Inflammatory Bowel Disease and Primary Sclerosing Cholangitis: A Review of the Phenotype and Associated Specific Features

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disease of the gastrointestinal tract. Up to 50% of patients may develop extraintestinal manifestations (EIM) during their disease course. One such EIM is primary sclerosing cholangitis (PSC), described for the first time in 1965. PSC is a chronic and progressive cholestatic disease, characterized by inflammation and fibrosis of the intrahepatic and/or extrahepatic ducts, that may result in liver cirrhosis and eventually end-stage liver disease. Orthotopic liver transplantation (OLT) is the only potentially curative therapy for PSC, with survival rates of 85% and 70% at 5 and 10 years, respectively. Without OLT, half of symptomatic patients die within 12 to 15 years.

In Western countries, the reported incidence of PSC is 0.07 to 1.3 per 10^5 yr, and the prevalence is 8.5 to 13.6 per 10^5. About 70% of patients with PSC have underlying IBD, most frequently ulcerative colitis (UC) in over 75% of cases. The prevalence of IBD in PSC patients ranges from 50% to 99% across different studies. Several factors could explain this large variation. In a recent systematic review, the studies that used both endoscopic and histological criteria for IBD diagnosis, showed a higher median percentage of IBD among PSC patients. Geographic differences could also contribute to this variation. Asian studies report a lower prevalence of IBD in PSC patients in comparison to European and American populations. However, in some of these studies, IBD diagnosis was established or excluded based on registry data or notes in medical files without reviewing original endoscopy or histology. In fact, a recent Japanese report by Sano et al. using strict case ascertainment criteria reported an IBD incidence of 68.9% among PSC patients. Since disease activity of IBD in PSC patients is often mild and occasionally asymptomatic, it is important to assure the use of endoscopic and histological criteria when assessing IBD incidence in this population. Conversely, in patients with known IBD, PSC is found much less commonly, occurring in about 2% to 8% of UC patients and 3% of Crohn’s disease (CD) cases.

Although there may be a possible common pathogenesis...
between PSC and IBD, the two disorders can occur at different times. PSC may be diagnosed many years after proctocolectomy for colitis, and conversely IBD can appear many years after the initial diagnosis of PSC or even after OLT altogether. In most reports, IBD diagnosis precedes that of PSC. In a recent report, Sinakos et al. demonstrated an increased frequency of PSC being diagnosed first when comparing two time cohorts (35% in 1993–1997 vs 50% in 2003–2007, p=0.0009). An inherent bias in determining the timing of diagnosis pertains to the fact that PSC may have a silent asymptomatic period, and equally the IBD associated with PSC may be mildly symptomatic or even asymptomatic, and therefore can go undiagnosed. Since 70% of PSC cases are associated with IBD, the presence of CD or UC makes the diagnosis of PSC easier. In patients with known IBD, the presence of persistent unexplained cholestasis obliges one to exclude concurrent PSC through magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography, especially if the patient is symptomatic for biliary obstruction. When PSC is diagnosed first, half of the cases have only abnormal laboratory tests; the typical diagnostic hallmarks of fever, itching, and jaundice are rarely seen nowadays. Symptomatic patients usually present with fatigue and pruritus and can also exhibit jaundice, hepatosplenomegaly or scratching injuries. Recurrent episodes of bacterial cholangitis with fevers, chills, right upper quadrant pain and jaundice can also be a part of the clinical presentation, and usually develops in about 10% to 15% of patients during the course of the disease. The diagnosis of PSC is based on the findings of diffuse multifocal strictures and dilations in the intrahepatic and/or extrahepatic biliary tree. Patients with a confirmed diagnosis of PSC should undergo colonoscopy with biopsies to exclude concomitant IBD or any malignancy, even if they report no gastrointestinal symptoms. As the majority of PSC-IBD patients have mild disease activity and even possible normal endoscopic appearances, histological sampling is crucial to avoid underdiagnosis. Although no evidence-based guidelines are available, if the index colonoscopy is negative for IBD, a repeat colonoscopy every 3 to 5 years should be performed to monitor for possible onset of IBD.

**DISEASE PATHOGENESIS**

PSC is likely to have an underlying multifactorial etiology, with a predominant immune-mediated process. PSC and IBD are interrelated conditions that may well share an underlying predisposition (Fig. 1). Both diseases share common antibodies, such as those directed against cytoplasmic and nuclear antigens of neutrophils with a characteristic perinuclear staining pattern (p-ANCA). p-ANCA antibodies have been found in 26% to 85% of PSC patients and in up to 68% of patients with UC.

