20 years [25]. The majority of asymptomatic patients develop symptoms in 2–4 years [26]. Without prompt treatment, the disease progresses to cirrhosis

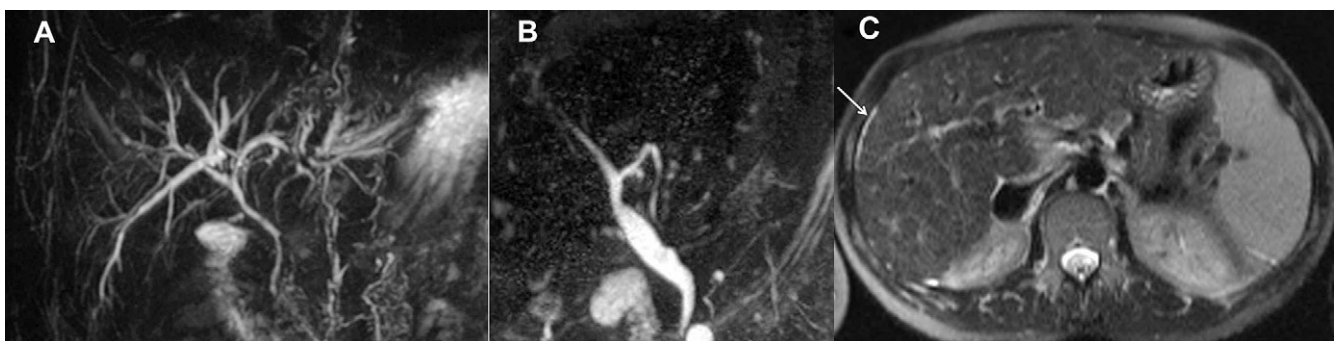


Fig. 3. MRCP findings in primary biliary cirrhosis. Thick slab MRCP shows normal intrahepatic biliary ducts in an asymptomatic patient (A). MRCP in a 58-year old woman with advanced disease shows reduction and obliteration of peripheral intrahepatic ducts as a sign of vanishing bile duct syndrome (B). Corresponding T2-weighted image in the same patient demonstrating end-stage micronodular liver cirrhosis (arrow) (C).

in 4–6 years. Median survival time without liver transplantation has been reported to be 9.3 years [27]. Liver transplantation remains the only curative treatment for patients with advanced PBC with 1- and 5-year survival of 85% and 72%, respectively [28, 29]. Recurrence of PBC after liver transplantation has been described in 9 to 30% of patients, with usually a mild course under immunosuppressive treatment [30]. To date, the reasons for recurrence have not been elucidated, and risk factors such as the age of the recipient and the immunosuppression regimen remain controversial [31, 32].

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis is a chronic inflammatory large duct cholangiopathy resulting in fibrotic biliary duct strictures, cholestasis, and biliary cirrhosis. The prevalence of PSC is 0 to 16.2 per 100,000 people, with a rising tendency either due to increased disease awareness or new environmental factors leading to a true increase [33]. Primary sclerosing cholangitis typically occurs in young and middle-aged men with an age of onset 30-40 years [34]. There is a strong association between PSC and inflammatory bowel disease (IBD). Approximately 70-80% of the patients with PSC develop IBD during the life, of which 87% have ulcerative colitis and 13% have Crohn's disease, while the incidence of PSC in IBD patients is 4% [35]. Primary sclerosing cholangitis typically progresses slowly over 10–15 years, eventually leading to biliary cirrhosis and death due to decompensated liver disease in the majority of patients. Moreover, the long-standing PSC is associated with serious complications such as hepatic osteodystrophy, development of dominant bile duct strictures, recurrent cholangitis, and disease-associated malignancies including cholangiocarcinoma (CCC) [36]. Although the etiopathogenesis of PSC is still unclear, it is widely accepted that the interaction of different autoimmune, genetic and environmental factors is responsible for the changes occurring in PSC [37].

