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REVIEW

Pathogenesis and clinical spectrum of primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is a disease of the biliary tract, which has been documented in the literature since 1867. This disease has a strong predilection for affecting men and can be seen in individuals as young as 2 years of age. PSC has a strong associated with inflammatory bowel disease, more commonly with ulcerative colitis, and is also part of the clinical spectrum of IgG4-related diseases. Small-duct PSC, a variant of PSC, also has an association with inflammatory bowel disease. The exact pathogenesis of PSC is not well understood at present, however, is likely a combination of a genetic predisposition with alteration of the molecular structure of the gut. Abnormal serum liver chemistry and presence of certain autoimmune markers are usually the first indicators leading to a diagnosis of PCS, however, these may often be normal in early stages of this disease. The diagnosis is made by cholangiography, which is now considered the gold standard. PSC is a known pre-malignant condition. Such patients have an increased risk of developing cholangiocarcinoma, gallbladder neoplasia, and colon cancer. Many new treatment modalities have emerged in the recent past, including anti-tumor necrosis factor-α and anti-integrins; however, liver transplantation is the only known cure for PSC. Despite past and present research, PSC remains an enigmatic biliary disease with few viable treatment options.

Key words: Primary sclerosing cholangitis; Cholestasis; Inflammatory bowel disease; Autoimmune; Gallbladder neoplasia; Cholangiocarcinoma; IgG4 related disease; Colon cancer; Liver transplant

Core tip: Primary sclerosing cholangitis (PSC) is a fascinating disease with numerous and overlapping theorized pathogenetic models. An autoimmune etiology is in part due to its association with inflammatory bowel disease and autoimmune hepatitis, and inclusion within the IgG4 spectrum of diseases. Though PSC has been

documented in the literature for more than a century, only sparse details exist regarding its true pathogenetics and even less about successful medical therapy. More rigorous research is needed to truly understand and treat this disease entity.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a cholestatic liver and biliary tract disease associated with chronic inflammation of the biliary epithelium that cannot be attributed to another cause. This inflammatory process results in multifocal intra- and/or extrahepatic biliary strictures and fibrosis eventually leading to biliary cirrhosis and malignancy[1,2]. PSC often goes undiagnosed since approximately 40%-50% of patients with this disease are asymptomatic[3-5]. Fatigue, fever, jaundice, pruritus, and vague upper abdominal discomfort are the most commonly described symptoms at the time of diagnosis[3,6].

PSC has a strong association with inflammatory bowel disease (IBD)[7-9] with approximately 60%-80% of patients with PSC having coexisting ulcerative colitis (UC)[10,11].

PSC is a challenging condition whose pathogenesis continues to remain elusive despite extensive research of this disease in the 21st century. The only know cure for PSC is liver transplantation (LT) and symptomatic management with ursodeoxycholic acid and immunosuppressive agents.

Here we present a comprehensive review of the pathogenesis and clinical spectrum of PSC.

EPIDEMIOLOGY

PSC was first described in 1867 by Hoffman[12]. The incidence of PSC greatly varies from country to country but is increasing over time as evidenced by population-based studies from the United States, United Kingdom, and Northern Europe[13]. This variability may be related to human leukocyte antigen (HLA)-susceptibility among different ethnic groups and also varying frequency of IBD among populations across the world[14]. The incidence rate of PSC in the United States ranges from 0 to 0.92 per 100000 inhabitants per year, with no PSC patients being identified in Alaska between 1984 and 2000[4,15,16]. The prevalence of PSC in the United States is reported to be 13.6 per 100000 inhabitants[4]. Norway has the highest incidence rate at 1.31 per 100000 inhabitants and a prevalence of 8.5 per 100000[17]. The true prevalence of PSC may be higher than the aforementioned estimates both nationally and internationally because cholangiography may not be widely available in many parts of the world and patients with PSC may have normal levels of serum alkaline phosphatase (ALP)[18].

