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Update

Primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is defined as a disease with inflammation and obliterative fibrosis usually affecting both the intrahepatic and extrahepatic portions of the biliary tree. PSC is most often a slowly progressive disease that frequently results in cirrhosis, portal hypertension, and premature death due to liver failure [1, 2]. The present criteria for diagnosis of PSC are summarized in Table 1 [3]. Approximately 71% of patients with PSC have inflammatory bowel disease, usually ulcerative colitis, and rarely Crohn's disease [4, 5]. Because clinical, biochemical, and hepatic histologic findings in PSC patients are, for the most part, nonspecific cholangiography has become the gold standard technique for diagnosing this disease [1–5]. Given the growing number of conditions that have been recognized to cause sclerosing cholangitis (i.e., secondary sclerosing cholangitis), it is important to exclude each of these etiologies carefully before establishing a diagnosis of the primary variety, as the treatment and prognosis of these entities vary. Confusion can result in patients with coexisting diseases that appeared to develop as a result of PSC, such as cholangiocarcinoma or biliary stone disease [3]. Detection of advanced disease, manifested by signs of portal hypertension due to secondary biliary cirrhosis, is important, as it may help to select patients for liver transplantation. This article reviews the role of imaging techniques with regard to the diagnosis and follow-up of PSC.

Cholangiography

Cholangiography, usually endoscopic but occasionally percutaneous, is considered the gold standard technique

for the diagnosis of PSC [1–5]. Cholangiograms obtained by endoscopic retrograde cholangiopancreatography (ERCP) with a catheter at the papilla rarely provide adequate detail of the intrahepatic ducts; contrast spills into the gallbladder and the pancreas. Good intrahepatic studies are best obtained by advancing the catheter deeply to a position above the cystic duct, which may require use of a balloon occlusion technique. The diagnosis is missed in some patients with isolated intrahepatic disease unless these techniques are used [6]. The radiologic appearances of PSC represent a broad spectrum of cholangiographic features [7–9]. The gallbladder and cystic duct are usually spared. Multifocal strictures involving both intra- and extrahepatic bile ducts are most commonly seen; they are usually diffusely distributed and are short and annular, alternating with normal or slightly dilated segments, producing a beaded appearance (Fig. 1). Short band-like strictures occur in most patients.

Biliary tree diverticula (Fig. 2) and webs (short band-like strictures) have been considered by several authors to be specific cholangiographic features of PSC [2, 5, 7, 9]. The experience of other authors suggests, however, that these findings can be seen, though rarely, in patients without PSC [10]. In a review of 861 ERCP studies, 32 cases of webs or diverticula were found: 9 patients with well documented PSC, 2 with uncertain diagnosis, and 21 without PSC. All 21 patients without PSC had other biliary abnormalities, including common bile duct (CBD) stones or cholangitis ($n = 11$), post-operative stricture ($n = 4$), bile duct stent and balloon dilatation ($n = 3$), malignant stricture ($n = 2$), and choledochoduodenostomy ($n = 1$). The appearances of the individual webs and diverticula were indistinguishable from those seen in the PSC group [10].

In a small number of cases only the intrahepatic or extrahepatic ducts are involved [7–9]. When only intrahepatic duct involvement is demonstrated, differentiation must be made from primary biliary cirrhosis. The

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Table 1. Criteria for diagnosis of PSC

1. Presence of typical cholangiographic abnormalities of PSC (involving bile ducts segmentally or extensively)
2. Compatible clinical, biochemical, and hepatic histologic findings (recognizing that they are frequently nonspecific)
3. Exclude the following in most instances
 - a. Biliary calculi (unless related to stasis)
 - b. Biliary tract surgery (other than simple cholecystectomy)
 - c. Congenital abnormalities of the biliary tract
 - d. AIDS-associated cholangiopathy
 - e. Ischemic strictures
 - f. Bile duct neoplasms (unless PSC previously established)
 - g. Exposure to irritant chemicals (e.g., floxuridine, formalin)
 - h. Evidence of another type of liver disease, such as primary biliary cirrhosis or chronic active hepatitis

Reprinted from [3], with permission
PSC, primary sclerosing cholangitis

latter can be differentiated clinically from PSC. Primary biliary cirrhosis is a disease of young women with histologic signs of nonsuppurative cholangitis and the presence of high titers of antibodies in the blood. The extrahepatic bile ducts are not affected in this disease. PSC shows marked male predominance; most patients have ulcerative colitis, and serologic markers are absent or present in low titers. In cases of segmental or diffuse stenosis of the CBD, differentiation from cholangiocarcinoma may be difficult, especially when the intrahepatic ductal system is not involved. Extensive dilatation of the intrahepatic ductal system is more often seen with carcinoma and is uncommon with PSC. However, cholangiocarcinoma must be considered when there is stenosis of the extrahepatic duct; brush cytology or, when negative, biopsy may be necessary to exclude it [9].

