

Inflammatory Bowel Disease

Chapter 2

Primary Sclerosing Cholangitis (PSC) and Inflammatory Bowel Disease (IBD)

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Abstract

Primary sclerosing cholangitis is a chronic cholestatic syndrome affecting both extrahepatic and intrahepatic bile ducts that is frequently progressive, leading to liver cirrhosis, portal hypertension, and eventually to end-stage liver disease. Primary sclerosing cholangitis is strongly associated with inflammatory bowel disease. The prevalence of inflammatory bowel disease (typically ulcerative colitis) among primary sclerosing cholangitis patients is approximately 70-80% while only 2-7.5% of patients with ulcerative colitis will develop primary sclerosing cholangitis. Primary sclerosing cholangitis is accompanied by an increased risk of liver failure, cholangiocarcinoma, and colorectal cancer. Cholangiography is considered the gold standard for the diagnosis of primary sclerosing cholangitis. It is noteworthy that medical, endoscopic, and surgical therapies do not convincingly alter disease progression in primary sclerosing cholangitis patients. Liver transplantation is currently the only available therapeutic modality for patients with end-stage primary sclerosing cholangitis.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease that characterized by inflammation and fibrosis with the development of bile duct stenosis. The term 'primary' is used to differentiate PSC from other secondary conditions including choledocholithiasis, bacterial cholangitis, prior biliary surgery, and acquired immunodeficiency syndrome associated with cholangiopathy that may lead to a similar clinical and cholangiographic syndrome [1,2]. PSC may eventually progress to liver cirrhosis and subsequent liver failure, and is accompa-

nied by an increased risk of cholangiocarcinoma. The pathogenesis of PSC remains poorly understood, however, current evidence suggests that genetic, immunologic and environmental factors appear to play key roles in the disease [3,4].

PSC is strongly associated with inflammatory bowel disease (IBD) and especially ulcerative colitis (UC) and less often with Crohn's disease (CD). Approximately 80% of IBD is represented by ulcerative colitis, 10% by Crohn's disease, and 10% by indeterminate colitis. It is noteworthy that in up to 80% of cases PSC also suffering from IBD [2,5]. Although the relationship between PSC and IBD suggests a possible common pathogenesis, the two disorders may occur at different times [1,6].

PSC may occur in the presence or absence of IBD. IBD can be diagnosed at any time during the course of PSC, and PSC can occur at any time during the course of IBD. Given that IBD as well as PSC can be asymptomatic diseases, the time of diagnosis is driven by the clinician's awareness of the diagnosis of disease [3,7]. The diagnosis of PSC is now most frequently established using magnetic resonance cholangiography (MRCP), although direct cholangiography may be more sensitive. Furthermore, the diagnosis of IBD and the differentiation between CD and UC are usually made by considering clinical, laboratory, radiological, endoscopic, and pathological criteria [2,8].

Currently, there is no effective medical therapy for PSC and liver transplantation remained the only treatment option. Thus, clinicians might not feel an urgency or need for early detection or diagnosis of PSC [9,10].

2. PSC associated with IBD

PSC is a chronic progressive disease, which is strongly associated with IBD (Typically ulcerative colitis [UC]). Chronic UC is most commonly associated with PSC, but patients with Crohn's colitis also have a higher risk of developing PSC than the general population [5,11]. The relationship between PSC and UC was first shown in 1965 by Smith and Loe, and was subsequently confirmed by others. Although cause of PSC is unknown, its strong association with IBD suggests an immune dysbalance etiopathogenesis. Complex and multiple mechanisms are likely to be involved in PSC etiology. Current evidence suggests that genetic, immunologic and environmental factors appear to play key roles in the disease [4,12].

3. Prevalence of PSC-IBD

The prevalence and incidence of PSC-IBD varies in different series from different regions of the world. Furthermore, the frequency of the associated occurrence of PSC-IBD varies considerably between different studies partly due to differences in the diagnostic techniques used and probably also to differences in patients selection [13,14].

PSC is more common in men than woman (2:1 ratio), with a median presentation in the third and fourth decades of life. In addition to liver disease, PSC is closely associated with IBD. Approximately 75% of patients with PSC have IBD, and of these, nearly 80-90% are diagnosed with UC. Epidemiological studies have reported that the incidence of PSC ranges from 0.04 to 1.30 per 100000 person-years [1,11]. Conversely, it is clear that between 2.5 and 7.5% of individuals with IBD will eventually develop PSC. When further differentiated, about 3-8% of UC patients suffer from PSC, whereas among CD patients the reported prevalence of PSC is probably between 1 and 3.5% [15,16].