PSC can present itself at any age. The youngest individual documented to have PSC was under 2 years old[19]. UC is a major risk factor for the development of PSC, with approximately 60%-80% of patients having the PSC-UC phenotype[10,11]. However, only 4% of patients with UC have concomitant PSC[10,11].

PATHOGENESIS

The pathogenic mechanisms of PSC remain incompletely understood. Much like other autoimmune diseases, it has been theorized that the development of PSC is more likely to occur in a genetically susceptible individual after exposure to a trigger. PSC is the result of a complex immune-mediated response rather than a true autoimmune disease as it does not present with classic autoimmune features: female predominance, pathogenic autoantibodies, and response to immunosuppressive medications[20].

There is a 100-fold increased risk of developing PSC among siblings, however, the specific pattern of inheritance is much more complex[21,22].

Numerous studies have attempted to identify specific genes, which either predispose or protect an individual from the development of PSC. Many loci within the major histocompatibility complex have been linked to increased risk of PSC[23-25]. These are several class II HLA haplotypes including DRB1*0301-DRB3*0101-DQA1*0501-DQB1*0201, DRB1*1301-DRB3*0101-DQA1*0103-DQB1*0603, DRB1*1501-DRB5*0101-DQA1*0102- DQB1*0602, DRB1*0101-DQA1*0101, and B*0801[26-32].

HLA haplotypes associated with decreased risk of disease are DRB1*0401-DRB4*0103-DQA1*03-DQB1*0302, DRB1*0701-DQA1*0201-DQB1*0303, DRB4*0202-DRB1*1101-DQA1*0501-DQB1*0301, and MICA*002[29,31,32].

Due to the association of IBD with PSC, a "leaky gut" hypothesis has also been postulated[33]. Translocation of gastrointestinal (GI) flora from an inflamed GI tract to the portal venous system causes a systemic inflammatory response, which may disrupt the tight junctions in biliary epithelial cells[34,35]. This alteration exposes cholangiocytes to bile acids that could promote injury and inflammation[36].

Immune activation to an antigen (or a cross-reactive autoantigen or an enteric microbiome) also leads to inflammation of the gut and of the biliary tree[37]. Toll-like receptor and nucleotide oligomerization domain-like receptors assist in the detection of pathogens, which results in the secretion of pro-inflammatory cytokines[38]. Tumor necrosis factor (TNF)-α, transforming growth factor β1, interleukin (IL)-1β, and IL-6, along with involvement of CD8+ and CD4+ T cells

have been proposed to cause myofibroblast activation and fibrosis[38,39]. IL-2 has also been proposed as a key player in the regulation and programming of the immune system. IL-2 receptor α gene deficiency in mice causes biliary inflammation resembling PSC[40]. Integrin ligands, intracellular adhesions molecule 1, and vascular cell adhesion molecule 1 are also expressed by the biliary epithelium and contribute to the recruitment of inflammatory leukocytes that play a role in development of biliary inflammation seen in PSC[41]. Gut-specific T and B cells can be programmed to perpetuate biliary inflammation after encountering an enteric pathogen, providing an important rationale of how liver and gut inflammation may be linked[42].

A critical driver of disease development may be an altered biliary mucosal milieu, giving rise to biliary colonization of non-commensal bacteria[43]. Reduced biliary Proteobacteria and increased firmicutes due to a non-functional galactoside 2-α-L-fucosyltransferase 2 (FUT-2) enzyme appears to alter the commensal bacteria in the biliary tree[44].

The pathogenesis of PSC is likely the result of an amalgamation of a heightened immune response to a pathogen in a host with both an altered biliary mucosal milieu and a genetic predisposition to PSC.

DIAGNOSIS OF PSC

Signs and symptoms

Approximately 40%-50% of patients with PSC have no symptoms at initial presentation[3-5]. Among the symptomatic patients, fatigue, fever, jaundice, pruritus, and vague upper abdominal discomfort are most commonly described[3,6]. A sudden onset of jaundice, however, should prompt the clinician to inquire about an obstructive biliary process. As approximately 60%-70% of patients with PSC have coexisting UC, GI bleeding may also be seen in these patients.

