Specific Features of Patients With Inflammatory Bowel Disease and Primary Sclerosing Cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic and progressive disease of the biliary tract. PSC is strongly associated with inflammatory bowel disease (IBD), mainly with ulcerative colitis, and most PSC patients have underlying IBD. The pathophysiological interactions between IBD and PSC are unclear, although it seems that the patients with IBD and PSC have a distinct phenotype. IBD with coexisting PSC is more extensive and is characterized by milder activity compared to IBD alone. The coexistence of PSC increases the risk for colorectal cancer in IBD patients and lifelong annual surveillance colonoscopy is recommended. Also, liver transplantation (LT) for PSC may affect the course of IBD. In addition, the management of IBD after LT includes many specific problems. On the other hand, the effect of IBD on the natural history of PSC appears to be milder. However, IBD may increase the risk of postsurgical complications after LT and is a risk factor for recurrent PSC after LT. Overall, the coexistence of IBD with PSC changes the management, natural history and prognosis of both diseases.

Keywords: Primary sclerosing cholangitis; Inflammatory bowel disease; Ulcerative colitis; Crohn’s disease; Colorectal cancer

Introduction

Inflammatory bowel disease (IBD) is an idiopathic chronic disease of the gastrointestinal tract, and Crohn’s disease (CD) and ulcerative colitis (UC) are the two major forms. As a multisystemic disease, it has been associated with many extraintestinal manifestations and their frequency in IBD patients ranges from 6% to 47% [1]. Among them, hepatobiliary manifestations are frequent in both CD and UC and include a varied heterogeneous group of diseases [2]. It is estimated that 5% of patients with IBD have developed chronic liver disease [3]. Primary sclerosing cholangitis (PSC) is a chronic, progressive disease of an unknown etiology, and is characterized by fibrosclerotic stenoses and destruction of intra- and extra-hepatic bile ducts. PSC has been strongly correlated with IBD, mainly with UC, and may lead to life-threatening complications, such as cirrhosis and end-stage liver failure.

The clinical presentation of PSC is varied and patients might be asymptomatic or present with fatigue, right upper quadrant pain or recurrent cholangitis. Laboratory tests show an elevation of cholestatic enzymes, mainly increased alkaline phosphatase (ALP) [4]. A variety of auto-antibodies, which include anti-nuclear antibodies (ANAs), anti-smooth muscle antibodies (ASMAs) and anti-perinuclear antibodies (pANCA), have been detected in patients with PSC. Particularly, up to 80% of PSC patients have positive pANCA, without which being disease-specific or prognostic markers [5, 6]. The diagnosis of PSC is based on liver function tests, characteristic bile duct changes in magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP), and the exclusion of causes of secondary sclerosing cholangitis, such as IgG4-associated cholangitis, ischemic cholangitis and acquired immunodeficiency syndrome (AIDS)-related cholangiopathy [7, 8]. Furthermore, there is small-duct PSC, which is characterized by typical cholestatic laboratory tests, histological features of PSC, and normal bile ducts in cholangiography. Liver biopsy is required for the diagnosis of small-duct PSC [9]. The etiology of PSC remains unclear and several hypotheses have been proposed, such as alteration in the gut microbiota and genetic predisposition [10-12].

Treatment of PSC is limited and the two major goals of management are the treatment of complications and the relief of symptoms of PSC. The medical treatment options include ursodeoxycholic acid (UDCA) and immunosuppressive agents, such as azathioprine, infliximab and cyclosporine, and they do not seem to improve the course of disease [13]. On the other hand, endoscopic treatment of dominant extra-hepatic strictures may improve the symptoms and liver functions, and delay the need for liver transplantation (LT) [14], but LT continues to be the only potential curative therapy for PSC. The reported survival rates after transplantation are 85% and 70% at 5 and 10 years, respectively [15]. The median survival of patients with PSC from diagnosis until death or LT ranges from...
It seems that PSC affects the course of IBD and IBD coexisting with PSC represents a distinctive phenotype compared to IBD alone [17]. The reason for the distinctive phenotype of PSC-IBD is unclear. Genetic studies have found different HLA class II associations in UC patients with and without PSC [18]. Also, intestinal microbiota may play a role, because PSC appears to be characterized by intestinal dysbiosis independent from IBD [10].