From a genetic standpoint there is increasing evidence that PSC is distinct from UC and CD. Large-scale genome-wide association studies (GWAS) have identified close to 200 independent loci associated with IBD. Most of these loci are shared between UC and CD. GWAS studies in PSC have identified a total of 16 PSC susceptibility loci. In the most recent genetic analysis there was surprisingly limited overlap between PSC and IBD loci. Half of the PSC loci failed to show a robust association with IBD, suggesting overlapping yet distinct genetic mechanisms. Genetic predisposition to autoimmune bile duct injury triggered by toxic or infectious agents that may gain access through the diseased colon is potentially a major mechanism leading to PSC in IBD patients.

Two hypotheses that link PSC and IBD include the "gut lym-

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**Fig. 1.** Possible hypothesis linking primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) pathogenesis, including the genetic predisposition, immune-mediated processes, altered gut microbiota and altered bile acid (BA) metabolism. GWAS, genome–wide association studies.
phocyte homing” hypothesis and the “leaky gut” hypothesis.20 Activated lymphocytes from the inflamed and permeable gut may enter the enterohepatic circulation and persist as memory cells that cause hepatic inflammation.21,22 Some molecular features, such as chemokines and adhesion molecules, are shared by the liver and intestine and could contribute to lymphocyte binding at both sites.21 T cells activated in the gut during active IBD could differentiate into effector cells with the ability to bind to both hepatic and mucosal endothelium. The activation and expansion of these memory cells in the liver could eventually lead to the induction of MADCAM-1 and CCL25 in the liver, promoting the recruitment of CCR9+ α4β7+ mucosal T cells and the development of inflammation.23 Findings such as PSC development after colectomy for IBD, or the development of IBD after OLT for PSC, have led some investigators to suggest that aberrant homing of lymphocytes between the intestine and liver could be involved in the pathogenesis of the PSC-IBD phenotype.21

The “leaky gut” hypothesis refers to the association between progressive hepatic and biliary injury and increased intestinal permeability and translocation of bacterial metabolites from the gut.24 The liver receives approximately 75% of its blood supply from the splanchnic circulation and is constantly exposed to both beneficial and noxious molecules from the intestinal microbiome.25 This so-called “gut-liver axis” is essential for the maintenance of health but may also play an important role in pathogenesis of liver and intestinal diseases.25,26 In IBD there is a known intestinal microbiome dysbiosis, characterized by lower biodiversity and decreased bacteria of the Firmicutes phylum.27 In PSC-IBD patients there is also an altered microbiome composition, and it appears to be different from IBD-only patients.28,29 Recent evidence suggests a marked increase in Veillonella, Escherichia, Lachnospiraceae and Megasphera genera in PSC-IBD patients.28,29 Other genera such as Prevotella, Roseburia, and Bacteroides are significantly reduced.28 This dysbiosis may be associated with mucosal immunity dysregulation by modulating intestinal permeability and altering homing of gut-specific lymphocytes.28 Recently, evidence for an etiologic role of the intestinal microbiome in PSC has been provided by animal model studies. Tabibian et al.30 used MDR2 knockout mice (a widely utilized animal model of PSC) to assess the role of the commensal microbiota in the pathogenesis of biliary injury. Germ-free MDR2 knockout mice exhibited a dramatically worsened PSC phenotype, with exacerbated biochemical and histological features and an increase in cholangiocyte senescence.30 Additionally the authors found that ursodeoxycholic acid (UDCA), which is a commensal microbial metabolite, had an antisenescence effect in an in vitro model.30 These findings demonstrate the protective role of commensal microbiota and its metabolites against biliary injury and hint at possible new targets for future studies of therapeutic interventions in PSC.

The interaction between microbiota and bile acid (BA) metabolism may also play an important role in the PSC-IBD phenotype. Recent evidence supports the existence of BA dysmetabolism in IBD patients due to impaired microbiota enzymatic activity.25 One of the contributing factors for the difference in phenotype between PSC-IBD patients and IBD controls may be altered concentration and/or composition of colonic BA impacting on gut microbiota and stool BA metabolism.

In summary, PSC-IBD pathogenesis is still unclear but this phenotype is likely to have an underlying multifactorial etiology, influenced by genetic predisposition, immune-mediated processes and altered gut microbiota (Fig. 1).