Serologic markers

The hallmark of PSC is an elevation of alkaline phosphatase (ALP). ALP may vary throughout the course of disease and may also be normal in patients with PSC[45]. Improvement of serum ALP during the disease is a predictor of better outcomes and prolonged transplant-free survival[46]. Serum alanine (ALT) and aspartate (AST) aminotransferase levels may also be elevated to 2- to 3-fold above the upper limit of normal[10,47]. Serum bilirubin is usually normal at time of diagnosis of PSC, however, may be elevated in patients with advanced disease, malignancy, or superimposed choledocholithiasis[47,48].

Detectable autoantibodies are found in as many as 97% of patients with PSC[49]. The most commonly noted autoantibodies are anti-smooth muscle antibodies (ASMA) and antinuclear antibodies (ANA), which can be seen in up to 75% of patients[50]. Perinuclear antineutrophil cytoplasmic antibody and anti P-40 autoantibody can also be detected in approximately 30%-80% of patients with PSC and UC[51,52].

Proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA) has been studied extensively for disease severity in patients with UC[53,54]. More recently, when measured using chemiluminescence immunoassay, PR3-ANCA was seen in 38.5% of patients with PSC compared to only 10.6% of patients with liver disease suggesting it is a better biomarker for the diagnosis of PSC[55]. Numerous other autoantibodies have been detected in patients with PSC, including anticardiolipin antibodies, thyroperoxidase, and rheumatoid factor[49]. These autoantibodies, however, are not routinely assessed for the diagnosis of PSC, as they may not be present in patients with PSC, and furthermore do not correlate with disease severity or disease prognosis.

Imaging

Cholangiography is considered the gold standard for the diagnosis of PSC. Historically, endoscopic retrograde cholangiopancreatography (ERCP) was the initial diagnostic procedure of choice, however, magnetic resonance cholangiopancreatography (MRCP) has become the preferred method of diagnosis of PSC in the past decade due to comparable specificity (> 90%) and sensitivity (80%-90%), associated lower cost, less invasive testing, and fewer complications[56-58]. The characteristic features include multifocal annular stricturing within intrahepatic and/or extrahepatic bile ducts, with alternating normal or slightly dilated segments of bile ducts (Figure 1), giving rise to the typical beads-on-a-string appearance[59]. Diffuse involvement of the hepatobiliary system may be seen, including stricturing of the gallbladder, cystic duct and pancreatic duct, however, approximately 25% of patients have isolated intrahepatic involvement[59]. Although MRCP is recommended as the initial imaging modality for the diagnosis of PSC, ERCP may be necessary in patients with a non-diagnostic MRCP or those who require therapeutic intervention for bile duct strictures.

Histologic features

A liver biopsy is rarely needed to confirm a diagnosis of PSC if characteristic cholangiographic findings are seen. Additional reasons why liver biopsies are not routinely obtained is the pathognomonic periductal fibrosis or "onion skinning" is not a common histologic finding in PSC[60]. Patients may have non-specific histologic findings and findings may be patchy and include more than one histological stage in at a given time indicating high sample variability[61].

When determining the stage of fibrosis, newer surrogate markers of cirrhosis including FibroSure (LabCorp) and transient ultrasound elastography (Echosens) have limited the need for a liver biopsy.

