

A Review of the Challenges Associated with the Diagnosis and Therapy of Primary Sclerosing Cholangitis

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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.

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that predominantly affects young males and has a reported prevalence of up to 16.2 per 100,000.¹ PSC is

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Abbreviations: ABBS, Atypical Biliary Brushing Score; ACR, acute cellular rejection; ANA, antinuclear antibodies; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; CCA, cholangiocarcinoma; CT, computed tomography; ERC, endoscopic retrograde cholangiography; EUS, endoscopic ultrasound; FISH, fluorescence in situ hybridization; FNA, fine needle aspiration; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; IgG4, immunoglobulin G4; MRC, magnetic resonance cholangiography; NKG2D, natural killer group 2, member D; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; PBC, primary biliary cirrhosis; pCLE, probe-based confocal laser endomicroscopy; PNPLA3, palatin-like phospholipase-3; PSC, primary sclerosing cholangitis; SOC, single operator cholangioscopy; SSC, secondary sclerosing cholangitis; UC, ulcerative colitis; UDCA, ursodeoxycholic acid; UNOS, United Network for Organ Sharing; US, ultrasound.

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characterized by inflammation and fibrosis of both the intrahepatic and extrahepatic bile ducts² leading to the formation of multifocal bile duct strictures. PSC is an immune-mediated, progressive disorder that will eventually develop into cirrhosis, portal hypertension, and hepatic decompensation in the majority of patients.³ In contrast, the disease variant small duct PSC presents with typical cholestatic and histological features of PSC but with normal bile ducts on cholangiography.⁴ PSC overlaps diagnostically with many conditions that have features of both PSC and other immune-mediated liver diseases, including autoimmune hepatitis and autoimmune pancreatitis.⁵ Secondary sclerosing cholangitis (SSC) is characterized by a similar multifocal biliary stricturing process, but is due to identifiable causes such as long-term biliary obstruction, infection, or inflammation, leading to the destruction of bile ducts and secondary biliarycholangitis.⁶ Immunoglobulin G4 (IgG4)-positive sclerosing cholangitis might represent a separate entity from PSC.⁷

PSC is a potentially fatal disease with a poor prognosis and without an effective medical therapy. This article will summarize the challenges associated with the diagnosis and therapy of PSC and its complications.

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.⁸ Many experts suggest that a combination of genetic and environmental factors are required for the development of PSC (e.g. vitamin D deficiency).⁹ 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.¹⁰ 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.¹¹ Recently, the rs738409 variant (I148 polymorphism), encoding an isoleucine-to-methionine substitution at position 148 in the adiponutrin/ palatin-like phospholipase-3 (PNPLA3) gene,¹² 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 PNPLA3.¹³ In a prospective cohort study of 468 German and Norwegian PSC

patients, I148 polymorphism was associated with decreased survival in male patients with severe PSC and bile duct stenosis requiring endoscopic intervention.¹⁴ 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.¹⁵ 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.^{15,16} 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.^{17,18} Clinical trials which utilized antibiotics,^{19,20} or antibiotics in combination with ursodeoxycholic acid, for the treatment of PSC demonstrated improved liver function tests but no effect on disease progression.²¹ 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 antinuclear antibodies (ANA), in a patient's serum with PSC supports a role for autoimmunity in the pathogenesis of PSC.²² 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).²³ Due to the overlap with autoimmune hepatitis²⁴ 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,^{25,26} they are at increased risk for developing symptoms over time.²⁷ The clinical presentation is variable; typical symptoms include right upper quadrant abdominal discomfort, fatigue, pruritus, and weight loss.²⁸ 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).²⁹ Table 1 describes the prevalence of symptoms in several PSC studies.

Table 1. Prevalence of PSC symptoms

| Symptoms | Frequency % |
|-------------------|--------------|
| None | 15–55 |
| Fatigue | 50–75 |
| Pruritus | 40–70 |
| Jaundice | 9–69 |
| Abdominal pain | 16–60 |
| Weight loss | 10–34 |
| Fevers and chills | 5–28 |

Serum biochemical features:

Elevation of alkaline phosphatase is the most common biochemical abnormality and the hallmark of PSC.³ 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 choledocholithiasis, or malignancy. There is no significant difference between serum biochemistry 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.^{3,30}

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.²² 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.^{31,32} Perinuclear antineutrophilic antibodies are detected in frequencies ranging from 30% to 80% but lack diagnostic specificity for PSC. The antisaccharomyces cerevisiae antibody occurs in 50% of cases independent of IBD status.³³

Radiological modalities:

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

Table 2. Serum Autoantibodies in PSC

| Type of antibody | Prevalence |
|--------------------------------------|------------|
| Anti-neutrophil cytoplasmic antibody | 50–80% |
| Anti-nuclear antibody | 7–77% |
| Anti-smooth muscle antibody | 13–20% |
| Anti-endothelial cell antibody | 35% |
| Anti-cardiolipin antibody | 7–16% |
| Thyroglobulin | 4% |
| Rheumatoid factor | 15% |