**CLINICAL FEATURES OF PSC-IBD**

1. **Demographic features of patients with PSC-IBD**

Patients with the PSC-IBD phenotype have demographic features resembling PSC cases, although the PSC diagnosis tends to occur at a younger age, when compared with PSC-only controls (mean age, 33.6±17.2 years vs 58.9±18.2 years; p<0.001).31 The incidence is higher in males and is more prevalent in young and middle-aged patients.13-15 The age at clinical onset of IBD is controversial. Some reports indicate that the mean age for IBD diagnosis is higher among PSC-IBD patients compared with IBD controls,13 but a recent study reported that PSC-UC patients had a UC diagnosis at a significantly earlier age compared with UC controls (mean age, 24.5 years vs 33.8 years).31

2. **The IBD phenotype of PSC-IBD patients**

As stated above, the co-occurrence of PSC with IBD is associated with a distinct IBD phenotype (Fig. 2). PSC-IBD patients typically have mild intestinal disease activity and an increased incidence of extensive colitis and pancolitis, rectal sparing and...
backwash ileitis (Table 1).\textsuperscript{5,9,10,12,15,16,18-38} Extensive colonic involvement, irrespective of the IBD subtype (i.e., CD vs UC), is the primary IBD phenotype associated with PSC. From a population-based cohort of 579 PSC patients in the Netherlands, pancolitis was observed in 94\% of PSC-UC patients and in 96\% of PSC-CD patients.\textsuperscript{37} Though rare, some patients with ulcerative proctitis and Crohn’s ileitis have concomitant PSC.\textsuperscript{37,29} Although pancolitis is a characteristic finding of PSC-IBD patients, it occurs at variable rates (35\% to 95\% of patients).\textsuperscript{5} Some cases are endoscopically diagnosed as right-sided IBD.\textsuperscript{11} In a recent systematic review, the majority of studies addressing disease activity found that the prevalence of inflammation was highest in the right colon and lowest toward the distal colon.\textsuperscript{6,11} This pattern of inflammation was significantly different from matched non-PSC IBD-controls.\textsuperscript{6,12}

The frequency of rectal sparing and backwash ileitis in PSC-UC patients differs among reports. A recent systematic review reported an incidence of rectal sparing from 6\% to 66\% (versus 2\% to 25\% in IBD without PSC) and of backwash ileitis between 2\% to 25\% in IBD without PSC).\textsuperscript{6} It is worth noting that since PSC-IBD patients typically have quiescent disease, microscopic inflammation may still be present in spite of an endoscopically normal-appearing rectum.\textsuperscript{12} The frequency of rectal sparing and backwash ileitis should be investigated in future studies using a consensus definition.

In PSC-CD patients, the anatomic location of the disease differs from patients with isolated CD. Colonic involvement is the most often reported (37\% to 82\%), followed by ileocolic involvement (22\% to 58\%), and rarely isolated ileal involvement (2\% to 5%).\textsuperscript{6} In PSC-CD patients there is a lower frequency of strictureting and penetrating disease compared to patients with isolated CD.\textsuperscript{5,29}

### 3. IBD disease activity in PSC-IBD patients

Despite the higher prevalence of pancolitis, the intestinal inflammation in PSC-IBD patients is usually quiescent leading to mild symptoms, reduced use of steroids and decreased rates of hospitalization.\textsuperscript{5,30} On histological grounds, the colonic inflammation is also very mild, with only focal basal plasmacytosis and occasional mild cryptitis.\textsuperscript{30} Schaeffer et al.\textsuperscript{10} reported histological findings of 97 PSC-IBD patients and found no evidence of severe disease activity (active cryptitis with crypt abscesses, surface erosion or ulceration) in any of the patients. In a matched case-control study by Joo et al.,\textsuperscript{21} PSC-UC patients demonstrated an overall significantly lower grade of inflammation in the colon compared with UC controls (mean grade, 2.09±0.085 vs 2.59±0.92; p<0.05). Furthermore, there are some data to suggest that there is an inverse relationship between PSC disease severity and IBD activity. Marelli et al.\textsuperscript{25} evaluated 96 patients with PSC-UC, 52\% of whom needed OLT for worsening PSC, and compared them with the PSC-IBD group that did not need OLT. The PSC-IBD group that needed OLT more frequently had clinically quiescent UC, fewer UC flares, and required less steroids and immunosuppressives. By contrast, the group where OLT was not performed showed an increased need for intestinal surgery and more frequent colorectal neoplasia (CRN).\textsuperscript{35} These data suggest that PSC severity may have a “protective” effect on UC’s activity.