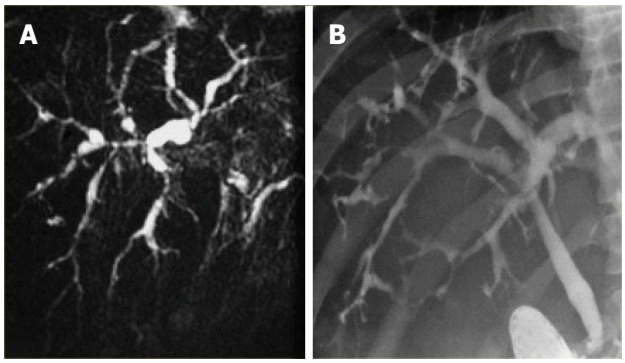

Figure 1 Imaging and endoscopy demonstrating primary sclerosing cholangitis. A: MRCP of a patient with PSC demonstrating intrahepatic stricturing with alternating normal and dilated segments of bile ducts; B: ERCP of a patient with PSC with similar findings. (Reproduced from Radiology Assistant. Levy AD, Chief of Gastrointestinal Radiology, Department of Radiologic Pathology, Armed Forces Institute of Pathology, Washington, D.C, United States). PSC: Primary sclerosing cholangitis; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

VARIANT PSC SYNDROME

Small-duct PSC

Individuals with biochemical markers and histologic features suggestive of PSC with normal cholangiography are considered to have small-duct PSC[62]. Small-duct PSC represents a small proportion of patients with PSC and may even be an earlier stage of PSC[63]. This subgroup of PSC has been less studied than the classic large-duct PSC. Several studies suggest better prognosis in individuals with small-duct PSC, however, available data on this population is limited due to lack of long-term follow up[50,63,64]. A recent study with one of the longest follow-up of patients with small-duct PSC suggested that approximately a fourth of patients' progress to classic PSC in an average of 8 years[65]. Furthermore, individuals with small-duct PSC may progress to end-stage liver disease even without developing large duct disease and cholangiocarcinoma does not seem to occur in patients with small-duct disease in the absence of progression to large-duct PSC[65].

Lastly, the association of small-duct PSC appears to be stronger with Crohn's colitis than with UC[8,66].

Overlap syndrome (autoimmune hepatitis-PSC)

An overlap syndrome of PSC with autoimmune hepatitis (AIH) is more often diagnosed in younger adults, adolescents and in children[67,68]. Patients who exhibit features of both hepatocellular and cholestatic disease with the presence of ANA antibodies, the presence or absence of ASMA antibodies, and/or histological changes in the absence of AMA antibodies are considered to have autoimmune sclerosing cholangitis[69-71].

The diagnosis of AIH is based on the presence of characteristic clinical, laboratory and histologic findings, abnormal levels of serum globulins, and the presence of typical autoantibodies which ultimately provides the clinician with either a "definite" or a "probable" diagnosis of AIH based on the modified scoring system of AIH[72-74]. ANA and ASMA are typically seen in type 1 AIH whereas liver/ kidney microsomal type 1 antibody and liver cytosol type 1 antibody are observed in type 2 AIH[75]. Histologic lesions typically present in AIH are periportal lymphocytic or lymphoplasmacytic infiltration (interface hepatitis) with hepatocyte swelling[75]. In case of fulminant presentation, massive necrosis may also be present[75]. Treatment is largely based on immunosuppressive therapy with corticosteroids and azathioprine.

Many similarities exist between PSC and AIH, including the autoimmune serology, histologic findings, and the disease response to treatment with immunosuppressive agents. The International Autoimmune Hepatitis Group scoring system can help in the making a diagnosis of AIH, however, it is not recommended in making a diagnosis of AIH-PSC overlap syndrome[72]. In 2001, a cohort of 55 patients was evaluated to assess this overlap syndrome[67]. Approximately 50% of these patients had bile duct changes diagnostic of sclerosing cholangitis (SC) at the time of presentation and all but one of these patients would have been diagnosed with AIH type 1. Several other studies have also assessed this overall phenomenon in similar populations[19,76]. It is possible that the juvenile form of SC may represent an early stage of PSC in patients with concomitant AIH and progression to PSC is delayed with early use of immunosuppressive therapy.