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,³⁴ gallstones, cholecystitis, or mass lesions.³⁵

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.^{36,37} Abdominal lymphadenopathy is a common finding in PSC and should not be over interpreted as metastases or a lymphoproliferative disorder.³⁷

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.³⁸ 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.³⁹

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.⁴⁰ 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.⁴⁰ 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.⁴¹ 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^{42,43} 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.⁴⁴

One of the first studied pharmacologic agents for PSC was ursodeoxycholic acid (UDCA), a drug which is efficacious in treating other cholestatic liver diseases.⁴⁴ 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 corticosteroids⁴⁵ or other immunosuppressant agents like methotrexate,⁴⁶ budesonide, azathioprine, cyclosporine, mycophenolate mofetil,^{47,48} oral and transdermal nicotine,⁴⁹ penicillamine,⁵⁰ pentoxifylline,⁵⁰ silymarin,⁵¹ tacrolimus,^{52,53} and moexipril.⁵⁴

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.⁵⁵⁻⁵⁷ 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.⁵⁸ 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

Table 3. Mimics of PSC

| |
|---|
| Secondary sclerosing cholangitis |
| Portal hypertensive biliopathy |
| Overlap syndrome of PSC and autoimmune hepatitis |
| IgG4-associated cholangitis |
| Ischemic-like cholangiopathy in critically ill patients |

recent systematic review, which included seven randomized control trials with a total of 553 patients, found that not only does UDCA lack a clear beneficial effect on patient survival, liver histology, prevention of CCA, and improvement of clinical symptoms, but it was actually associated with increased mortality in one of the large randomized trials.⁵⁹⁻⁶¹

Modulation of fibrosis, especially in the histologic precirrhotic stage, is a promising treatment pathway for slowing the progression of PSC to the development of end-stage liver disease and cirrhosis.⁶² Pirfenidone is a known antifibrotic agent that has been investigated in 24 PSC patients. This treatment did not demonstrate any significant improvement of PSC symptoms, with more than 80% of the included patients in the study suffering from medication side effects.⁶³ Intrabiliary rapamycin inhibited hepatic fibrosis in animal models; however, human studies are still lacking.⁶⁴ Colchicine reduced mortality in primary biliary cirrhosis in one study. There is no evidence of a favorable effect of colchicine on survival, symptoms, serum biochemistry, or liver histology in patients with PSC.⁶⁵

Cholestyramine, rifampicin, and opioid antagonists are proven to be effective in alleviating symptoms of pruritus in patients with PSC in several randomized trials and systematic reviews.⁶⁶⁻⁶⁸ Treatment targeted for osteoporosis and fat soluble vitamin deficiency should be also considered in patients with PSC.⁶⁶

Immunosuppressive agents such as corticosteroids, etanercept, tacrolimus, cyclosporine, azathioprine, methotrexate, and infliximab are not clinically beneficial for patients with PSC.^{69,70} Not only have glucocorticoids been shown to be ineffective in treatment of PSC, but patients with PSC tend to have bone loss that can lead to osteoporosis that is exacerbated by glucocorticoid therapy. A study of 21 patients treated with oral budesonide found marginal improvement in serum alkaline phosphatase and AST levels. However, the Mayo Clinic Risk Score did not change significantly, and significant femoral neck bone loss was observed.^{71,72} Cyclosporine was shown to decrease serum alkaline phosphatase levels in treated PSC patients. However, it did not improve symptom or disease progression.⁷³ Therapy with tacrolimus (FK506), a macrolide antibiotic with immunosuppressive activity, improved pruritus and decreased serum bilirubin and alkaline phosphatase levels by over 50%. These patients, however, did not show a significant change in ERCP findings or histology.⁵² Immunosuppressants, therefore, have no role in the treatment of classic PSC and are not recommended.^{74,75} Currently, there are no medical therapies that have been proven to alter the natural course of PSC.⁷⁶

Endoscopic treatment:

PSC patients are at risk for developing superimposed CCA.^{28,77-79} The life time risk of developing CCA in PSC patients is 10% to 15%.⁸⁰ 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.^{78,81} 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 2, member D (NKG2D) gene (encoding a protein involved in NK cell activity).^{78,82,83} 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.⁷⁷ 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,^{84,85} may serve as primary indicators of concomitant CCA.⁸⁶ 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%⁸⁷⁻⁸⁹ with high specificity (97% to 100%) in the diagnosis of CCA.^{90,91} 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.^{92,93} 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.⁹⁴ 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.⁹⁵