### 4. Course of IBD after OLT

There is conflicting evidence regarding the course of IBD after OLT for PSC. Several reports demonstrated worsening

### Table 1. Studies Evaluating IBD Extension, Backwash Ileitis, and Spared Rectum in PSC-IBD Patients Compared to IBD-Only Controls

| Study               | Year   | No. of patients | IBD extension (proctitis/left-sided/pancolitis) % | Backwash ileitis % | Rectal sparing % |
|---------------------|--------|-----------------|-------------------------------------------------|--------------------|-----------------|
| Olsson et al.\textsuperscript{32} | 1991   | 55, 1,445       | 5.5/NA/94.5                                     | 38.2/NA/61.8       | NA/NA/NA        |
| Loftus et al.\textsuperscript{15}  | 2005   | 71, 142         | NA/NA/87                                       | NA/NA/54           | 51/7/52         |
| Sokol et al.\textsuperscript{23}   | 2008   | 75, 150         | NA                                             | NA                 | 18.7/24/20      |
| Joo et al.\textsuperscript{31}     | 2009   | 40, 40          | 0/7.5/85                                       | 0/35/45            | 10/7.5/27.5     |
| Sano et al.\textsuperscript{3}     | 2011   | 20, 60          | 5/5/35                                         | 30/31.7/35         | NA/NA/NA        |
| Ye et al.\textsuperscript{34}      | 2011   | 21, 63          | NA/NA/95.2                                      | NA/NA/55.6         | 42.9/3.2/38.1   |
| Marelli et al.\textsuperscript{35} | 2011   | 96, 0           | 0/10/90                                        | NA                 | NA/NA/NA        |
| Jorgensen et al.\textsuperscript{12} | 2012    | 110, 0         | NA/3/55                                        | NA                 | 20/NA/65        |
| O’Toole et al.\textsuperscript{36} | 2012   | 103, 2,649      | 1/22.3/54.4                                     | 7.9/24.5/25        | NA/NA/NA        |
| Boonstra et al.\textsuperscript{27} | 2012   | 80, 80          | 2.5/2.5/65                                      | 5/20/43.8          | 5/2.5/10        |
| Gelley et al.\textsuperscript{38}  | 2012   | 20, 0           | 15/15/55                                        | NA                 | NA/NA/NA        |
| Schaeffer et al.\textsuperscript{10} | 2013   | 97, 0           | 0/17.5/43.4                                     | NA                 | NA/NA/NA        |
| Sinakos et al.\textsuperscript{22} | 2013   | 129, 0          | NA/12.4/58.9                                    | NA                 | 11.6/NA/24      |

IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; NA, not available.
colitis activity following OLT in approximately 30% of PSC-IBD patients. Furthermore, de-novo IBD after OLT has also been reported and it may develop in 14% to 30% of PSC patients up to 10 years after transplantation. Retrospective studies comparing IBD activity before and after liver transplantation found that endoscopic colonic inflammation was more frequent after OLT, as was the rate of relapse and overall clinical IBD activity. A retrospective study of 31 patients with PSC-UC who received OLT, showed that the Mayo score was higher after transplantation compared with the pre-transplant score (mean score, 2.91±0.9 vs 6.64±3.7; p=0.009). The above findings have led to the speculation that the diseased PSC liver somehow keeps colonic inflammation in check. Several factors may be associated with a worse course of IBD after OLT such as a new balance in the immune system favoring an immune-mediated attack against the colonic mucosa, the presence of active IBD at the time of transplantation, discontinuation of 5-aminosalicylates, infrequent use of azathioprine and the use of tacrolimus. Proposed that patients treated with tacrolimus had a stronger suppression of interleukin-2 production by T-cells and that resulted in an inability to activate regulatory responses. However, subsequent studies did not confirm this suggestion. Although further studies are required, cyclosporine and azathioprine are preferred over tacrolimus because they seem to have a more favorable outcome on IBD after OLT for PSC. Anti-tumor necrosis factor treatment may also be effective and safe for treating IBD in this context. Early colectomy should be considered for patients with severe colonic inflammation after OLT. A recent systematic review, reported a colectomy rate after OLT ranging from 4% to 20%.

Of note, the worsening of IBD after OLT has not been universally confirmed. Jorgensen et al. performed a cross-sectional study in 155 PSC-IBD patients. Forty-two patients (38%) had undergone OLT and had a lower clinical and histologic disease activity when compared to the nontransplanted cohort. The authors suggested this could be due to the implementation of immunosuppressive medication in the transplanted group, namely long-term prednisolone therapy that may be a predictor of less severe IBD posttransplant.

5. Course of IBD after proctocolectomy

PSC-IBD patients who undergo proctocolectomy with ileal pouch anal anastomosis (IPAA) have a higher risk of developing pouchitis, which affects 13.8% to 90% of cases (versus 33% in patients with conventional IBD). Nonetheless, the long-term outcomes are often satisfactory, with the incidence of pouch failure in PSC-IBD patients subjected to IPAA being similar to IBD-only patients. Mathis et al. reported retrospectively on 100 patients with PSC-UC who underwent IPAA with 6 years of follow-up. Pouch failure was observed in only 3% of patients due to refractory pouchitis, pouch cancer or fistula formation. The mechanism underlying the association between PSC and pouchitis remains unclear.