IgG4-related Sclerosing cholangitis

A common manifestation of IgG4-related diseases (IgG4-RD) is IgG4-sclerosing cholangitis (ISC). Type 1 autoimmune pancreatitis (AIP) is the leading manifestation of IgG4-RD, affecting approximately 60% of patients with IgG4-RD, followed by sialadenitis affecting 34% of patients, followed by tubulointerstitial nephritis (23%), dacryoadenitis (23%), and periaortitis (20%)[77]. ISC is seen in approximately 20%-88% of patients with IgG4-RD[77-79]. Individuals with ISC are commonly diagnosed with concomitant AIP[80]. Similar to PSC and unlike classic autoimmune disease, ISC is more commonly seen in males with a male-to-female ratio of 4:1[77].

Analogous to PSC, patients typically present with vague abdominal pain. Individuals may also present with obstructive jaundice with concurrent AIP[79,81].

An elevated serum level of IgG4 is the most sensitive and specific method of diagnosing ISC, however, elevated levels of IgG4 may be seen in approximately 10% of patients with PSC, in approximately 15% of those with cholangiocarcinoma, and also in approximately 7% of patients who may have other ailments[82-84]. Several additional serologic

abnormalities may be seen in patients with ISC including elevated levels of IgG (approximately 60%), ANA positivity (approximately 40%), rheumatoid factor (approximately 20%), and IgE elevation (approximately 30%)[85-87].

Cholangiography may reveal multifocal biliary strictures, thickened bile duct wall and gallbladder wall thickening without vascular invasion[88].

Histologically, ISC demonstrates transmural fibro-inflammation with both fibrosis and inflammation evenly distributed from the mucosal surface to subserosa[89]. Immunostaining of the biopsy sample for IgG4 demonstrates diffuse infiltration of IgG4-positive plasma cells.

An approach for the diagnosis of ISC is the HISTORt criteria, which includes features on histology, imaging, serology, other organ involvement, and response to treatment with corticosteroids, and was initially utilized for the diagnosis of AIP and has been extended to include additional IgG4-related biliary diseases[78,90].

As the diagnostic algorithm suggests, rapid disease remission is achieved with immunosuppression using high-dose steroids[91]. Relapse of ISC can be seen in 30%-50% of patients and affected individuals may require re-induction of remission with additional high-dose steroids[91,92].

Long-term outcomes of patients with ISC are inconclusive and it remains unclear whether patients progress to end-stage liver disease or go on to develop cholangiocarcinoma.

PSC AND ASSOCIATED CONDITIONS

IBD and colorectal neoplasia

As previously mentioned, PSC has a strong association with IBD[7-9] with approximately 60%-70% of patients with PSC having coexisting UC, which often precedes the diagnosis of PSC or is diagnosed concomitantly[10,11]. Thus patients with PSC should undergo colonoscopic evaluation with biopsies despite the absence of typical symptoms[10]. If an initial evaluation does not reveal IBD, a repeat colonoscopy should be performed every 5 years to either confirm or exclude IBD[93].

Patients with IBD in the setting of PSC are considered to have a different phenotype (PSC-UC), which predicts a milder clinical course of the disease[9,94-96]. There also appears to be a right-sided predominance of diseased colonic mucosa, inflammation observed in the ileum and milder histologic inflammation in patients with PSC-IBD[97,98]. Due to the association of multiple malignancies with PSC, this disease entity should be considered a premalignant condition.

Patients with PSC-IBD have a significantly increased risk of developing colorectal malignancy compared to those with UC alone[99]. The cumulative CRC risk after 10 years of disease is 9% and 2%, which increases to 21%-30% and 5% in patients with PSC-IBD and isolated UC, respectively[99]. Moreover, colorectal cancer (CRC) and dysplasia are most often located in the right colon[95,96,98], which are associated with a worse prognosis when compared with left-sided colon cancer[100]. Annual or biennial surveillance colonoscopy is recommended in patients with PSC-IBD from the time of PSC diagnosis[101].

