Abstract

Primary sclerosing cholangitis (PSC) is a chronic and progressive cholestatic liver disease that often leads to the development of cirrhosis. Complications of PSC include pruritus, fatigue, vitamin deficiencies, metabolic bone disease, dominant biliary strictures, gallstones, and hepatobiliary malignancies, most commonly cholangiocarcinoma (CCA). Despite the presumed autoimmune etiology of PSC, a clear benefit from immunosuppressive agents has not yet been established, and their use is limited by their side effects. Endoscopy is required in evaluation of biliary strictures in PSC to rule out the possibility of CCA. Liver transplantation is currently the only life-extending therapy for patients with end-stage disease. However, disease recurrence can be a source of morbidity and mortality as transplanted patients survive longer. Further studies are needed to develop an optimal therapeutic strategy for patients with PSC to decrease the incidence of complications of the disease, to decrease the need for transplantation, and to extend life expectancy.

Pathogenesis

The etiology and pathogenesis of PSC raise many unresolved questions, and PSC remains a scientific and clinical challenge to many experts. There is evidence supporting a genetic predisposition theory for PSC since PSC exhibits obvious familial and geographic clustering patterns with higher prevalence in Northern Europe (e.g. Norway, Sweden) and North America compared to Southern Europe and Asia. Many experts suggest that a combination of genetic and environmental factors are required for the development of PSC (e.g. vitamin D deficiency). The proportion and number of CD8+ T cells in the peripheral blood are decreased, and the CD4/CD8 ratio is increased in patients with autoimmune diseases, such as PSC. It has been proposed that deprivation of sunlight and vitamin D aggravates the genetically determined CD8+ T cell deficiency, thereby contributing to the high prevalence of autoimmune diseases. Recently, the rs738409 variant (I148 polymorphism), encoding an isoleucine-to-methionine substitution at position 148 in the adiponutrin/ palatin-like phospholipase-3(PNPLA3) gene, was identified as a male sex-specific disease modifier in patients with PSC and bile duct stenosis that impacted the disease course of PSC. Rs738409 is a missense variation (I148M) in PNPLA3. In a prospective cohort study of 468 German and Norwegian PSC
patients, 1148 polymorphism was associated with decreased survival in male patients with severe PSC and bile duct stenosis requiring endoscopic intervention. The association between PSC and inflammatory bowel disease (IBD) suggested that a common genetic agent or inflammatory pathway is possibly involved in the pathogenesis of both diseases. Some experts believe that the “leaky gut hypothesis” could explain this close link. An inflamed gut with concomitant induction of an inflammatory reaction concentrated in the portal region can lead to increased intestinal permeability with bacterial translocation into the portal venous system. Bacteria penetrate the damaged colonic mucosal layer during the acute inflammatory response, enter the liver, and stimulate the release of inflammatory mediators like chemokines/cytokines by Kupffer cells and macrophages. This can lead to cholangitis resulting in a wound healing process with subsequent concentric periductal fibrosis. Many studies hypothesize that in genetically susceptible individuals, bacterial antigens can trigger this immune reaction that is responsible for the development of PSC. However, these studies do not reveal any direct clinical evidence for increased portal vein bacteremia in PSC/IBD patients. Clinical trials which utilized antibiotics or antibiotics in combination with ursodeoxycholic acid, for the treatment of PSC demonstrated improved liver function tests but no effect on disease progression. Future studies are needed to determine if gut microbiome plays a role in the pathogenesis of PSC.

The presence of various autoantibodies, including perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) or antineutrophil antibodies (ANA), in a patient’s serum with PSC supports a role for autoimmunity in the pathogenesis of PSC. In general, there are two distinct staining patterns of ANCA, cytoplasmic (c-ANCA) and perinuclear (p-ANCA). P-ANCA can be further subdivided into so-called classical p-ANCA or atypical p-ANCA. Atypical p-ANCA appears to be specific for PSC with predominant IgG classes of antibodies (in more than 80% of PSC patients). Due to the overlap with autoimmune hepatitis and the lack of correlation with PSC activity, p-ANCA has a limited clinical value in PSC diagnosis. The identity of the specific autoantigen that causes atypical p-ANCA staining in PSC remains to be determined by future research.

### Diagnosis

#### Clinical features

Although approximately 15% to 55% of PSC patients are asymptomatic, they are at increased risk for developing symptoms over time. The clinical presentation is variable; typical symptoms include right upper quadrant abdominal discomfort, fatigue, pruritus, and weight loss. The most frequent abnormal physical exam findings are jaundice, hepatomegaly, and splenomegaly. Episodes of cholangitis (i.e. fever and chills) are infrequent features at initial presentation of PSC, especially in the absence of prior biliary surgery or instrumentation, such as ERCP. The diagnosis of PSC is typically made when incidental findings of persistent abnormal cholestatic liver function test are investigated. Approximately 60% to 80% of patients with PSC have concomitant IBD, most often ulcerative colitis (UC). Table 1 describes the prevalence of symptoms in several PSC studies.