4. Clinical manifestations of PSC-IBD

The clinical manifestations of PSC have substantially changed through the decades. A large number of patients (44%-56%) may be without symptoms at presentation, but symptoms may develop over time [13,17]. Nowadays among symptomatic patients, fatigue and pruritus are the initial presenting symptoms, and with progression, these patients tend to develop jaundice, hepatomegaly, splenomegaly, abdominal pain, and weight loss. Notably, PSC may eventually progress to liver cirrhosis and subsequent liver failure, and is accompanied by an increased risk of cholangiocarcinoma. In addition, episodes of bacterial cholangitis are uncommon at presentation in the absence of dominant strictures or biliary manipulation and usually present with fevers, chills, right upperquadrant pain, and worsening liver biochemistries [3,11, 17].

Moreover, the association between PSC and IBD leads to specific clinical features, different from patients with IBD alone. PSC-IBD has been reported to show an increased incidence of pancolitis, rectal sparing, backwash ileitis, mild symptoms, and colorectal malignancy [1,6].

5. PSC and IgG4-related sclerosing cholangitis/ autoimmune pancreatitis

PSC probably represents a spectrum of disease processes from classic PSC to IgG4-related sclerosing cholangitis (IgG4-SC), small-duct PSC and autoimmune sclerosing cholangitis, with differing clinical manifestations, disease courses and prognoses. Moreover, PSC might coexist with other immune-mediated disorders such as autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) [1,9].

IgG4-SC is a recently recognized entity which shows the cholangiographic findings similar to those of PSC. IgG4-SC is one of several diseases associated with autoimmune pancreatitis (AIP). AIP is a chronic pancreatic condition characterized by stricturing of the pancreatic duct, focal or generalized pancreatic enlargement, raised serum IgG4 level, lymphocytic infiltrate on biopsy. AIP in association with intrahepatic and/or extrahepatic bile duct stricturing similar to those present in PSC is termed autoimmune pancreatitis-sclerosing cholangitis

(AIP-SC) [18,19].

The differential diagnosis of PSC from AIP and IgG4-SC is needed as the two entities show different therapeutic responses. Both IgG4-SC and AIP respond well to steroid therapy or other immunosuppressive agents and biliary drainage. In contrast, PSC is progressive and resistant to therapy, eventually involving both the intra-hepatic and extra-hepatic bile ducts and resulting in biliary cirrhosis. The rare association between IBD and IgG4-SC and the unique characteristics of PSC-IBD are useful findings for distinguishing PSC from IgG4-SC. Notably, an elevated serum IgG4 level and the association with type 1 AIP are the most useful findings for discriminating between IgG4-SC and PSC. However, elevation of the serum IgG4 level alone is not useful because some PSC cases also show increased IgG4 levels. In addition, some IgG4-SC cases are not associated with AIP [1,6,20].

6. PSC-IBD and colorectal cancer

PSC is usually a progressive disorder, which ultimately leads to severe complications including cholestasis and hepatic failure. The main causes of death in these patients are liver failure, cholangiocarcinoma (CCA), and colorectal cancer (CRC) [1,6].

PSC-IBD patients show an increased incidence of pancolitis, rectal sparing, backwash ileitis, mild symptoms, and different malignant conditions such as colorectal malignancy. The risk of development of CRC is significantly higher (Approximately four- to fivefold) among patients with PSC-IBD compared with those with IBD alone [1,13]. The association between IBD and CRC has been recognized by Crohn since 1925 and still accounts for 10%-15% of deaths in IBD. The prognosis for sporadic CRC and IBD-CRC is similar, with a 5-year survival of approximately 50%. Identifying at risk patients and implementing appropriate surveillance for these patients is central to managing the CRC risk in IBD [5,21].

Furthermore, the risk of CRC may increase after liver transplantation (LT) in PSC-IBD patients because of errors in mucosa sampling during colonoscopy or perhaps due to the immunosuppression treatment of anti-reject therapy. A large range with rates of risk of colorectal cancer after LT for PSC, from 0 to 31.5 per 1000 person/year, is present in literature in recent years. It is noteworthy that the mechanism for increased risk of colon cancer in PSC-IBD is unknown, but exposure of the colonic mucosa to toxic bile acids, namely secondary bile acids that may promote carcinogenesis such as deoxycholic acid, has been proposed. In addition, family history of sporadic colorectal cancer, active inflammation of the mucosa, and the presence of PSC increase the risk of colorectal cancer/ dysplasia in patients with IBD [7,13,22].

