Primary sclerosing cholangitis: Inflammatory bowel disease and colorectal cancer

AUTHOR: Kris V Kowdley, MD, FAASLD, FACP, FACG, AGAF
SECTION EDITOR: J Thomas Lamont, MD
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

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Literature review current through: **Sep 2023.**
This topic last updated: **Jan 06, 2023.**

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease. The majority of patients with PSC have underlying inflammatory bowel disease (IBD). Patients with concurrent PSC and IBD have an increased risk of colorectal cancer (CRC) [1-6]. This topic review will focus on the epidemiology, pathogenesis, clinical features, diagnosis, and management of IBD in patients with PSC in addition to the risk of CRC and guidelines for CRC surveillance. CRC surveillance in patients with IBD is presented separately. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease".)

INFLAMMATORY BOWEL DISEASE

Epidemiology — The prevalence of inflammatory bowel disease (IBD) in patients with primary sclerosing cholangitis (PSC) approaches 90 percent [7-10]. Ulcerative colitis (UC), Crohn disease, and indeterminate colitis of the colon account for 80, 10, and 10 percent, respectively [11]. (See "Primary sclerosing cholangitis: Epidemiology and pathogenesis", section on 'PSC and inflammatory bowel disease'.)

Clinical manifestations

Clinical features — Colitis in patients with PSC often presents at an earlier age as compared with patients with IBD alone [12]. The colitis usually has a mild or quiescent course. Patients are often asymptomatic but in rare cases present with rectal bleeding. Several studies have suggested that PSC-IBD is clinically distinct, with milder course, fewer clinical exacerbations, and lower need for biologic treatments but higher risk of colorectal neoplasia [13,14]. PSC-IBD is also associated with a greater prevalence of pancolitis, "backwash ileitis," and rectal sparing [9]. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Colitis' and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Clinical features'.)

Following colectomy, patients can present with stomal and peristomal variceal bleeding secondary to portal hypertension associated with PSC. Patients with proctocolectomy with ileal pouch anal anastomosis (IPAA) also have an increased risk of pouchitis [11,15,16]. Symptoms of pouchitis include increased stool frequency, urgency, abdominal cramps, pelvic pressure, tenesmus, and night-time fecal seepage to incontinence. (See "Ileostomy or colostomy care and complications", section on 'Stomal bleeding' and "Pouchitis: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Clinical features'.)

The course of colitis following liver transplantation for PSC is variable. Although the colitis may remain quiescent in some patients, other patients may have severe symptoms (10 or more stools per day with severe cramps and continuous bleeding) despite the immunosuppression used for the transplant [17-19]. Presence of IBD prior to liver transplantation does not appear to affect patient or graft survival [20]. A retrospective study found the 10-year cumulative probability of an IBD flare requiring additional therapy to be 26 percent, and the risk of new-onset IBD after liver transplantation was 25 percent [21]. (See "Primary sclerosing cholangitis in adults: Management", section on 'Inflammatory bowel disease' and "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Colitis'.)

Endoscopic features — IBD in patients with PSC often involves the entire colon. Less often, the colitis is right-sided with relative sparing of the rectum or there is terminal ileal involvement [9,11]. Endoscopic features of colitis are non-specific and include erythema, granularity of the mucosa, petechiae, exudates, edema, and erosions. The endoscopic appearance of the colon may be normal even in the presence of active underlying colonic inflammation [22]. Studies that included both endoscopic and histologic criteria for diagnosis of PSC-IBD have found a higher prevalence of IBD in PSC than those using either criterion alone [10].

Diagnosis — Given the high prevalence of IBD in patients with PSC, colonoscopy is recommended at the time of initial diagnosis of PSC regardless of the presence of symptoms of colitis (eg, rectal bleeding, diarrhea). As with all cases of IBD, the diagnosis requires evidence of

colonic inflammation and chronic changes on biopsy. Since these features are not specific for UC or Crohn disease, establishing the diagnosis also requires the exclusion of other causes of colitis by history, laboratory studies, and by biopsies of the colon obtained on colonoscopy [23]. Random biopsies of the colon should be obtained even if the mucosa appears endoscopically normal as a significant number of patients may not have symptoms or endoscopic evidence of colitis [8,18]. The evaluation to exclude other causes of colitis is discussed in detail separately. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Evaluation'.)