**Epidemiology**

PSC is a rare disease, its incidence ranges from 0.04 to 1.3 per 100,000 person-years [19-21] and it occurs more often in middle age with a 2:1 male predominance [22]. PSC is strongly associated with IBD, the prevalence of IBD in patients with PSC ranges from 46.5% to 98.7%, and UC seems to be the most common type of IBD (> 75%) [23]. In addition, there is a close correlation between IBD and small-duct PSC and 88% of patients with small-duct PSC have concomitant IBD, mainly UC. However, it seems that the incidence of CD is higher in patients with small-duct PSC than in those with large-duct PSC [24]. Furthermore, geographical variations between PSC and IBD have been reported, including a second peak for age with a lower association with IBD in the Japanese population and a female predominance in a single study from Turkey [25-27]. On the other hand, a minority of patients with IBD develop PSC and the prevalence of PSC in IBD patients ranges from 2% to 8.1%. Male sex, nonsmoker status and a history of appendicectomy have been associated with the development of PSC in patients with IBD [28, 29]. IBD mostly presents prior to PSC, but can appear after PSC, including after LT [30].

**IBD Associated With PSC**

PSC may have an effect on the activity, extension and prognosis of IBD, and IBD associated with PSC has a unique phenotype (Table 1). PSC-IBD patients often have a less active disease, but more extensive disease [31]. Particularly, the incidence of pancolitis, backwash ileitis and rectal sparing is increased in patients with PSC and UC. The frequency of rectal sparing ranges from 10% to 66% and the frequency of backwash ileitis ranges from 10% to 51% [31-34]. Also, the number of hospitalizations and courses of steroids because of UC activity seem to be greater in patients with UC alone compared to those with UC-PSC [35]. A recent retrospective study compared UC patients with and without coexisting PSC who were in clinical remission, and showed that patients with UC and PSC had a significantly greater subclinical endoscopic (odds ratio (OR), 4.21) and histologic activity (OR, 5.13) in the right colon [36]. It is noteworthy that UC-PSC presents a unique phenotype even in the pediatric population. In a single-center retrospective study, pediatric PSC appears to associate with mild ulcerative colitis and UC, but PSC-IBD activity does not appear to have any correlation [37]. Also, a study compared a multi-center cohort of pediatric PSC-IBD patients to pediatric IBD patients without PSC. They found that the patients with IBD and PSC were more likely to present with pancolitis (89.7% vs. 72.4%, P = 0.051), while there were no statistical differences in the rates of colectomy, rectal sparing and IBD-related hospital admissions [38].

In addition, it seems that the severity of PSC influences the clinical course of UC. A retrospective study compared 46 PSC-UC patients without the need for LT with 50 PSC-UC patients who were transplanted, and showed that PSC requiring LT is associated with a reduced need for surgery and use of steroids and azathioprine [39]. Also, another study including 273 IBD-PSC patients found that LT is associated with a lower risk of colectomy (hazard ratio (HR), 0.57) [40].

PSC affects the course and phenotype of CD, and the location of CD with coexisting PSC differs compared with CD alone. The colonic involvement is more often in CD-PSC than in CD alone. Also, CD-PSC presents milder activity and the rates of penetrating and stricturing disease are lower [41].
addition, the severity of PSC seems not to be associated with the course of CD. A study including 41 PSC-CD patients described that in contrast to UC, severe PSC requiring LT does not appear to impact the clinical outcome of CD [42].

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for the majority of patients with UC who require surgery and PSC may affect the complications of IPAA. Patients with UC, who undergo IPAA, have an increased risk for acute and chronic pouchitis, when having coexisting PSC [43]. Moreover, LT seems not to reduce the risk of the development of pouchitis and not improve the preexisting chronic pouchitis [44, 45]. The incidence of pouchitis in PSC-UC ranges from 13.8% to 90%, while in UC the frequency ranges from 11.9% to 52.8% [23, 46]. On the other hand, the frequency rates of pouch failure appear to be similar in IBD-PSC patients compared to IBD patients without PSC and range from 11.2% to 16% [47, 48]. Also, development and bleeding of peristomal varices in the abdominal wall surrounding the ileostomy stoma have been observed in PSC-UC patients who underwent proctocolectomy [49].

Furthermore, CD of the pouch is one of the most common complications of IPAA and can develop in patients with prior Crohn’s colitis without previous small intestinal or perianal disease or de novo in UC patients after colectomy with IPAA. Its prevalence ranges from 2.7% to 13% [50, 51]. A retrospective study analyzed the data from 1,425 IBD patients (1,314 UC, 85 indeterminate colitis, and 23 CD) who have undergone IPPA, including 265 (18.6%) with CD of the pouch and 78 (5.5%) with PSC. They found that the presence of PSC is inversely associated with the development of CD of the pouch, with a HR of 0.39 [52].