6. The PSC phenotype of PSC-IBD patients

While PSC is often associated with a distinctive IBD phenotype, the effect of IBD on the natural history and disease behavior of PSC is less well defined. In PSC patients with concomitant IBD, the PSC phenotype may differ when compared to PSC patients without IBD. Combined intrahepatic and extrahepatic biliary involvement has been described to be more common in PSC-IBD patients compared to PSC patients alone (81.5% vs 46.2%, p<0.05), but has not always been described in the literature. At least two other retrospective reviews have refuted the finding of a higher prevalence of intra- and extra-hepatic biliary involvement in patients with coexisting IBD.

Long-term PSC outcomes also do not seem to be associated with the presence or disease severity of IBD. In a natural history study of 305 Swedish PSC patients, associated IBD had no prognostic significance on the need for OLT or liver-related deaths. Similarly, transplant-free survival rates, cirrhosis rates, and mortality of PSC patients were found to be independent of concomitant IBD in a retrospective Israeli study of 141 PSC patients. Navaneethan et al. also concluded that UC did not affect the long-term liver outcomes in PSC patients including death or need for OLT, after controlling for liver disease severity. As corroborative evidence to this study, Ludwig et al. found that there were no significant histological differences including periductal fibrosis, periductal inflammation, portal edema and fibrosis or cholestasis between PSC patients and PSC-UC patients on liver biopsy specimens. Nevertheless, in a population-based epidemiologic study of PSC patients from New Zealand, PSC-IBD patients when compared to PSC patients were more likely to require OLT or die (p=0.03).

In contrast to the majority of findings reported in the aforementioned studies, some of the PSC-IBD literature suggests that the rapidity of PSC disease progression may be contingent upon the specific IBD phenotype. A retrospective case-controlled study utilizing the Oxford PSC and IBD databases revealed that major event-free survival (cancer, OLT or death) was prolonged in the PSC-CD group compared to the PSC-UC group (Cox regression, p=0.04). The authors postulate that this may be explained by the increased prevalence of small-duct PSC in PSC-CD patients compared to PSC-UC patients, which was also suggested by Rasmussen et al. Furthermore, in a retrospective review of 240 PSC patients, even large duct PSC-CD patients had less liver-related morbidity and mortality compared to PSC-UC patients and PSC patients without IBD.

7. The effect of IBD on recurrent PSC post-OLT

PSC recurrence (rPSC) after OLT occurs in 30% to 50% of patients, usually 10 years posttransplantation. Akin to the data available regarding the relationship between IBD and PSC disease progression, the presence of concomitant IBD in PSC
patients has not been unanimously identified as a risk factor for rPSC. In a systematic review of autoimmune liver diseases after transplantation, there was no statistically significant difference in the rate of rPSC in patients with and without IBD. In another retrospective analysis of 31 PSC patients who underwent OLT, 5-year survival rates, infectious complications, frequency of rejection and need for re-transplantation did not differ based on whether patients had coexisting IBD. Moreover, a retrospective analysis of 105 PSC patients who underwent OLT revealed no correlation between rPSC and IBD activity. On the contrary however, in another study PSC patients with UC had significantly more rPSC compared to PSC patients without UC. Several publications have described that an intact colon is a strong predictor of rPSC and that colectomy potentially has a protective effect against rPSC. In a cohort of 230 PSC patients who underwent OLT, colectomy pre- and peri-OLT conferred a protective effect against rPSC in the transplanted graft. Moreover, an intact colon prior to OLT was the strongest predictor of rPSC. Joshi et al. reviewed 110 PSC patients who underwent OLT to help understand the impact of IBD on graft survival. Although the mean time to rPSC following OLT and graft survival rates were similar between the PSC group and PSC-IBD group, multivariable analysis revealed that active IBD at the time of OLT was a significant predictor of graft failure. Furthermore, on univariate analysis, colectomy pre-OLT was associated with improved graft survival. The authors speculate that decreased graft survival in the posttransplant period may be related to cases of hepatic artery thrombosis in the context of active IBD. Another retrospective study of 59 PSC patients post-OLT found that the presence or severity of IBD did not affect patient survival nor the incidence of rPSC. Furthermore, on multivariable analysis, colectomy pretransplant was not associated with rPSC (hazard ratio, 0.32; 95% confidence interval [CI], 0.04 to 2.51; p=0.207). Though colectomy may be beneficial in a subset of PSC-IBD patients, concerns regarding operating on decompensated PSC and the potential for parastomal varices postoperatively must be considered.