Differential diagnosis — The differential diagnosis of IBD includes other causes of colitis. This includes infectious, radiation, diversion, medication-induced colitis, and diverticular colitis. These can be differentiated from IBD by history, laboratory studies, and biopsies of the colon obtained on colonoscopy. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Differential diagnosis' and "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Evaluation'.)

Management — The management of IBD in patients with concurrent PSC is the same as in patients with IBD alone and is discussed in detail, separately. However, patients undergoing colectomy should be informed of surgery-related complications including a higher risk of pouchitis and peristomal varices, and patients should be monitored closely for hepatic decompensation following surgery. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis" and "Management of the hospitalized adult patient with severe ulcerative colitis" and "Management of moderate to severe ulcerative colitis in adults" and "Overview of the medical management of mild (low risk) Crohn disease in adults" and "Medical management of moderate to severe Crohn disease in adults".)

COLORECTAL CANCER

Epidemiology — Patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) are at increased risk of colorectal cancer (CRC) and colonic dysplasia [24,25]. Dysplasia was less often visible endoscopically among PSC patients [26]. Among patients with IBD, an increased risk of CRC in patients with ulcerative colitis (UC) complicated by PSC has been observed in a number of studies. In one case-control study, the cumulative absolute risk of CRC or dysplasia after 10, 20, and 25 years of colitis in patients with PSC and UC was significantly higher as compared with patients with UC alone (9, 31, and 50 percent versus 2, 5, and 10 percent, respectively) [2].

However, the CRC risk in patients with concomitant Crohn disease and PSC is unclear and results have been conflicting [1-3,27-30]. This was illustrated in a 2016 meta-analysis that included 16 observational studies. The meta-analysis concluded that the CRC risk was increased by approximately threefold in patients with PSC and IBD as compared with those with IBD alone (odds ratio [OR] 3.24; 95% CI 2.14-4.9) [31]. When the results were stratified by IBD subtype, the presence of PSC in patients with UC but not Crohn disease was associated with an increased risk of colorectal neoplasia and CRC. However, only three studies in the meta-analysis included patients with Crohn disease and PSC. In a Scandinavian population-based study, patients with Crohn disease and PSC had an increased risk of CRC-related death [32].

Several studies have suggested that the risk of CRC is increased following liver transplantation, however, the CRC risk may be related to the duration of IBD and not the transplant itself [33]. The risk of CRC among patients with PSC-IBD after liver transplantation has been estimated to be as high as 31.5 per 1000 person-years [34]. In a meta-analysis of 16 cohort studies that included 1017 patients, the incidence of CRC in patients with PSC-IBD and an intact colon at the time of liver transplantation was 13.5 per 1000 person-years; the presence of an intact colon was estimated to increase the risk of CRC to 20-fold compared with the general population [34,35]. A long duration of IBD and extensive colitis were identified as risk factors for CRC [17,35]. However, other studies have found no difference in the risk of CRC among PSC-IBD patients after liver transplantation and some have even found a lower risk [34,36]. Several studies have also found conflicting results between type of immunosuppression and CRC risk [34]. (See "Primary sclerosing cholangitis in adults: Management", section on 'Liver transplantation'.)

Pathogenesis — The mechanism by which concomitant PSC increases the risk of colonic neoplasia in patients with IBD is unknown. It has been hypothesized that this is due to the increased concentration of secondary bile acids in the proximal colon [3]. Secondary bile acids (eg, deoxycholic acid and lithocholic) are cytotoxic to colonic epithelial cells, induce hyperproliferation, and may also influence the development of sporadic colonic adenomas and CRC [37-41]. In support of this hypothesis is the observation that patients with UC, colonic dysplasia, or CRC have higher fecal bile acid concentrations than those without colonic neoplasia [42]. Furthermore, IBD in PSC tends to be characterized by rectal sparing and backwash ileitis, suggesting that epithelial injury may be relatively more severe in the proximal colon [11]. PSC patients also have a disproportionately higher likelihood of developing CRC proximal to the splenic flexure [3,27]. MicroRNA-346 expression appears to be increased in the ascending colon of PSC patients, resulting in suppression of its target genes, vitamin D receptor and TNF-alpha, which may disrupt suppression of neoplasia [43].