#### Serum biochemical features:

Elevation of alkaline phosphatase is the most common biochemical abnormality and the hallmark of PSC. However, normal alkaline phosphatase activity does not exclude the diagnosis. Aminotransferase levels are also elevated in most patients, usually two to three times above the upper limit of the normal range. Although bilirubin levels are normal at diagnosis, an elevated total bilirubin is worrisome for advanced disease, superimposed cholecystolithiasis, or malignancy. There is no significant difference between serum chemistry profiles reported for asymptomatic and symptomatic patients. Normal albumin and prothrombin time, which reflect preserved hepatic synthetic function, are found in the majority of cases.

#### Serum serological features:

Testing for specific autoimmune antibodies is not helpful in the diagnosis of PSC, as multiple autoantibodies can be detected. Table 2 shows the prevalence of different autoantibodies in PSC patients. Elevations in IgG and IgM are observed in 45% to 80% of the cases. Antinuclear antibody and smooth muscle antibody can be found in 20% to 50% of cases, respectively. Antimitochondrial antibodies are rarely found in PSC patients. The clinical significance of antibodies to biliary and colonic antigens in patients with PSC and IBD is still unclear. Perinuclear antineutrophilic antibodies are detected in frequencies ranging from 30% to 80% but lack diagnostic specificity for PSC. The antiascardromyces cerevisiae antibody occurs in 50% of cases independent of IBD status.

#### Radiological modalities:

Transabdominal ultrasound (US) can identify bile duct wall thickening and/or focal bile duct dilatations but is usually

<table>
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<th>Table 1. Prevalence of PSC symptoms</th>
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<td>Symptoms</td>
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<tr>
<td>None</td>
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<tr>
<td>Fatigue</td>
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<td>Pruritus</td>
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<td>Jaundice</td>
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<td>Abdominal pain</td>
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<td>Fevers and chills</td>
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<tr>
<th>Table 2. Serum Autoantibodies in PSC</th>
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<td>Type of antibody</td>
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<td>-------------------------------------</td>
</tr>
<tr>
<td>Anti-neutrophil cytoplasmic antibody</td>
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<tr>
<td>Anti-nuclear antibody</td>
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<tr>
<td>Anti-smooth muscle antibody</td>
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<tr>
<td>Anti-endothelial cell antibody</td>
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<tr>
<td>Anti-cardiolipin antibody</td>
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<tr>
<td>Thyroglobulin</td>
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non-diagnostic and may be normal in PSC. One study reported that up to 41% of patients with PSC who underwent US examinations had some abnormal findings, such as wall thickening, gallbladder enlargement, gallstones, cholecystitis, or mass lesions. The findings on computed tomography (CT) cross-sectional or coronal imaging of the upper abdomen are non-specific. CT imaging with contrast enhancement can detect thickening of the bile ducts consistent with inflammation, saccular dilatations of the intrahepatic ducts, or heterogeneous bile duct dilatation. Additionally, CT can document the presence of any mass lesions or stigmata of portal hypertension, such as varices, splenomegaly, and ascites. Abdominal lymphadenopathy is a common finding in PSC and should not be over interpreted as metastases or a lymphoproliferative disorder.

Magnetic resonance cholangiography (MRC) is considered to be the "gold standard" for the non-invasive diagnosis of PSC and is the imaging modality of choice when PSC is suspected. It is a non-invasive test, and radiation exposure can be avoided. Characteristic cholangiographic findings include multifocal, short, annular strictures that alternate with normal or slightly dilated segments producing a "beaded" pattern. Segmental fibrosis of bile ducts with saccular dilatation of normal intervening areas results in the characteristic "beads-on-a-string" appearance identified in PSC patients. Long confluent strictures may also be observed, although these are concerning for the development of superimposed cholangiocarcinoma (CCA). Intrahepatic and extrahepatic duct involvement is universal in nearly all PSC patients.