Cholangiocarcinoma

The most important risk is that of cholangiocarcinoma, which is several hundred times higher in patients with PSC than in patients without this disease[102]. Cholangiocarcinoma occurs in 1%-2% of patients annually following a diagnosis of PSC and is frequently detected within the first 1-3 years after the initial diagnosis[103,104].

Diagnosing cholangiocarcinoma in patients with PSC poses a tremendous challenge, as distinguishing between a benign dominant stricture from ductal cholangiocarcinoma requires the use of serologic, imaging, and ERCP over time. There are no designated risk stratification criteria, however, a commonly used approach involves annual MRCP or ultrasound examinations in conjunction with serum carbohydrate antigen 19-9 (CA19-9)[10]. If an individual is noted to have increasing serum levels of CA19-9, dominant strictures on imaging, and/or deterioration in either clinical status or liver test results, further assessment is made with an ERCP[105]. It is important to note that some individuals may not produce CA19-9 due to genetic reasons thus disease surveillance with this serologic test will not prove beneficial[106].

Routine brush cytology evaluation detects cholangiocarcinoma with low sensitivity (40%)[10] and near 100% specificity. Fluorescent *in situ* hybridization is used in conjunction with brush cytology specimens to apply a probe to subpopulations of cells with chromosome amplifications to assess for aneusomy. Individuals with the presence of a dominant stricture and polysomy [5 or more cells which have gained 2 or more chromosomes (3, 7, 17, and band 9p21)] are eventually diagnosed with cholangiocarcinoma with 88% specificity[107]. Cholangioscopy allows direct biliary visualization and directed biopsies of the dominant stricture and has been reported to have increased sensitivity and specificity to > 90%[108]. It is also being used to interrogate indeterminate strictures in an effort to enhance detection of cholangiocarcinoma. Confocal laser microscopy has not been studied in dominant strictures in PSC despite a high reported sensitivity and moderate specificity for indeterminate strictures in general[109]. Intraductal ultrasound may also offer improved diagnostic yield but is not widely adopted since its initial report for diagnosis of indeterminate strictures[110].

Gallbladder neoplasia

Concurrent abnormalities such as gallstone disease and PSC involving the gallbladder or cystic duct are seen

in approximately 41% of patients with PSC[111]. This population is also at an increased risk of developing gallbladder neoplasia, although the exact prevalence is unknown[112]. Although the malignant potential of gallbladder polyps smaller than 8 mm is small[113], the 2010 American Association for the Study of Liver Diseases (AASLD) guidelines recommend annual ultrasound and cholecystectomy if lesions are detected, regardless of the size[10]. Despite annual surveillance for gallbladder polyps, there is a lack of consensus regarding the malignancy potential of small polyps and surgical intervention in patients with advanced liver disease poses its own set of risks. It is important for the clinician to weigh the risks *vs* benefits of routine surveillance and surgical intervention.

TREATMENT OF PSC

Medical management

Historically, ursodeoxycholic acid (UDCA) has been used for the symptomatic improvement in cholestatic pruritus, which can be a debilitating consequence of PSC, and to improve abnormal liver chemistries. High dose UDCA (28-30 mg/kg per day) has been shown to increase the risk of colonic neoplasia in patients with PSC-IBD[114]. Additionally, there is a lack of definitive evidence that the use of moderate dose UDCA (15-20 mg/kg per day) improves survival in PSC patients or is efficacious in the prevention of colorectal cancer in those with PSC-IBD or biliary neoplasia[115,116]. Although the current AASLD guidelines recommend against the routine use of UDCA in patients with PSC, clinical practice varies between centers[10].

Azathioprine and steroids are recommended for use in patients with AIH as well as those with AIH-PSC overlap syndrome[10]. However, the use of immunosuppressive therapy (azathioprine, cyclosporine, tacrolimus, and methotrexate) and anti-TNF agent, infliximab, failed to demonstrate sustained improvement in abnormal liver chemistries and prevention of progression to end-stage liver disease in patients with PSC[117-120].