Chronic inflammatory activity may be the driver of carcinogenesis. Colitis in patients with PSC can have low endoscopic activity, which may mask an active histologic inflammation that possibly contributes to an increased risk of malignancy [22]. (See 'Endoscopic features' above.)

Clinical features — CRC in patients with concomitant PSC and IBD is more often right-sided and is diagnosed earlier as compared with sporadic CRC with a median age at diagnosis of 49 years [28]. Most patients are asymptomatic and are diagnosed as a result of CRC screening. Less often patients present with symptoms of CRC, including hematochezia or melena and abdominal pain, otherwise unexplained iron deficiency anemia, and/or a change in bowel habits. (See 'Diagnosis' above and 'Colorectal cancer screening' below.)

Diagnosis — The diagnosis of CRC should be suspected in PSC patients with IBD and symptoms of hematochezia, melena, abdominal pain, otherwise unexplained iron deficiency anemia, and/or a change in bowel habits. However, most patients are asymptomatic and are detected on CRC screening. The diagnosis of CRC is established by examination of tissue biopsies obtained on colonoscopy. The diagnosis, differential diagnosis, and staging of CRC are discussed in detail, separately. (See "Clinical presentation, diagnosis, and staging of colorectal cancer".)

Management — The management of CRC in PSC associated with IBD does not differ from other patients with CRC. However, patients undergoing colectomy should be informed of surgery-related complications, including a higher risk of pouchitis and peristomal varices, and patients should be monitored closely for hepatic decompensation following surgery. (See "Overview of the management of primary colon cancer" and "Primary sclerosing cholangitis in adults: Management", section on 'Proctocolectomy'.)

Prevention

Colorectal cancer screening — The goal of CRC screening is to detect IBD early and to detect colorectal neoplasia at an earlier stage in those with established IBD. Evidence to guide screening intervals is lacking and guidelines are largely based on consensus opinion. Our approach is largely consistent with recommendations of the American Gastroenterological Association [44], the American College of Gastroenterology (ACG) [45], and the British Society of Gastroenterology (BSG) [46].

PSC and IBD — Due to the high risk of colonic dysplasia in PSC patients with IBD and right-sided predominance of CRCs, surveillance with colonoscopy should be performed annually [23,47-49]. The management of colonic dysplasia in PSC patients with IBD does not differ from other patients with IBD and is discussed in detail separately. (See "Surveillance and

management of dysplasia in patients with inflammatory bowel disease", section on 'Patient selection and timing'.)

PSC without IBD — In patients with PSC without IBD, we perform surveillance colonoscopy every five years [50].

Chemoprevention — Although several agents have been evaluated for prevention of CRC in PSC patients with IBD, none have conclusively been demonstrated to decrease the risk of CRC. (See "Surveillance and management of dysplasia in patients with inflammatory bowel disease", section on 'Chemoprevention'.)

- Ursodeoxycholic acid – Ursodeoxycholic acid (UDCA) is not recommended for chemoprevention of CRC in patients with PSC [23]. It was hypothesized that UDCA, a hydrophilic bile acid, may have a chemoprotective effect on CRC by reducing the colonic concentration of toxic secondary bile acids [37,40,42,51-53]. UDCA also inhibits proliferation of colon cancer cell lines in animal models [38,51,52,54]. UDCA slows intestinal cell proliferation by sustained hyperphosphorylation of extracellular signal–regulated 1 kinase, which in turn slows down the cell cycle and reduces expression of insulin receptor substrate 1 protein [55]. High-dose UDCA (28 to 30 mg/kg/day) appears to be associated with significant adverse effects, with increased risk of colorectal neoplasia [34,56,57]. (See "Primary sclerosing cholangitis in adults: Management", section on 'Ursodeoxycholic acid'.)

- **Folate** – Few studies have evaluated the effect of folate/folic acid supplementation on the development of colonic neoplasia in PSC patients with IBD and their role in the prevention of CRC is unclear [3,58]. In one observational study that included 98 patients with UC, of whom 30 percent developed colorectal neoplasia, the relative risk of developing colonic dysplasia or cancer was not significantly lower in patients who received folate supplementation (0.47, 95% CI 0.18-1.20) [58].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Colorectal cancer" and "Society guideline links: Primary sclerosing cholangitis".)