Because PSC may be predisposed to malignant change, the possibility of malignancy must be considered during initial presentation as well as at follow-up. Sudden worsening of jaundice should raise the possibility of the development of cholangiocarcinoma. Cholangiographic findings that suggest malignant degeneration include markedly dilated ducts or ductal segments, the presence of a polypoid mass ≥ 1 cm in diameter, and progressive stricture formation or ductal dilatation [11]. Comparison with previous ERCP results is essential to signal the presence of complicating cholangiocarcinoma because with PSC uncomplicated by malignancy the cholangiographic appearance frequently remains static for years [9].

Cholangiographic features of PSC can be used to predict clinical outcome. In a study of 129 patients, high grade strictures and diffuse strictures of the intrahepatic ducts were found to be indicators of a poor prognosis of PSC and were more predictive of a poor prognosis than was extrahepatic duct disease [12]. High grade intrahepatic ductal strictures ($>75\%$ narrowing) were associated with a 19% decrease in 3-

year survival ($p = 0.05$) compared with lower grade strictures. Diffuse intrahepatic strictures (involving $>25\%$ of the ducts) were associated with a 16% decrease in 3-year survival compared with lower grade strictures. Statistically insignificant ($p > 0.5$) but measurable decreases in survival were observed with high grade extrahepatic ductal strictures, diffuse involvement of the extrahepatic ducts, long confluent strictures anywhere in the biliary tree, and marked dilatation of the intrahepatic ducts [12].

The quality of cholangiography is crucial to the detection of biliary debris, which is present in some patients with strictures. Passage of debris may be an important cause for intermittent attacks of clinical cholangitis and forms a justification for mechanical treatment [6]. Deterioration in liver function may be aggravated or accelerated by back pressure from dominant strictures, debris, and stone formation. Biliary tract calculi are a part of the spectrum of otherwise typical PSC, and so their presence should not necessarily exclude the diagnosis. Calculi should be suspected whenever symptoms such as pain, jaundice, and especially ascending cholangitis develop in a patient with known PSC. Biliary stasis secondary to multiple strictures may account for calculus formation [13]. Relief of the obstruction may halt, delay, or even reverse progression to cirrhosis or liver failure [6]. In some cases a localized high grade stricture (dominant stricture) may be superimposed on the diffuse changes. About 10% of patients with PSC show a dominant stricture that may be located at any level from the intrahepatic ducts to the distal CBD [14]. When it occurs, it may be associated with jaundice or bacterial cholangitis, or it may be asymptomatic. Percutaneous balloon dilatation is a beneficial, relatively safe alternative to surgical techniques in symptomatic patients with PSC who have a dominant stricture.

In a previous study the number of episodes of cholangitis was significantly decreased in a series of 14 patients who underwent percutaneous balloon dilatation of dominant strictures [14]. Endoscopic stent placement was beneficial in 13 of 16 patients with PSC [15].

Nonsurgical intervention is appropriate in symptomatic patients with PSC who have impressive intra- or extrahepatic strictures (especially with debris). The endoscopic approach is preferred in cases of distal strictures, as it does not involve the trauma of liver puncture or the use of prolonged external drainage [6]. The percutaneous approach is indicated for dominant proximal strictures.

Ultrasonography

Endoscopic retrograde cholangiography (ERC) and percutaneous transhepatic cholangiography (PTC) are inva-

Fig. 1. Endoscopic retrograde cholangiogram shows typical beaded appearance of the intrahepatic ducts with multiple short band-like strictures and saccular dilations. The extrahepatic ducts are also involved: The common hepatic duct and common bile duct demonstrate segmental stenoses. (Reproduced from [9], with permission)

Fig. 2. Endoscopic retrograde cholangiogram shows a highly irregular margin of the common bile duct with diverticulum-like outpouchings. (Reproduced from [9], with permission)

sive techniques that are impractical for screening patients who present with nonspecific hepatobiliary complaints. Ultrasonography (US) can serve as a noninvasive screening alternative for the diagnosis of sclerosing cholangitis.

Few reports regarding the sonographic manifestations of PSC are available [16–20]. An awareness of the sonographic findings associated with PSC is important because patients may initially undergo sonography for evaluation of hepatobiliary symptoms and for follow-up once the diagnosis is established. Sonographic findings of PSC reflect the changes seen on CT and cholangiography. Because of the sclerotic nature of PSC, marked dilatation of the intrahepatic ducts is usually absent. Discontinuous dilatation or nonvisualization of the intrahepatic ducts is usually found. The major limitation of ultrasonography is its inability to exclude intrahepatic ductal disease. In a prospective study of 23 patients with PSC, 6 patients with multiple strictures and pruning, but without dilatations on ERC, sonography showed no intrahepatic duct abnormalities [18]. With meticulous technique ultrasonography may demonstrate extrahepatic duct disease adequately. Mural thickening of the CBD was demonstrated in 17 of 18 cases with a corresponding stenosis on ERC in a previous study (Figs. 3 and 4) [18]. In the appropriate clinical setting, as in patients with ulcerative colitis and hepatobiliary symptoms, the sonographic finding of CBD wall thickening is highly suggestive of PSC [16–19]. However, when taken in isolation, thickening of the wall of the CBD is a nonspecific finding and may also be caused by cholangiocarcinoma, other causes of sclerosing chol-