As newer investigations shine light on the link between biliary inflammation, bile acid homeostasis, and the gut microbiota, there is increasing interest in pharmacologic treatment of PSC with antimicrobial agents. The use of non-absorbable antibiotics, such as vancomycin, demonstrated improvement in liver chemistries in a small subset of patients[121]. An improvement in liver biochemistries was also observed with use of absorbable antimicrobials including metronidazole, azithromycin, and minocycline[122-124]. More data points are necessary to provide the clinician with definitive and accurate treatment options for PSC.

Novel treatment strategies, including the use of biologic therapy against lymphocytic trafficking in the pathogenesis of PSC, are being investigated. Vedolizumab (Millennium Pharmaceuticals, Takeda) is a gut-specific monoclonal antibody that selectively targets against $\alpha4\beta7$ heterodimer resulting in improvement in gut histology and mucosal T-cell infiltration[125]. It was approved by the Food and Drug Administration for induction and maintenance therapy for moderate to severe UC and Crohn's disease in 2014[126,127]. Its use in patients with PSC-IBD is theorized to take effect by the presence of gut adhesion molecules and the entero-hepatic expression in PSC, however, the clinical utility of vedolizumab in PSC-IBD patients remains under investigation[37,128].

Management of biliary strictures

Patients with worsening symptoms over the disease course require investigation to exclude the presence of an extrahepatic dominant biliary stricture. A dominant stricture is defined as an area of stenosis $\leqslant$ 1.5 mm in the common bile duct or $\leqslant$ 1 mm in the common hepatic duct and is present in approximately 50% of PSC patients[10,129].

Dominant strictures are treated by either dilation alone or with dilation and placement of temporary plastic biliary stents during the ERCP[130]. It is important to note that PSC patients undergoing ERCP should be provided with prophylactic antibiotics to prevent possible cholangitis[131]. The duration of endoscopic therapy is variable and can range from 6 weeks to 12 mo before strictures resolve. ERCP with repeated stenting may be required in some patients who are refractory to dilation[130]. Due to the risk of cholangiocarcinoma masquerading as a dominant stricture, brush cytology and/or biopsy samples should be obtained during the endoscopic procedure[132]. The utility of ERCP is solely for the exclusion of cholangiocarcinoma and to provide therapy for dominant biliary strictures and does not modify the progression of the disease[130].

Liver transplantation

Due to the lack of durable pharmacologic and endoscopic therapy, liver transplantation (LT) remains the sole curative option in patients with progressive disease. PSC is the fifth most frequent indication for LT in the United States[133]. Intractable pruritus, recurrent bacterial cholangitis, and perihilar cholangiocarcinoma are additional indications for LT in PSC patients.

Post-transplant acute rejection can be seen within the first 30 d of transplantation, but usually resolves with systemic corticosteroids and does not appear to alter graft survival[134].

In patients with cholangiocarcinoma, LT in conjunction with neoadjuvant chemotherapy and radiation should be considered[135,136].

Patients with PSC-IBD may develop worsening disease post LT and approximately 14%-30% of patients with PSC may go on to develop de novo IBD up to 10 years post LT[10]. Patients should be monitored with serial serum ALP measurements post

LT as increasing levels indicate recurrence of disease. Recurrent PSC, despite LT, is seen in 30%-50% of patients within 10 years of transplantation[137]. To date, no medical therapy has been identified to halt the progression or recurrence of disease.

CONCLUSION

PSC is a fascinating and largely elusive entity within the realm of hepatobiliary diseases. This is a chronic cholestatic liver disease, which has a tremendous impact on survival of those who are affected. Over time, many treatment modalities have been evaluated, however only LT is a known therapeutic option in these patients. Although newer drugs continue to be investigated for the treatment of PSC, effective treatment options remain limited. Future research in genomic-based therapies will hopefully allow for alteration of the natural course of this disease.

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