SUMMARY AND RECOMMENDATIONS

- The prevalence of inflammatory bowel disease (IBD) in patients with primary sclerosing cholangitis (PSC) approaches 90 percent. Ulcerative colitis (UC), Crohn disease, and indeterminate colitis account for 80, 10, and 10 percent, respectively. (See 'Inflammatory bowel disease' above and 'Epidemiology' above.)

- Colitis in patients with PSC presents earlier in life as compared with patients with IBD alone. IBD in PSC patients usually has a mild or quiescent course. Patients are often asymptomatic, but in rare cases, present with rectal bleeding. (See 'Clinical features' above.)

- PSC patients with IBD often have a pancolitis. Less often, the colitis is right sided with relative sparing of the rectum or there is terminal ileal involvement. The colon may also be normal in endoscopic appearance even in the presence of active underlying inflammation. (See 'Endoscopic features' above.)

- Given the high prevalence of IBD in patients with PSC, colonoscopy should be performed at the time of initial diagnosis of PSC regardless of the presence of symptoms of colitis (eg, rectal bleeding, diarrhea). IBD in PSC does not have any characteristic endoscopic or histologic features. The diagnosis requires evidence of colonic inflammation and chronic changes on biopsy and exclusion of other causes of colitis. (See 'Diagnosis' above and 'Differential diagnosis' above.)

- Patients with PSC and IBD have an approximately three- to four-fold increase in risk of colorectal cancer (CRC) as compared with patients with IBD alone. Among patients with IBD, an increased risk of CRC in PSC patients with concomitant UC has been demonstrated in multiple studies, however, the CRC risk in patients with concomitant Crohn disease is unclear. (See 'Epidemiology' above.)

- CRC in patients with concomitant PSC and IBD is more often right sided and is diagnosed earlier as compared with sporadic CRC with a median age at diagnosis of 49 years. Most patients are asymptomatic and CRCs are detected on screening. (See 'Clinical features' above.)

- The management of CRC in PSC associated with IBD does not differ from other patients with CRC. However, patients undergoing colectomy should be informed of surgery-related complications including a higher risk of pouchitis and peristomal varices, and patients should be monitored closely for hepatic decompensation following proctocolectomy. (See 'Management' above.)

- Although several agents have been evaluated for prevention of CRC in patients with concomitant PSC and IBD, none have conclusively been demonstrated to decrease the risk of CRC. (See 'Chemoprevention' above.)

ACKNOWLEDGMENT — The UpToDate editorial staff acknowledges Paul Rutgeerts, MD (deceased), who contributed as a section editor for UpToDate in Gastroenterology.

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Contributor Disclosures

Kris V Kowdley, MD, FAASLD, FACP, FACG, AGAF Equity Ownership/Stock Options: Inipharm [NASH]. Grant/Research/Clinical Trial Support: 89Bio [NASH]; BMS [NASH]; Celgene [NASH]; Corcept [NASH]; CymaBay [PBC]; Genfit [PBC]; Gilead [PSC, NASH]; GSK [PBC]; Hanmi [NASH]; HighTide [NASH]; Intercept [NASH]; Madrigal [NASH]; Mirum [PSC]; NGM Bio [NASH]; Novo Nordisk [NASH]; Pfizer [NASH]; Pliant [PSC]; PTG [HH]; Terns [NASH]; Viking [NASH]. Consultant/Advisory Boards: 89Bio [NASH]; CymaBay [PBC]; Enanta [NASH]; Genfit [PBC]; Gilead [PSC]; HighTide [PSC, PBC]; Inipharm [NASH, PBC]; Intercept [PSC, NASH]; Madrigal [NASH]; Mirum [PSC, NASH]; NGM [NASH]; Novo Nordisk [NASH]; Pfizer [NASH]; Zydus [PBC]. Speaker's Bureau: AbbVie [HCV]; Gilead [HCV, HDV]; Intercept [PBC]. All of the relevant financial relationships listed have been mitigated. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion

[Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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