angitis, choledocholithiasis, AIDS-related cholangitis, oriental cholangiohepatitis, and pancreatitis [21–23]. In a study of 121 patients with well documented PSC, 41% had intrinsic abnormalities of the gallbladder including gallstones (26%), PSC involving the gallbladder (15%), and benign or malignant neoplasms (4%) [20]. US is also valuable for demonstrating advanced disease. It may demonstrate hepatic morphologic changes suggestive of secondary biliary cirrhosis and portal hypertension. Findings include hepatomegaly, splenomegaly, and portal vein abnormalities (flow decreased, thrombosis, cavernous transformation, collaterals, and ascites) [19].

Two patterns of hepatic parenchymal change may be demonstrated with US [18, 19]. Diffuse parenchymal change (increased echogenicity and loss of fine detail) has an appearance similar to that seen with other forms of cirrhosis and chronic liver disease and is likely due to secondary biliary cirrhosis [19].

Focal lesions consist of increased periportal or intrahepatic echogenicity. Increased periportal echogenicity most likely represents periportal fibrosis, which must be differentiated from periportal fibrosis due to schistosomiasis [18, 19]. Intrahepatic hyperechoic lesions are probably due to pericholangitis, fibrotic areas around the biliary tree, or some stage of secondary biliary cirrhosis [19]. The differential diagnosis of these focal intrahepatic hyperechoic lesions includes hemangiomas, metastases, oriental cholangiohepatitis, and cholangiocarcinomas [19, 23]. Because cholangiocarcinoma can occur in patients with long-standing PSC, a biopsy may be needed to exclude it [19].

Fig. 3. Longitudinal oblique sonogram of the common bile duct (*D*) shows wall thickening and luminal narrowing (*arrow*). *PV*, portal vein.

Fig. 4. Magnified transverse sonogram shows wall thickening of the common bile duct (*arrow*) and narrowing of its lumen.

Fig. 5. CT of a patient with long-standing primary sclerosing cholangitis shows the nodular appearance of the enlarged liver due to secondary biliary cirrhosis.

Computed tomography

Awareness of the CT findings in PSC is important because patients may initially undergo CT scanning for evaluation of hepatobiliary symptoms and for follow-up once the diagnosis is established. In 16 of 19 patients with extrahepatic duct disease diagnosed by cholangiography, CT demonstrated abnormalities of the common hepatic duct or CBD, including duct stenosis, mural nodularity, duct dilatation, wall thickening, and mural enhancement. CT demonstrated intrahepatic disease in all 20 cases of PSC, including duct dilatation, duct stenosis, pruning, and beading. CT was superior to cholangiography for characterizing the status of the intrahepatic duct system in 11 of 20 cases. In addition, CT demonstrated extrabiliary complications of PSC in 12 cases and superimposed cholangiocarcinoma in 3 cases [24]. The finding of focal discontinuous areas of minimal intrahepatic dilatation without an associated mass lesion seems to be highly suggestive of sclerosing cholangitis [24]. Only the rare, diffuse form of cholangiocarcinoma would be likely to produce a similar CT appearance [25]. CT, like US, may demonstrate signs of advanced disease, such as secondary biliary cirrhosis (Fig. 5).

Magnetic resonance imaging

Over the past few years, magnetic resonance cholangiography (MRC) has developed rapidly [26, 27]. MRC can potentially be used to screen patients for, or probably replace, ERCP and PTC, which are invasive techniques with a risk of bleeding, biliary sepsis, complications related to sedation, and anesthesia, and, in the case of ERCP, pancreatitis and aspiration [28]. However, MRC has not yet reached the high resolution of ERCP and PTC that is necessary to detect minor degrees of biliary duct dilatation and stenosis, as seen with PSC. Furthermore, the primary reason for performing an invasive technique such as ERCP or PTC is not merely diagnostic; it also can alleviate biliary obstruction in symptomatic patients by endoscopic or percutaneous intervention, which is of course not possible with MRC [28]. With further improvements in resolution, MRC can probably be used to diagnose PSC and to select patients for endoscopic or percutaneous intervention.

Conclusions

Endoscopic or percutaneous cholangiography remains the gold standard for diagnosing PSC. Cholangiographic fea-

tures of PSC can also be used to predict clinical outcome, guide interventional procedures (e.g., balloon dilatation of dominant strictures, stone extraction, or stent placement), and detect complicating cholangiocarcinoma. US and CT can serve as noninvasive screening alternatives for diagnosing PSC. Awareness of the US and CT findings of PSC is important because patients may initially have US or CT scanning for the evaluation of hepatobiliary symptoms and for follow-up once the diagnosis is established. MR cholangiography needs further improvement in resolution before it can detect the minor degrees of biliary ductal dilatation and stenoses encountered in PSC.

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