**Endoscopic modalities:**

Endoscopic retrograde cholangiography (ERC) has been traditionally used in the diagnosis of PSC. ERC and MRC have comparable diagnostic accuracy, although the visualization of bile ducts with MRC may be less than optimal for certain patients. Despite the high sensitivity and specificity of MRC in the diagnosis of PSC (80% and 87% respectively), some patients with early changes of PSC may be missed by MRC. ERC has a significant role in excluding small duct PSC, whereas MRC may not be effective. It is worth mentioning that ERC is an invasive procedure that can be associated with potentially serious complications such as pancreatitis, and in rare cases, bacterial cholangitis. During ERC, a detailed cholangiographic examination of the extrahepatic and intrahepatic biliary tree needs to be performed in order to establish a diagnosis of large duct PSC. In a majority of cases, both the intrahepatic and extrahepatic bile ducts are involved. In 25% of patients, the disease only involves the intrahepatic ducts; rarely (5% of patients) the disease is limited to the extrahepatic ducts. In this case, the diagnosis should be made with adequate filling of the intrahepatic ducts in order to demonstrate PSC findings limited to the extrahepatic ducts. Occasionally, the gallbladder, cystic duct, and pancreatic duct may be involved in PSC patients as well.

**Histopathological features:**

Given the accuracy of cholangiography in diagnosing PSC, a liver biopsy is only required for assessing the stage of the disease. A retrospective study of 138 patients with cholangiographic features of PSC found that obtaining a liver biopsy rarely added any useful diagnostic information. The characteristic pathologic feature of PSC is concentric periductal fibrosis ("onion-skinning"). This progresses to a narrowing and then an obliteration of the small bile ducts, leaving bile duct scarring, which occurs in less than 15% of patients with PSC. In 1978, Ludwig et al. described the histological classification of PSC in four stages; stage one is cholangitis or portal hepatitis, stage two is periportal fibrosis or periportal hepatitis, stage three is septal fibrosis, bridging necrosis, or both, and stage four is biliary cirrhosis. In certain circumstances, liver biopsy could add value, especially in patients with cholestasis and IBD with normal cholangiographic findings. It can also be useful when diagnosing patients with small duct PSC with chronic cholestatic disease who present with very high transaminase levels and hypergammaglobulinemia.

**Other diseases that can mimic PSC:**

Table 3 highlights the differential diagnoses and variant syndromes of PSC.

**Management of PSC and its complications**

**Medical treatment**

Different forms of pharmacotherapy have been evaluated for PSC treatment. Unfortunately, no medical treatment for PSC has proven efficacy in randomized controlled studies. This might be secondary to the uncertainty regarding the pathogenesis of PSC and factors responsible for its progression. One of the first studied pharmacologic agents for PSC was ursodeoxycholic acid (UDCA), a drug which is efficacious in treating other cholestatic liver diseases. UDCA is a hydrophilic, dihydroxy-bile acid which is routinely used in the treatment of primary biliary cirrhosis (PBC). UDCA has been tested alone and in combination with corticosteroids or other immunosuppressant agents like methotrexate, budesonide, azathioprine, cyclosporine, mycophenolate mofetil, oral and transdermal nicotine, penicillamine, pentoxifylline, silymarin, tacrolimus, moexipril, and moexipril. A number of small trials using UDCA as treatment for PSC demonstrated biochemical and histological improvement with dosages of 10 to 15 mg/kg/day. A more substantial double-blinded placebo controlled trial recruited 105 patients and followed them for two to five years, using dosages of 13 to 15 mg/kg of UDCA. The results indicated improvement in serum liver tests, however, there was no improvement in symptoms and most importantly, there was no difference noted in the progression of PSC to cirrhosis. Higher doses of UDCA were subsequently studied on the basis that larger doses could provide sufficient enrichment of the bile acid pool in cases of cholestasis and enhance the potential immunomodulatory effect of the drug. However, the most
Pirfenidone is a known antifibrotic. The lifetime risk of developing CCA in PSC patients is 10% to 15%. Up to 50% of CCA cases are diagnosed simultaneously with PSC or within the first year of diagnosis of PSC, with an incidence rate of 0.6% to 1.5% each year thereafter. Median survival associated with CCA is only six months. Risk factors for developing CCA in PSC patients include elevated serum bilirubin, chronic ulcerative colitis with colorectal cancer or dysplasia, variceal bleeding, proctocolectomy, and polymorphisms of the natural killer group 2a (NKG2D) gene (encoding a protein involved in NK cell activity). The duration of PSC may not be a risk factor for the development of CCA, which is contrary to the risk factors of neoplasia in inflammatory bowel disease. It is suggested that dominant strictures, defined as a common bile duct stenosis with less than 1.5 mm diameter remaining in the common bile duct or a common hepatic duct stenosis close to the bifurcation leaving less than 1.0 mm diameter of the common hepatic duct, may serve as primary indicators of concomitant CCA. It is very challenging to distinguish between benign strictures from PSC activity and CCA as they can have similar characteristics on imaging. Although the appearance of a mass lesion is diagnostic, mass lesions are often not present in early stages of CCA.