Diagnosis and imaging features

The diagnosis of PSC is usually made on the basis of clinical, biochemical and cholangiography findings [38]. Primary sclerosing cholangitis might be discovered in asymptomatic patients during routine examination and detection of cholestatic biochemical profile with alkaline phosphatase levels

more than three times higher than the normal limit. In all patients with a clinical doubt of PSC, further cholangiographic examination should be performed [39]. According to the latest recommendations of the American Association for the Study of Liver Diseases (AASLD) and the European Association of the Study of the Liver (EASL) guidelines, MRCP is the first line modality for investigating bile duct abnormalities in PSC patients [40, 41]. MRCP provides non-invasive insight into bile duct abnormalities without radiation exposure. Moreover, MRCP allows for visualization of small ducts proximal to tight strictures, which are often not visualized during ERCP [42]. Comparable to ERCP, sensitivity and specificity of MRCP is 88% and 99%, respectively [43]. However, when there is clinical suspicion with negative or non-diagnostic MRCP findings, ERCP should be performed. In addition, ERCP is also a therapeutic procedure with balloon dilatation or stenting possibilities, but with post procedural complications ranging from 3-8% [44], and which allows for histological sampling.

Liver biopsy is not a necessary procedure for the diagnosis of PSC [45]. Primary sclerosing cholangitis is characterized by concentric periductal fibrosis which progresses gradually and results in obliteration and destruction mostly of medium- and large-sized bile ducts [46]. However, these changes are not specific and must be evaluated only together with clinical and cholangiographic findings. Biopsy is necessary when a small bile duct type of PSC is suspected and when a patient presents with cholestatic disease but shows normal cholangiogram and a negative AMA profile [47].

Diffuse involvement of both intrahepatic and extrahepatic bile ducts is the most common PSC manifestation, seen in 75% of patients. Isolated intrahepatic bile duct involvement is observed in 15% of patients, while only extrahepatic bile duct affection is the least common pattern and can be seen in 10% of patients [48]. Cholangiographic findings in PSC patients differ among particular disease stages. The early stage is characterized by multiple annular or short segmental strictures (1-2 mm) with slightly dilated ducts among them which can create “beaded” appearance (Fig. 4) [49, 50]. Strictures are usually seen at the bile duct bifurcation. With disease progression small peripheral ducts can become completely obliterated with “pruned tree” appearance on MRCP (Fig. 5) [51]. Moreover, the angles among peripheral and central bile ducts become obtuse. One of the major characteristics of PSC is that the bile duct dilatation is subtle, although there are many strictures [52]. This could be

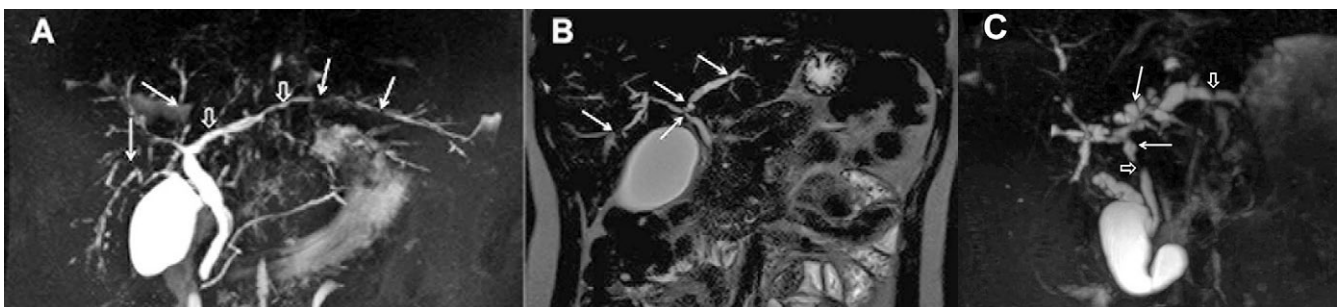


Fig. 4. MRCP image shows classical beaded appearance of bile ducts – multiple strictures (arrows) and focal luminal dilatation (open arrows) predominantly in the left hepatic duct in a 35-year old man with primary sclerosing cholangitis (A). PSC in another 38-year old patient reveals multiple short segmental and annular strictures (arrows) with slightly dilated bile ducts (B). Diverticular outpouching (arrows) and webs (open arrows) predominantly along left hepatic duct in the third patient (C).