8. The effect of IBD on acute cellular rejection post-OLT

Despite opposing evidence on the association of IBD with rPSC, data supports that PSC-IBD patients are at risk for a greater number of acute cellular rejection (ACR) episodes post-OLT. In a retrospective chart review of 55 PSC patients who underwent OLT, the incidence of acute rejection was higher in PSC-IBD patients compared to PSC patients (27/31 vs 10/24, p=0.0006). Moreover, PSC-IBD patients who were diagnosed with IBD at a younger age were more likely to develop severe acute rejection. In spite of the increased incidence of ACR in this study, 5-year survival rates and rPSC post-OLT did not vary based on the presence of concomitant IBD.

9. Colorectal dysplasia and cancer in PSC-IBD patients

Since its initial description by Broome et al., plenty of studies have now confirmed the increased risk of CRN (colorectal dysplasia and colorectal cancer [CRC]) in patients with PSC-IBD (Table 2). Even though there are small case series that have shown contradictory findings, a meta-analysis evaluating 13,379 patients with IBD, 1,022 (7.63%) of whom had concomitant PSC, showed that there was a 3-fold increased risk of CRN and cancer among patients with PSC-IBD compared to the IBD-only population (odds ratio [OR], 3.24; 95% CI, 2.14 to 4.90). This trend persisted even after evaluating CRC risk alone (OR, 3.41; 95% CI, 2.13 to 5.48). In a subgroup analysis, PSC-UC patients were found to have a higher risk of both dysplasia (OR, 2.98; 95% CI, 1.54 to 5.76) and cancer (OR, 3.01; 95% CI, 1.44 to 6.29) compared to UC-only patients, although there was high heterogeneity among the studies. Particularly, the PSC-CD population had a nonstatistically significant higher risk of CRN and cancer (OR, 2.32, p=0.133 and OR, 2.91, p=0.388, respectively). Interestingly, in one large cohort describing the risk of cancer in PSC patients, CRN risk was only increased when IBD was also present. Some have suggested that the increased risk of CRN in PSC-IBD patients could be related to the presence of longstanding underdiagnosed disease and colonic inflammation. This argument has been disputed by some reports describing the same duration of IBD in the PSC and non-PSC population in patients with CRC. However, there may be a bias since PSC patients may have a subclinical IBD phase, leading to an underestimation of the actual burden of disease. Most importantly, Navaneethan et al. suggested a higher risk in the first 2 years after diagnosis of PSC-UC, but did not find any increased risk in the subsequent years, which decreases the likelihood that a longer disease course would increase the CRN risk. There are some common features of CRN in PSC-IBD patients: extensive colon involvement, more frequent CRN in the right colon (proximal to the splenic flexure), and more frequent bile duct dominant stenosis (i.e., extrahepatic bile duct high-grade stenosis with obstruction).

The mechanisms underlying the increased risk of CRN in PSC-IBD patients remain unknown. Different authors proposed a variety of mechanisms that may be partially responsible for this outcome (summarized in Table 3), though these are still not conclusive. In rat models, BA have been found to have a carcinogenic potential (specifically secondary BA, like deoxycholic acid). A different stool BA abundance and/or composition could potentially be involved in the right-sided CRN risk observed in PSC-IBD, although this has never been demonstrated. Whether the specific dysbiosis that has been described in PSC-IBD could be involved in this risk remains unknown. Other mechanisms described include inactivation of the Farnesoid X receptor pathway, shown to be involved in hepatic and colonic inflammation and CRC, and
Table 2. Studies Evaluating the Risk of Colorectal Neoplasia in PSC-IBD Patients