**IBD After LT**

The course of IBD after LT seems to change, depending on many transplant-related factors. A total of 31% of patients with known IBD have been improved, while 30% of patients deteriorate and require intensification of medical therapy and/or surgery for treatment, after LT for PSC [53]. A study including 192 IBD-PSC patients, who underwent LT for PSC with a mean follow-up time of 5.91 years, reported a 3.1-fold increased risk for colectomy due to intractable disease after LT. On the other hand, LT did not influence the risk for colectomy due to colorectal cancer (CRC) [54]. However, in another study including 167 PSC-UC patients, the progressive PSC requiring LT was associated with a reduced need for colectomy in patients with UC [55].

Also, immunosuppressive agents used for LT might affect IBD activity. Particularly, tacrolimus has been associated with the worsening of IBD course. A recent study included 151 patients with PSC-IBD and intact colon after LT and showed that the patients, who received tacrolimus, had 3.51-fold higher risk for unfavorable IBD course compared with those treated with cyclosporine. Furthermore, azathioprine use after LT was associated with improved course (HR, 0.42) [56]. In another study including 353 patients, who had IBD at the time of LT, young age at diagnosis of IBD and dual treatment with tacrolimus and mycophenolate mofetil were associated with increased IBD activity after LT. Instead, combination treatment with cyclosporine and azathioprine had protective effects [57].

The safety of biological agents after LT remains an important problem and the data are not completely clear. Severe studies have described serious infections, such as cytomegalovirus (CMV) infection, bacterial pneumonia, cryptosporidiosis, or *Enterococcus faecalis* infection, in IBD patients after LT [58, 59]. A meta-analysis found that anti-TNF treatment in combination with LT-associated immunosuppression does not increase the serious infection rate, but it concluded that further studies are needed due to the lack of randomized clinical trials [60]. However, biological agents seem to be effective for achieving clinical and endoscopic improvement in IBD after LT [58, 61]. Also, vedolizumab has been successfully used in moderate to severe IBD after LT, without recorded serious complications [62].

De novo development of IBD can occur after LT despite immunosuppressive therapy, and the incidence of de novo IBD after solid organ transplantation is 10-fold higher compared to the general population [63]. A longitudinal multi-center study analyzed data from the Nordic Liver Transplant Group and described that 12.7% (11/86) of patients developed IBD after LT for PSC, in a follow-up period of 7 years after LT [57]. In addition, the development of de novo IBD in patients undergoing LT for indications other than PSC, such as autoimmune hepatitis, Wilson’s disease and acute-on-chronic hepatitis B, has been reported [64]. CMV infection has been implicated in the development of de novo IBD, due to high incidence of CMV in patients with de novo IBD [65]. Also, a retrospective study described that a combination of CMV positive donor/negative recipient increased 4.4-fold the risk of de novo IBD [66]. In a multi-center retrospective cohort study, the risk of de novo IBD increased with mycophenolate mofetil and decreased with azathioprine [56].

**The Influence of IBD on PSC**

The role of IBD in natural history and behavior of PSC has not been well determined. A retrospective study analyzed data from 167 patients with PSC and UC and 55 PSC patients without UC, and demonstrated that patients with concurrent UC had a lower Mayo risk score and serum bilirubin at diagnosis. However, the proportional hazards analysis showed that UC was not associated with death or LT when adjusting for gender, Mayo risk score and year of PSC diagnosis [67]. Also, differences in cholangiography have been described and combined intrahepatic and extra-hepatic bile duct involvement has been more often observed in PSC patients with IBD (81.5% vs. 46.2%) [68].

In addition, many studies have shown that IBD does not affect the outcomes of PSC. In a Swedish study including 305 PSC patients, the coexistence of IBD was not associated with the prognosis of PSC and the need for LT [69]. Also, in a retrospective multi-center Israeli study including 141 patients, there were no differences in the rates of cirrhosis, mortality of patients and the mean transplant-free survival between patients with isolated PSC and patients with PSC-IBD [70]. Furthermore, it seems that colectomy has a little effect on the pro-
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The risk of CRC is increased in patients with IBD, mainly UC, compared with that in the general population. A meta-analysis synthesized the results of 116 studies of IBD-correlated CRC in 54,478 patients and found that the overall incidence rate of CRC in UC patients was 3.7%, and the incidence rate was 2% at 10 years after the diagnosis of UC, 8% at 20 years and 18% at 30 years [81]. The risk of CRC in CD patients seems to be lower and is associated with colonic distribution of disease. Colonic involvement of CD is correlated with 4.5-fold relative risk for development of CRC, while ileocecal or ileal disease is not associated with an increased risk for CRC [82].