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%.⁹⁶

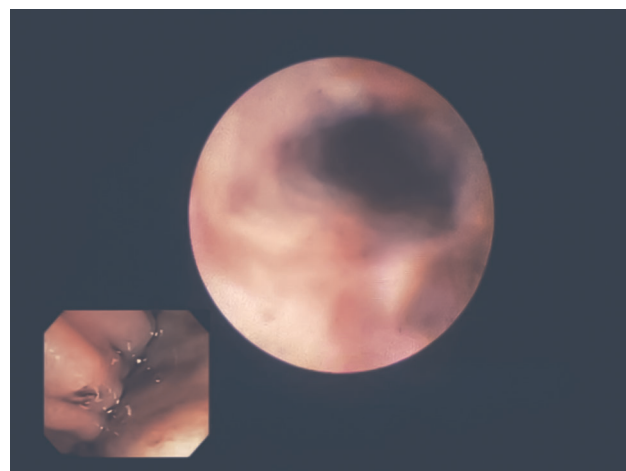


Fig. 1. CCA visualized by SOC in a dominant biliary stricture

Probe-based confocal laser endomicroscopy (pCLE) is a new technology that allows in-vivo histologic examination of the subepithelial mucosal layer of the indeterminate biliary stricture. The use of pCLE was investigated in 15 patients with PSC and biliary strictures. The sensitivity and specificity of pCLE in differentiating benign from malignant lesions was 100% and 61%, respectively.⁹⁷

In cases where ERCP with cytology is inconclusive in evaluating early stage CCA, endoscopic ultrasound (EUS) emerges as an additional modality to assist in the diagnosis of CCA. The sensitivity and specificity of EUS guided fine needle aspiration (FNA) in evaluating suspicious biliary strictures in PSC ranged from 43% to 86% and 95% to 100%, respectively.⁹⁸⁻¹⁰⁰ 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%).¹⁰¹ The only concerning issue with EUS-FNA is the possibility of tumor seeding.¹⁰² Although the incidence is believed to be quite rare,¹⁰³ 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.⁸⁶

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.¹⁰⁴ 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.¹⁰⁵ 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.¹⁰⁶ Some transplant centers report post-transplant survival rates of 90% to 97% at one year and 83% to 88% at five years.^{106,107} PSC liver transplant recipients may be more prone to acute and chronic cellular rejection^{108,109} 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.¹⁰⁸⁻¹¹⁰ 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.^{111,112} The presence of CCA prior to liver transplantation is also significantly predictive of disease recurrence.¹¹⁰ Re-transplantation rates are reported to be higher for patients with PSC than for those with other diagnoses.¹¹³

Post-transplant management in PSC patients is the same as the management of other liver transplant recipients with two exceptions. One exception is that approximately 60% of

PSC patients with IBD have increased IBD activity after transplantation.¹¹⁴ The rate of proctocolectomy for intractable IBD may be increased in PSC patients following liver transplantation.¹¹⁵ Patients with PSC and ulcerative colitis are at increased risk for developing colonic neoplasia that persists after transplantation.^{109,116,117} Therefore, these patients should have an annual colonoscopy for colorectal cancer surveillance. The other exception is that PSC patients have a higher prevalence rate for metabolic bone disease. Practice guidelines recommend bone density examinations to exclude osteopenia or osteoporosis at the time of diagnosis¹¹⁸ and at two to three year intervals thereafter. Supplemental calcium and vitamin D, to promote calcium absorption, are also recommended in patients with a diagnosis of osteopenia. In cases of documented osteoporosis, bisphosphonates may be added.¹¹⁹ Bisphosphonate therapy results in significant improvement in the bone density of PBC patients,¹²⁰ but it has been recently associated with jaw osteonecrosis and other problems. Thus it is now recommended for more limited use. Oral bisphosphonates have also been associated with esophageal ulcers, which could be problematic in patients with esophageal varices. In these patients, parenteral bisphosphonate therapy can be an alternative approach.

Conclusions

PSC is a chronic cholestatic liver disease that is generally progressive, and usually leads to the development of cirrhosis along with its complications. The pathogenesis of PSC remains unclear and there are currently no available medical therapies for treatment, with liver transplant representing the only available cure. Other disease-specific complications of PSC include pruritus, fatigue, vitamin deficiencies, metabolic bone disease, varices, cholangitis, biliary strictures, gallbladder stones and polyps, and malignancy, particularly CCA.

Despite the presumed autoimmune etiology of PSC, a clear benefit from immunosuppressive agents has not been established to date and their use can be limited by their side effects. Patients with PSC should be considered for therapeutic trials. Liver transplantation is currently the only life-extending therapy, but as transplanted patients live longer, disease recurrence can be a source of morbidity and mortality. Further studies are needed to develop an optimal therapeutic strategy for patients with PSC to decrease the incidence of disease related complications, need for transplantation, and to extend the life expectancy of patients with PSC.

Conflict of interest

None

Author contributions

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

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