7. PSC and cholangiocarcinoma

Studies have shown that PSC may eventually progress to liver cirrhosis and subsequent

liver failure, and is accompanied by an increased risk of cholangiocarcinoma (CCA). CCA is the most feared complication of PSC possibly due to inflammation-associated epithelial dysplasia, with a reported lifetime prevalence ranging between 7% and 14% that is probably [3, 23]. In developed countries, PSC is the most common risk factor for CCA. Indeed, the risk of CCA among patients with PSC is nearly 400-fold higher than that seen in the general population [10,24].

Several risk factors for CCA in PSC have been recognized, including older age at PSC diagnosis, smoking, alcohol use, elevated serum bilirubin, a longer duration of associated IBD, ulcerative colitis with colorectal cancer or dysplasia, proctocolectomy, variceal bleeding, and polymorphism of the Natural Killer G2D gene (encoding a protein involved in NK cell activity). However, Duration of PSC does not appear to be a risk for the development of CCA because 30% to 50% of patients with CCA are diagnosed within 1 year of diagnosis of PSC. In addition, the presence of advanced fibrosis is not required for development of cholangiocarcinoma, unlike hepatocellular carcinoma, which is typically found in conjunction with cirrhosis [17,18,25].

Given the risk of CCA in PSC patients, patients with deterioration in their constitutional performance status or liver biochemical-related parameters should undergo an evaluation for CCA [17,18].

8. PSC and *helicobacter pylori*

In recent years, the attention has been drawn to the possible association of *Helicobacter* infections not only with upper gastrointestinal tract diseases but also with extra-gastrointestinal diseases such as cardiovascular, liver or biliary diseases. PSC typically involves the intra-hepatic and extra-hepatic bile ducts that is characterized by a ductocentric chronic inflammatory process and eventually leads to biliary strictures. In addition, injured biliary epithelium in PSC often becomes metaplastic and gains a mucinous phenotype that is histologically similar to gastric metaplasia. Since the inflammatory process and gastric metaplasia of PSC resembles *Helicobacter pylori* (*H. pylori*) induced chronic gastritis, an association of *H. pylori* with PSC has been investigated. Both supportive and contradictory data exist concerning a possible link between *H. pylori* infection and PSC. Some studies detected *H. pylori* DNA in the livers biopsy tissue of patients with PSC. However, the role of *H. pylori* infection in cholestatic liver diseases such as PSC is controversial [26-28].

9. Diagnosis and surveillance of PSC

The diagnosis of PSC is based on characteristic typical cholangiographic findings in combination with clinical, biochemical, serologic, and in some cases histologic features. It is important to exclude the secondary sclerosing cholangitis (SSC) including biliary neoplasms,

previous biliary surgeries, choledocholithiasis, medication-induced bile duct damage, and chronic bacterial cholangitis. Secondary sclerosing cholangitis in critically ill patients (SSC-CIP) is a destructive cholangiopathy with a poor prognosis. SSC-CIP is most often diagnosed via endoscopic retrograde cholangiography but neither diagnostic algorithms and nor therapeutic approaches are sufficiently evaluated [11,18,29].

Patients with PSC typically present with a cholestatic pattern of abnormal liver enzymes. Elevations in serum alkaline phosphatase (ALP) values are the biochemical hallmark of PSC. Alkaline phosphatase is usually 3 to 10 times above normal in 95% of cases, whereas aminotransferase levels are only mildly elevated (Usually 2-3 fold). Serum bilirubin levels are normal at diagnosis in the majority of patients. However, hyperbilirubinemia may suggest advanced disease or the development of complications such as dominant strictures, cholangiocarcinoma, biliary stones, and bacterial cholangitis but may also occur in the absence of any of these conditions. IgG serum levels are modestly elevated in approximately 60% of patients with PSC (1.5 times the upper limit of normal). The liver tests can be normal and can fluctuate during the course of the disease [11,16,18].

Cholangiography (Such as Magnetic resonance cholangiopancreatography [MRCP], Endoscopic retrograde cholangiopancreatography [ERCP], Percutaneous transhepatic cholangiography [PTC]) is considered the gold standard for the diagnosis of PSC. The diagnosis of PSC is based on the demonstration of diffuse multifocal strictures and dilations in the intrahepatic and extrahepatic biliary tree [1,17]. Traditionally, ERCP was regarded as the gold standard in diagnosing PSC. However, ERCP is an invasive procedure associated with potentially serious complications such as pancreatitis and bacterial cholangitis, and may be associated with post-procedural hospitalization in up to 10% of patients. Recent studies show that MRCP is a valuable technique in the diagnosis and follow-up of patients with PSC. So, MRCP has replaced ERCP as the initial diagnostic test of choice that is non-invasive, avoids radiation exposure, has comparable sensitivity (80%-90%) and specificity (>90%) with ERCP, and is more cost effective. Other abdominal imaging studies, such as CT and ultrasonography, may suggest the diagnosis but are nonspecific [11,18].