| Study                      | Year | Type of study | No. of patients | Outcome                                                                 |
|----------------------------|------|---------------|-----------------|--------------------------------------------------------------------------|
| Broome et al.              | 1992 | Prospective   | 72 UC patients  | 28% of patients with CRN and/or DNA aneuploidy had IBD and PSC, which was statistically significant (p=0.0004). |
|                            |      |               | followed to see presence of CRN | Risk of CRN in PSC-UC was 9%, 31%, and 50% after 10, 20, and 25 years of disease, compared to 2%, 5%, and 10% in UC-only patients (p=0.001). |
| Brentnall et al.           | 1995 | Prospective   | 40 Patients vs 2 groups of 40 UC-only patients | Colonore neoplasia was present in 45% of PSC-UC patients, vs 16% in UC-only (p=0.002). |
| Leidenius et al.           | 1996 | Prospective   | 20 Patients vs 25 UC-only patients | CRN presented in 29% of PSC-UC patients, vs 9% in UC-only (p<0.05). |
| Shetty et al.              | 1997 | Prospective   | 27 Patients vs 1,185 UC-only patients | Colonore neoplasia was present in 59.5% of PSC-UC patients vs 11.5% in UC-only patients (RR, 6.9; 95% CI, 3.0–16.0). |
| Marchesa et al.            | 1999 | Prospective   | 132 Patients vs 196 UC-only patients | CRN presented in 25% of PSC-UC patients, vs 5.6% in UC-only (adjusted RR, 3.15; 95% CI, 1.37–7.27; p<0.001). |
| Jess et al.                | 2007 | Retrospective | 43 Patients vs 102 control patients | PSC was associated with a higher risk of developing CRN (OR, 6.9; 95% CI, 1.2–40). |
| Terg et al.                | 2008 | Prospective   | 1,333 Patients vs 25 Years cumulative risk of CRN was 23.4% in PSC-IBD vs 0% in IBD-only (p=0.002). PSC was a risk factor for CRC (OR, 10.8; 95% CI, 3.7–31.3). |
| Sokol et al.               | 2008 | Prospective   | 75 Patients vs 152 IBD-only patients | 7% in UC-only, respectively (p=0.002). |
| Lindstrom et al.           | 2011 | Prospective   | 28 Patients vs 152 IBD-only patients | CRN presented in 2% in CD-only (OR, 6.78; 95% CI, 1.65–27.9; p=0.016). |
| Ananthakrishnan et al.     | 2014 | Retrospective | 224 Patients vs 5,522 UC patients | PSC-IBD had a higher risk of CRC (OR, 5.00; 95% CI, 2.80–8.95) and digestive tract cancer (OR, 10.4; 95% CI, 6.86–15.76), compared to IBD-only patients. |
| Navaneethan et al.         | 2016 | Retrospective | 223 Patients vs 50 with PSC-CD | PSC-UC patients had higher risk for colonic neoplasia compared to PSC-CD (35.9% vs 18%, p=0.009). |

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; CRN, colorectal neoplasia; RR, relative risk; CI, confidence interval; OR, odds ratio; CD, Crohn’s disease.

Table 3. Proposed Mechanisms for the Increased Risk of Colorectal Neoplasia in PSC-IBD Patients

| Mechanism   | Explanation                                                                 |
|-------------|-----------------------------------------------------------------------------|
| Genetic     | Polymorphisms present in TNFα promoter and specific genome associations in proximity to HLA complex on chromosome 6p21 have been associated with a higher likelihood of developing CRN. |
| Bile acid   | Cholestasis favors decreased intestinal BA reabsorption. Microbiota convert primary BA to secondary BA, which have a carcinogenic potential. |
| FXR pathway | FX secretion by the intestine is induced by the presence of BA. Normally, FX leads to a decrease in the production of BA by the liver. |
| Microbiome  | Gut bacteria are presumed to act on altered BA composition resulting in proinflammatory and procarcinogenic compounds. |

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; HLA, human leukocyte antigen; CRN, colorectal neoplasia; BA, bile acid; FXR, farnesoid X receptor; FX, farnesoid X.
polymorphisms in two genes in the chromosome 6p21. A more comprehensive understanding of the PSC pathogenesis and the involved BA dysmetabolism and microbiota dysbiosis will probably help to clarify the mechanisms involved in the increased CRN risk in these patients.

One would hypothesize that once indefinite or low-grade dysplasia (LGD) is diagnosed in PSC-IBD, the rate of progression to high-grade dysplasia or CRC would be faster than in IBD patients. However, while some studies have described the rate of progression of indefinite and LGD in IBD-only patients, the rate of progression of CRN in patients with PSC-IBD has not been thoroughly studied. In a small study with 10 patients, one-third of the patients progressed from LGD to advanced neoplasia over a mean follow-up of 13±11 months, suggesting a faster rate of progression as compared to what has been described in IBD alone.105

Since many patients with PSC require OLT,106 some uncertainty exists regarding the effect of the strong immunosuppressive agents in the post-OLT setting, leading to an increased risk for CRN versus the “protective” effect of curing the PSC on the risk of CRN. Some of the initial studies107,108 showed that there was no difference in the rate of CRN in the post-OLT PSC-IBD group compared to post-OLT non-IBD/PSC and nontransplanted PSC-IBD patients. More recent studies have suggested that there may be even a 4-fold greater risk of CRN, though there was no evidence of any relevant impact on mortality.109,110 Particularly, one study suggested that patients who developed LGD after OLT had a slower rate of progression and were less likely to have progressive neoplasia or persistent LGD.111

Another subset of the PSC-IBD population who are at risk for neoplasia are the patients who have undergone an IPAA, given that their increased incidence of pouchitis theoretically leads to severe mucosal atrophy and subsequent pouch malignancy.112 Although a small study showed an increased risk of ileal pouch dysplasia in PSC-IBD compared to non-IBD and non-PSC populations separately,113 a larger study that included 65 patients suggested a low risk of 5.6% in 5-year for pouch or cuff dysplasia (95% CI, 1.8% to 16.1%).114 Particularly, CRC has been documented but is extremely uncommon after IPAA.115 There are no specific surveillance guidelines for post-IPAA PSC-IBD patients, so most experts prefer annual pouchoscopies as standard care for PSC patients, even though the risk seems to be low.