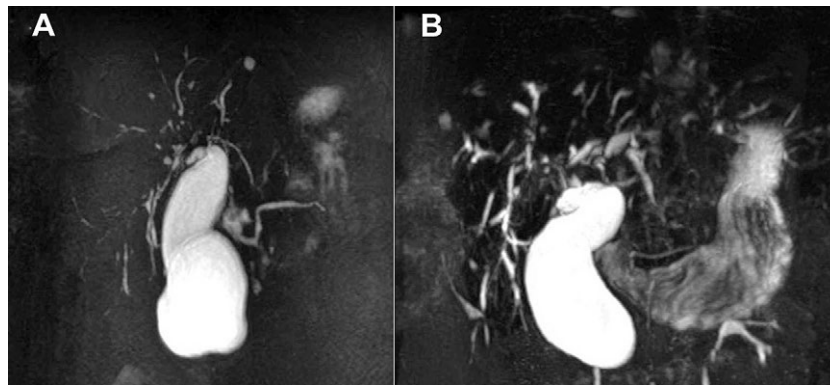


Fig. 5. Advanced primary sclerosing cholangitis with obliterated peripheral bile ducts resulting in “pruned tree” appearance. MRCP in a 33-year old man with long-standing PSC (A). MRCP in another 44-year old patient with PSC (B).

explained by the fact that periductal inflammation and fibrosis do not allow significant dilatation. If significant dilatation of proximal bile ducts is seen in a PSC patient, then some other process should be suspected such as bacterial cholangitis or CCC. Other MRCP findings include webs, diverticula (Fig. 4C), and pigmented stones. Webs are defined as focal 1-2 mm thick areas of incomplete circumferential narrowing. Webs and diverticula are not characteristic findings for PSC and could also be seen in traumatic or inflammatory processes of the bile duct wall [53].

Besides ductal changes, MRI also provides insight into parenchymal liver changes in PSC. Among many nonspecific signs, caudate lobe hypertrophy and spherical liver shape due to atrophy of left lateral segments and posterior segments of the right lobe are considered characteristic for PSC [54, 55]. It is hypothesized that the autoimmune process spares bile ducts in the caudate lobe which leads to its compensatory hypertrophy. This is also seen in other cirrhotic livers, since the caudate lobe has its own venous, lymphatic and biliary drainage. The most common type of liver cirrhosis in PSC patients is macronodular cirrhosis seen in more than 50% of patients [51]. Large regenerative nodules are usually located in the central liver parts. Peripheral wedge-shaped slightly T2-weighted hyperintense areas (Fig. 6A) are also frequently seen in PSC patients [56]. This finding could be explained by vascular or lymphatic drainage impairment caused by periductal inflammation of segmental bile ducts. Although segmental

atrophy and scarring occur proximal to chronically obstructed bile ducts, these peripheral areas display hyperintensity on T2-weighted images due to increased free water content. Moreover, increased enhancement on arterial phase with persistent increased signal intensity on delayed contrast-enhanced MR phases in a patchy or segmental pattern (Fig. 6B, C) could be seen corresponding to T2-weighted hyperintense regions. Due to the inflammatory process, biliary wall thickening and increased mural enhancement could be observed after intravenous contrast agent administration. In addition, in PSC hilar lymphadenopathy can be detected in up to 33% of the patients [54]. Furthermore, periportal hyperintensity is commonly present. However, these findings are not specific for PSC but are also seen in cirrhosis with other etiologies.