Notably, liver biopsy is not requested for the diagnosis of PSC; in fact, histology is diagnostic in only 30% of patients and it is normal in about 20%, but it may be useful for staging the disease and for determining prognosis [1,13].

9.1. Surveillance colonoscopy in patients with PSC-IBD

As it mentioned before, approximately 60-80% of PSC cases are associated with IBD and the presence of IBD makes the diagnosis of PSC easier and faster. IBD in PSC is often quiescent or even inapparent by history, and many patients with PSC are diagnosed with IBD by active screening with colonoscopy. Notably, once the diagnosis of PSC has been estab-

lished, a colonoscopy with surveillance biopsies is recommended to exclude underlying IBD or any malignancy such as CRC. The current surveillance strategy of surveillance colonoscopy with multiple random biopsies most likely reduces morbidity and mortality associated with PSC-IBD-related CRC. It is noteworthy that screening for CRC is recommended every 1-2 years starting at the time of PSC-IBD diagnosis. Unfortunately, surveillance colonoscopy has severe limitations including high cost, sampling error at time of biopsy, and interobserver disagreement in histologically grading dysplasia. Furthermore, once dysplasia is detected there is disagreement about its management. Advances in endoscopic imaging techniques are already underway, and may potentially aid in dysplasia detection and improve overall surveillance outcomes [1,30,31].

9.2. Surveillance for cholangiocarcinoma in PSC

Cholangiocarcinoma (CCA) is a well-known and often devastating sequel of PSC. Surveillance for CCA is recommended in patients with PSC. The diagnosis of cholangiocarcinoma in the setting of PSC can be difficult. Most experts recommend annual imaging (using MRI/MRCP or ultrasound) along with serum carbohydrate antigen 19-9 (CA19-9) level measurement. In patients noted to have abnormalities in either one of these, invasive testing with ERCP using conventional brush cytology and fluorescence in situ hybridization (FISH) is recommended. However, an evidence-based approach based on prospective data collection has not been identified [11,12,17].

A diagnosis of CCA, either sporadic or as a complication of PSC, is established by biliary brushing or by intraductal biopsy. Unfortunately, conventional brush cytology obtained via endoscopic retrograde or percutaneous cholangiography has a limited sensitivity albeit excellent specificity for the diagnosis of CCA in PSC. Recent studies have shown that FISH may increase the yield of conventional cytology [17,18].

In patients with CCA, imaging with MRCP as well as an assessment of serum CA19-9 level is warranted. Visualization of an intrahepatic mass lesion with characteristic imaging features (such as malignant-appearing mass with delayed venous phase enhancement) has virtually a 100% sensitivity and specificity for the diagnosis of CCA. Notably, the distinction between a benign dominant stricture and CCA in a PSC patient is challenging. The best studied CCA associated biomarker in PSC is the serum CA 19-9. However, the CA19-9 has limited diagnostic use because it can be increased in patients with bacterial cholangitis or significant intrahepatic cholestasis. Overall, screening for CCA with regular (Every 6-12 months) cross-sectional imaging with ultrasound or MR and serial CA 19-9 measures is recommended for all patients with PSC [13,17,18].

10. Management of PSC

The management of patients with PSC is challenging and complicated. It necessitates treatment of both the primary liver disease and coexisting conditions, as well as subsequent therapy for potential complications of end-stage liver disease. Several therapeutic modalities have been investigated for the treatment of PSC in an attempt to avoid disease progression. This may be partially explained by both the rarity of the disease, which makes it difficult to enroll enough patients for study designs of sufficient power, and the poor knowledge of the pathogenesis of the disease. Unfortunately none therapeutic modalities except liver transplantation has been proven to alter the course of the disease significantly [1,11].

10.1. Medical management

The treatment of patients with PSC-IBD does not differ from that of PSC without IBD. To date, there are no medical therapies that have been proven to alter the natural course of PSC. Several therapeutic options have been proposed for the treatment of PSC. Ursodeoxycholic acid (UDCA) is the most commonly prescribed drug in PSC. It is a 7- β -epimer of chenodeoxycholic acid that improves hepatobiliary secretion, is hepatoprotective, has immunomodulatory properties, and has been associated with biochemical and histologic improvements in PSC patients. In addition, there is some evidence that UDCA may modify the risk of colorectal neoplasia, with standard-dose UDCA decreasing the risk of colorectal neoplasia whereas high-dose UDCA potentially increasing the risk [1,17].