Given that the risks of CRN have been widely described in the PSC-IBD population, the different gastroenterology societies have commented on recommendations for surveillance in this group. Current recommendations support the use of annual colonoscopy and biopsies in PSC-IBD patients from the time of PSC diagnosis, without taking into account the duration of IBD since it is often not known.116,117 No specific recommendations on the management and follow-up of indefinite or LGD exist for this high-risk population that may be more prone to be referred for colectomy, given the elevated risk of CRC. Hence, further studies are needed to better determine the outcomes regarding low-grade and indefinite dysplasia in PSC-IBD patients.

UDCA118 has been in the past considered an option in the prevention of CRN in PSC-IBD patients. However, studies have shown mixed results: some of them with decreased risk of CRN,119-126 others not showing any effect in the incidence of neoplasia,127,128 and others even showing an increased risk with high-dose UDCA, usually in the first 6 years after the medication was started.129 A meta-analysis in 2013, evaluating eight studies with 763 PSC-IBD patients, concluded that there is a preventive effect for the development of advanced CRN when taking UDCA (OR, 0.35; 95% CI, 0.17 to 0.73), with a more pronounced effect with the 8 to 15 mg/kg/day dose (OR, 0.19; 95% CI, 0.08 to 0.49).130 Therefore, while there might be a protective effect, more studies are needed to draw more definitive conclusions.

10. Biliary cancer risk in PSC-IBD patients

In a recent large retrospective review of 399 PSC-IBD patients from the Mayo Clinic, a prolonged duration of IBD was associated with an increased risk of cholangiocarcinoma (CCA) in PSC patients.131 This increased risk equated to a 33% increased risk per 10 years of IBD and the risk was not modified by colectomy. Furthermore, in the subset of PSC-IBD patients requiring colectomy, patients who underwent surgery due to colonic neoplasia or dysplasia as opposed to refractory disease were also at a significantly higher risk of CCA. From an earlier published study conducted at Mayo Clinic, although IBD was not associated with CCA risk, proctocolectomy was a significant risk factor on univariate analysis for the development of CCA in PSC patients (relative risk, 4.43).132 It is unclear if the observed elevated cancer risk may be secondary to the effect of immunosuppression or the severity of intestinal inflammation.

The increased predisposition to malignant transformation may not only apply to the biliary system in PSC-IBD patients. From a population-based study in New Zealand, 14 of 60 PSC-IBD patients developed a malignant complication including CRC, hepatocellular carcinoma or CCA whereas none of the 19 PSC patients without IBD did.124 Nevertheless, in another study of 66 PSC patients, the prevalence of malignant complications was not dependent on the presence or absence of IBD,125 nor did it play a role in a natural history study of 305 Swedish PSC patients126 or a long-term single-center study of 200 PSC patients.127

CONCLUSIONS

IBD affects about 70% of patients with PSC. Although there is likely an underlying shared predisposition for PSC and IBD, the pathogenesis of these interrelated conditions is still unknown. These diseases are likely to be influenced by genetic predisposition, immune-mediated processes and altered gut microbiota.
Clinically, PSC-IBD patients demonstrate a right-to-left gradient of colonic inflammation as well as an increased incidence of extensive colitis, rectal sparing and backwash ileitis. Despite the higher prevalence of pancolitis, the intestinal inflammation is usually quiescent leading to mild symptoms, reduced use of steroids and decreased rates of hospitalization. Nevertheless, post-IPAA, the rates of pouchitis in PSC-UC patients are higher compared to non-PSC UC patients. While PSC is associated with a distinct IBD phenotype, the effect of IBD on the natural history and disease behavior of PSC, including recurrent PSC post-OLT, is less well defined. Overall, the PSC-IBD population has an increased risk of developing CRN and CRC compared to the IBD-only population. Moreover, IBD may also be also associated with an increased risk of CCA in PSC patients.

In summary, PSC-IBD is a puzzling disease with a very special phenotype (Fig. 2); a better understanding of the mechanisms underlying the cross talk between the liver and the gut is needed and could lead to the development of new strategies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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