Complications, therapy and prognosis

Cholangiocarcinoma is the most serious complication of long-standing PSC seen in up to 10-15% of patients [57]. The tumor most frequently develops on primary biliary confluence presenting as an infiltrative T1-weighted hypointense mass, slightly T2-weighted hyperintense with progressive enhancement in post-contrast MRI studies (Fig. 7). Nevertheless, the recognition of CCC in PSC patients can be very difficult since both benign dominant strictures and malignant strictures may have similar cholangiographic presentation [58]. If the symptoms in the PSC patient suddenly worsen with cholestasis and weight loss, CCC should be suspected. On MRI,

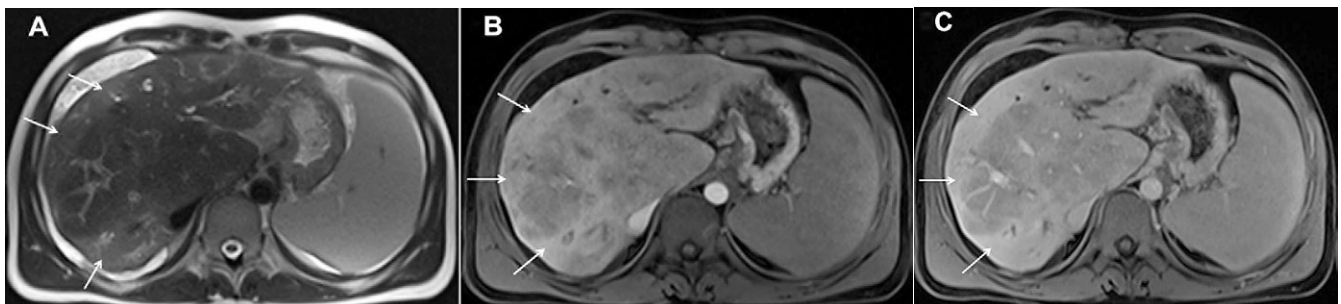


Fig. 6. Primary sclerosing cholangitis in a 44-year old man. Axial T2-weighted image shows increased signal in peripheral, atrophic regions in the right liver lobe (arrows), corresponding to areas of parenchymal inflammation, and increased water content (A). Axial 3-dimensional gradient-echo (GRE) VIBE (volumetric interpolated breath-hold examination) image in the same patient obtained after i.v. administration of gadolinium chelates during arterial phase (B) and portal-venous phase (C) shows increased enhancement of peripheral areas of liver (arrows) representing intrahepatic perfusion changes.

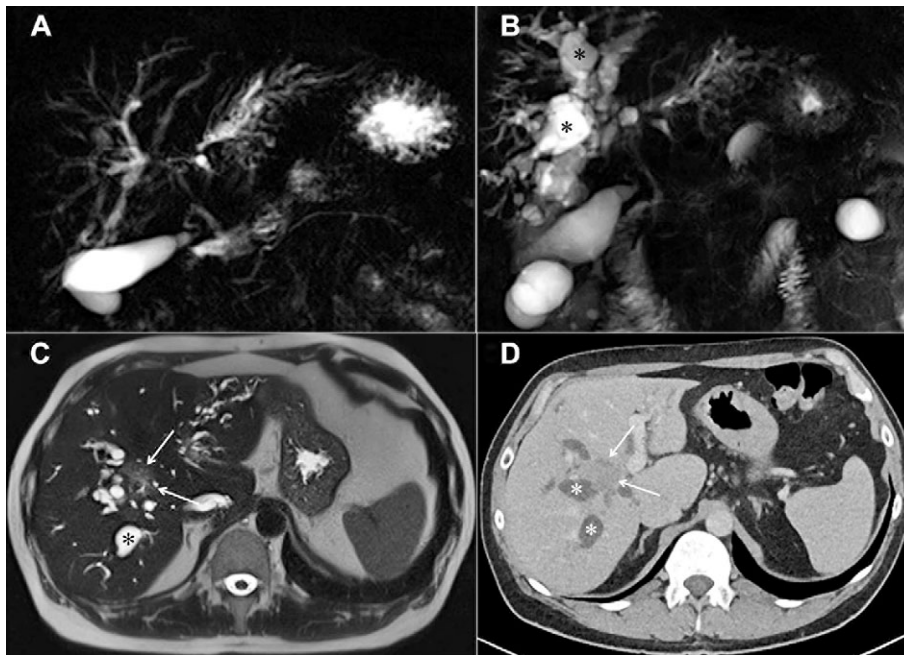


Fig. 7. Cholangiocellular carcinoma in a 52-year old man with primary sclerosing cholangitis. Thick slab MRCP demonstrates multifocal alternating strictures and dilations of intrahepatic bile ducts (A). Follow MR examination after 5 years reveals worsening of dilatation (asterisk) in the right liver lobe (B). Axial T2-weighted image (C) in the same patient shows slightly hyperintense soft tissue mass (arrows) with intrahepatic bile duct dilatation (asterisk) in the right liver lobe, compatible with intrahepatic CCC. The corresponding CT image obtained in portal-venous phase shows the typical hypovascular enhancement of CCC (arrows) in comparison to normal liver parenchyma and bile duct dilatation (asterisks) (D).