ERCP is widely used to evaluate dominant strictures concerning for CCA in PSC patients. When a suspicious lesion or a narrowed duct is seen during an ERCP, brush cytology can be used to obtain a tissue diagnosis. Based on numerous studies, the sensitivities of brush cytology range from 53% to 68% with high specificity (97% to 100%) in the diagnosis of CCA. Fluorescence in situ hybridization (FISH) can be added to brush cytology in order to increase its sensitivity for detecting CCA. However, FISH has a lower specificity (88%) compared to brush cytology in evaluating strictures in PSC patients. Overall, FISH has been demonstrated to detect more patients with carcinoma than routine cytology and may significantly improve the chances of detecting malignancy of bile duct strictures at an early stage. A significant proportion of brushings was reported by pathologists as “atypical” or “suspicious for CCA”. In these situations, further investigations are warranted. Recently, the Atypical Biliary Brushing Score (ABBS) has been proposed to identify those patients at high risk for malignancy in the setting of an atypical brushing. This scoring system suggested that patients with atypical brushings can be further stratified into “high risk” and “lower risk” based on a variety of factors, such as age greater than 60, presence of PSC, elevated CA 19-9 above 300 U/ml, and the presence of distal CBD or hepatic duct stricture.

Single operator cholangioscopy (SOC) has been used to evaluate indeterminate strictures in PSC. SOC gives us the ability to obtain a biopsy of an indeterminate stricture under direct visualization (Fig.1). The accuracy of SOC in detecting malignant strictures is up to 87%. Endoscopic treatment: PSC patients are at risk for developing superimposed CCA. The life time risk of developing CCA in PSC patients is 10% to 15%. Up to 50% of CCA cases are diagnosed simultaneously with PSC or within the first year of diagnosis of PSC, with an incident rate of 0.6% to 1.5% each year thereafter. Median survival associated with CCA is only six months. Risk factors for developing CCA in PSC patients include elevated serum bilirubin, chronic ulcerative colitis with colorectal cancer or dysplasia, variceal bleeding, proctocolectomy, and polymorphisms of the natural killer group 2a (NKG2D) gene (encoding a protein involved in NK cell activity). The duration of PSC may not be a risk factor for the development of CCA, which is
EUS-FNA is a promising modality for the early detection of CCA in distal strictures when ERCP with brush biopsy is not diagnostic. Sensitivity of EUS-FNA is also found to be significantly higher in detecting a distal CCA compared to a proximal malignancy (81% versus 59%). The only concerning issue with EUS-FNA is the possibility of tumor seeding. Although the incidence is believed to be quite rare, some liver transplant centers might not consider patients who have had a transmural FNA of a primary CCA as transplant candidates due to concern for possible tumor seeding.

Currently, there are no evidence-based screening guidelines for CCA in PSC. Nevertheless, endoscopic surveillance is used at various institutions to enhance early detection of CCA in patients with PSC, which has been shown to improve the chance of early resection of the tumor or liver transplant and increase survival.

**Surgical treatment:**

Liver transplantation is the treatment of choice for patients with end-stage liver disease secondary to PSC. Liver transplantation should be considered in patients with PSC before the patient progresses to end-stage disease in order to enhance the long-term survival rate after liver transplantation. Unique liver transplant indications for patients with PSC include intractable pruritus, recurrent bacterial cholangitis, and CCA. Certain PSC patients with early stage CCA can benefit from liver transplantation. In the United States, patients with these unique indications are listed for liver transplantation in the regional review board appeal process established by the Liver and Intestinal Committee of United Network for Organ Sharing (UNOS). Liver transplantation for PSC is reported to have the highest patient survival rate. Some transplant centers report post-transplant survival rates of 90% to 97% at one year and 83% to 88% at five years. PSC liver transplant recipients may be more prone to acute and chronic cellular rejection, however, with the use of immunosuppressive therapy, acute cellular rejection (ACR) is usually manageable and chronic rejection is becoming increasingly rare. The PSC recurrence rate is 20% to 25% within five to ten years after the transplant. A history of ACR and presence of human leukocyte antigen (HLA)-DRB1*08 are associated with increased risk of recurrent PSC, suggesting an immunologic mechanism for this syndrome. The presence of CCA prior to liver transplantation is also significantly predictive of disease recurrence. Re-transplantation rates are reported to be higher for patients with PSC than for those with other diagnoses.

**Conflict of interest**

None

**Author contributions**

Writing and preparing the work presented in this paper (MS, CY, MOO), final reviewing of this article (MOO).

**References**


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