Several other therapeutic options such as immunosuppressive agents (prednisolone, budesonide, azathioprine, methotrexate, tacrolimus, cyclosporine, mycophenolate mofetil), anti-tumor necrosis factor (anti-TNF) antagonists (infliximab, etanercept), antifibrotic agents (silymarin, pirfenidone, pentoxifylline, colchicine, penicillamine), and systemic antibiotics (vancomycin, minocycline, metronidazole) have been tried in the management of PSC, but none of them has shown clinical benefits to date. Given the immunologic basis for the pathogenesis of PSC, a few trials have looked into immunosuppressive and anti-inflammatory agents as a form of therapy for this condition [1,17]. Azathioprine is a steroid-sparing immunosuppressant and purine antimetabolite widely used for the maintenance of remission in IBD. However, studies of its efficacy in PSC have been limited. Azathioprine inhibits ribonucleotide synthesis and induces T-cell apoptosis by modulating Rac-1 cell signaling. Furthermore, several animal experiments demonstrated a link between the gut microbiota and development of PSC. Induction of small bowel bacterial overgrowth by ligating the jejunum in rats resulted in development of hepatic lesions compatible with PSC. Studies have shown that the use of vancomycin, metronidazole and minocycline led to a significant reduction in serum ALP, an important surrogate marker in PSC. Thus antibiotic therapy in PSC patients seems to be a promising tool in the treatment of PSC. However, larger studies are needed to clarify these results [10,19].

10.2. Endoscopic management

Several attempts have been made to change the progressive course of PSC by endoscopic methods such as endoscopic sphincterotomy, nasobiliary lavage, stent placement, and balloon dilatation. Endoscopic therapy seems most advantageous for patients with dominant strictures. ERCP is reserved for patients with significant bile duct strictures localized to the extrahepatic and large intrahepatic bile ducts, which are described as dominant strictures. Endoscopic dilation of dominant strictures, with or without stenting, has been shown to alleviate cholestasis, to improve laboratory test results, and improve the survival of patients with PSC. Balloon dilatation alone and dilatation with stent placement appear to be of equal efficacy, but a higher rate of complications including bacterial cholangitis is associated with the latter; thus, stent placement is limited to those cases not responding to dilatation alone. Notably, for patients with proximal dominant strictures or complex biliary anatomy and in patients who did not respond to endoscopic intervention, the PTC approach is required [1,11,13].

10.3. Surgical management

Indications for colectomy in patients with PSC-IBD include cancer, high-grade dysplasia, and unresectable low-grade dysplasia (LGD). Whenever colectomy is required for patients with PSC-IBD, an ileal pouch anal anastomosis may be both a safe and an efficacious option for selected patients. Overall, surgical treatment is now less commonly performed because of the advances in endoscopic techniques and the possibility that it may adversely affect outcome after liver transplantation [1,24].

10.4. Liver transplantation

As it mentioned earlier, medical, endoscopic, and surgical therapies do not convincingly alter disease progression in PSC patients. Liver transplantation (LT) is currently the only available therapeutic modality for patients with end-stage PSC that is associated with patient survival rates of up to 90% at 1 year, and 85% at 5 years after transplant. Due to the progressive nature of PSC, approximately 40% of patients with this disease will ultimately require LT. However, Recurrence of PSC is an important problem, occurs in up to 20-25% of patients after 5-10 years of LT [13,19,23]. It is noteworthy that indications for LT are similar to those for other chronic liver diseases. Additional indications include intractable pruritus, recurrent cholangitis, and early CCA. PSC liver transplant recipients may be more prone to acute and chronic cellular rejection. The little experience of the use of biological therapy in transplanted patients, with concomitant anti-rejection therapy, suggests there be a higher and more careful surveillance regarding the risk of infectious diseases, autoimmune diseases, and neoplasms [16,22].

11. Conclusion

PSC is a chronic progressive disease of the liver that ultimately leads to cirrhosis and liver failure. PSC is accompanied by an increased risk of liver failure, CCA, and CRC. Approximately 75% of patients with PSC are usually associated with underlying IBD. PSC-IBD patients represent an important public health concern. In terms of diagnosis, MRCP is a valuable technique in the diagnosis and follow-up of patients with PSC. Moreover, a colonoscopy with surveillance biopsies is recommended to exclude underlying IBD or any malignancy such as CRC. Despite active investigation of different therapeutic modalities with the goal of modifying disease progression, LT remains only available therapeutic modality to provide survival benefit in PSC patients.

12. References

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