a rapid evolution of strictures in follow-up studies, proximal bile duct dilatation, and/or polypoid masses should suggest CCC development. In order to detect CCC in an early stage, regular screening of PSC patients is proposed with CA 19-9 measurements every six months and MRCP every year [59].

The natural history of PSC is highly variable, with reported average survival rates from diagnosis to death or liver transplantation ranging from 12–18 years [60]. Liver transplantation remains the only life-extending therapeutic approach for patients with end-stage PSC with a five year post-transplant survival of 75–85% [61]. Nevertheless, recurrence of PSC occurs in up to 25% of patients 5 to 10 years after liver transplantation [62]. Recurrent PSC after liver transplantation is very difficult to diagnose, since there are a variety of causes responsible for post-transplant biliary strictures, including ischemia, rejection, allograft reperfusion injury etc. [63]. The majority of patients who have undergone orthotopic liver transplantation for PSC usually have a choledochojejunostomy with a Roux loop which precludes post-transplant ERCP, and the diagnosis of recurrent disease can be made only by percutaneous cholangiography, graft histology, or least invasively by using MRCP [61]. Thus, recently MRCP has been recommended as a preferred imaging modality in diagnosing biliary complications following orthotopic liver transplantation [64]. The diagnosis of recurrent PSC is possible only in the case of the detection of non-anastomotic strictures occurring three months after liver transplantation, confirmed PSC diagnosis in the native liver, and exclusion of other causes of biliary strictures [65, 66]. Moreover, the differential diagnosis between chronic rejection

and recurrence is still challenging, but some imaging features have been previously described [67]. The liver in recurrent PSC is usually enlarged, fibrotic with slightly nodular contour, while in chronic rejection it is usually normal in size. MRCP in recurrent disease reveals multiple non-anastomotic strictures with slightly dilated bile ducts among them (Fig. 8). In contrast, the cholangiogram in patients with chronic rejection depicts pruning of the peripheral biliary tree due to peripheral arterial insufficiency and chronic ischemia. In recurrent PSC, hilar lymphadenopathy can be seen similar to native PSC, while it is uncommon in chronic rejection. If differential diagnosis cannot be made using MRCP, liver biopsy is suggested.



Fig. 8. Recurrent primary sclerosing cholangitis in a 43-year old patient 3 years after liver transplantation. Thick slab MRCP demonstrates multiple diffuse segmental bile duct strictures (arrows) with moderate luminal dilatation.

CONCLUSIONS

Primary biliary cirrhosis and PSC are immune-mediated chronic cholestatic diseases, both characterized by cholangiocyte injury, however, on a different location along the axis of biliary tract. While in PBC small bile ducts are progressively destroyed, in PSC mainly medium sized and large bile ducts are affected. Although PBC and PSC differ in their clinical and imaging characteristics, they both lead to liver cirrhosis. Periportal halo sign, “lace-like fibrosis”, and portal lymphadenopathy are the most specific MRI features for PBC. In addition, normal cholangiogram or a vanishing bile duct appearance on MRCP indicates PBC in a patient with cholestatic biochemical profile and negative AMA. New MRI techniques, such as DWI, allow for the non-invasive measurement of liver fibrosis and thus eliminate the need for liver biopsy. Characteristic MRCP features of PSC include multiple diffuse annular or segmental strictures, with slight luminal dilatation among them. In a long-standing disease a peripheral obliteration and reduction of bile ducts can occur resulting in a “pruned tree” appearance. This cholangiographic image is sufficient for PSC diagnosis in clinically suspected patients.

Conflicts of interest: No conflict to declare.

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