Patients with IBD and coexisting PSC have a markedly increased risk of CRC compared to those with IBD alone, while the risk of development of CRC in PSC patients without IBD is low [83]. According to a meta-analysis, patients with PSC-UC have an increased risk of CRC compared with those with UC alone (OR, 4.09; 95% CI, 2.89 - 5.76) [84]. The risk of development of CRC in patients with PSC-CD is not as strong as that in PSC-UC. A cohort study analyzed the data from 28 patients with PSC-CD and compared them with the controls with CD alone. They found that PSC was a risk factor for the development of CRC in patients with CD (OR, 6.78; 95% CI, 1.65 - 27.9) [41]. The right colon is the prediction site of CRC in PSC-IBD patients in contrast with patients with IBD only (67% vs. 36%, P = 0.006). Also, PSC-IBD patients tend to be younger at CRC diagnosis [85]. Furthermore, colon neoplasms develop early in the course of IBD and PSC. The occurrence of CRC within 2 years of the diagnosis of IBD and PSC is similar to that within 8 to 10 years of the diagnosis of IBD and PSC [86]. In addition, the coexistence of PSC has been associated with 3.42-fold elevated risk for dysplasia progression in IBD patients with low grade dysplasia [87].

It is important to note that the risk for CRC does not resolve after LT. According to a meta-analysis, the incidence rate of CRC in patients with PSC-IBD and an intact colon at the time of LT is 13.5 per 1000 person-years and long duration of IBD and extensive colitis are risk factors for the development of CRC [88]. Additionally, a Nordic multi-center study found that the cumulative risk for CRC after LT was 0.6%, 1.8% and 3.3%, after 5, 10 and 20 years, respectively [89]. For this reason, guidelines recommend annual surveillance with colonoscopy and biopsies for CRC in IBD patients from the time of diagnosis of PSC, including liver transplant [90].

It has been suggested that the use of UDCA may reduce the risk of CRC in IBD-PSC patients due to the reduction of toxic secondary bile acids in the colon [91]. However, the results of studies are conflicting. Particularly, some of them showed that the use of UDCA may contribute to the prevention of CRC [92, 93], other studies found that UDCA does not have any effect on the prevention of development of CRC [94, 95], while a multi-center randomized placebo-controlled trial showed that long term use of high dose UDCA (28 - 30 mg/kg/day) is associated with the development of colorectal neoplasia in patients with UC and PSC [96]. A meta-analysis found that there was no significant protective association between UDCA and colorectal neoplasia. However, there was a significant chemopreventive effect on the risk of advanced colorectal neoplasia (CRC and/or high-grade dysplasia) (OR, 0.35; 95% CI, 0.17 - 0.73) [97].

Biliary Tract Cancer in PSC-IBD Patients

Cholangiocarcinoma (CCA) is a lethal complication of PSC. CCA has an estimated annual incidence of 1% and lifetime occurrence of approximately 20% in patients with PSC [98, 99]. The role of IBD in the development of CCA in PSC patients has not been elucidated. A retrospective study including 399 PSC-IBD patients found that IBD duration is associated with an increased risk for the development of CCA (HR, 1.37 per 10 years), while colectomy itself does not modify the risk [100]. However, in a long term single-center study including 200 PSC patients, the presence of IBD was not correlated with the development of CCA [101].

Conclusions

IBD with coexisting PSC presents a distinct phenotype compared to IBD alone. IBD patients with PSC have a more extensive disease, the frequency rates of pancolitis, backwash ileitis and rectal sparing are increased in UC-PSC patients, and the colonic involvement is more often in CD-PSC than in CD alone. Furthermore, PSC appears to affect complications of IPAA, and the incidence rates of acute and chronic pouchitis are increased in the patients with PSC and IBD. Also, the coexistence of PSC increases the risk for CRC, and annual surveillance with colonoscopy is recommended. On the other hand,
IBD seems to have a smaller impact on PSC, and increase the incidence of recurrence of PSC. Also, IBD may be a negative prognostic factor of complications of LT. The management of IBD after LT and the choice of combination of immunosuppressants remain a complex and not fully clarified problem, which requires more studies for this subgroup of IBD patients.

Abbreviations

CD: Crohn’s disease; CRC: colorectal cancer; IBD: inflammatory bowel disease; IPAA: ileal pouch-anal anastomosis; LT: liver transplantation; PSC: primary sclerosing cholangitis; UC: ulcerative colitis; UDCA: ursodeoxycholic acid; OR: odds ratio; HR: hazard ratio; AIDS: acquired immunodeficiency syndrome; ALP: alkaline phosphatase

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