Neoplasia in the ileoanal pouch following colectomy in patients with ulcerative colitis and primary sclerosing cholangitis

Mohamad H. Imam, John E. Eaton, Jason S. Puckett, Edward V. Loftus Jr., Kellie L. Mathis, Andrea A. Gossard, Jayant A. Talwalkar, Keith D. Lindor

Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, United States
Department of Medicine, Mayo Clinic, Rochester, MN, United States
Division of Colorectal Surgery, Mayo Clinic, Rochester, MN, United States
College of Health Solutions, Arizona State University, Phoenix, AZ, United States

Received 11 February 2014; received in revised form 3 March 2014; accepted 18 March 2014

KEYWORDS
Colorectal cancer; Autoimmune liver disease; Inflammatory bowel disease

Abstract

Background & Aims: Primary sclerosing cholangitis (PSC) is typically associated with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC). PSC–IBD patients are at an increased risk for colorectal neoplasia. The ileal pouch-anal anastomosis (IPAA) is a treatment option for patients with medically refractory UC or neoplasia. However, little is known about the development of pouch neoplasia in PSC–UC patients following an IPAA. We aim to describe the incidence of pouch neoplasia in PSC–UC patients after an IPAA.

Methods: We conducted a retrospective chart review of patients with a confirmed diagnosis of PSC and IBD who underwent colectomy with IPAA followed by pouch surveillance between 1995 and 2012.

Results: Sixty-five patients were included in the cohort and were followed up from the time of colectomy/IPAA for a median of 6 years. The most common indications for surgery were low-grade dysplasia (LGD) and refractory colitis. Only 3 patients developed evidence of neoplasia (LGD n = 1, high-grade dysplasia n = 1, adenocarcinoma n = 1). The cumulative 5-year incidence of pouch neoplasia was 5.6% (95% confidence intervals [CI], 1.8%–16.1%).

Abbreviations: CRC, colorectal cancer; ERCP, endoscopic retrograde cholangiopancreatography; HGD, high-grade dysplasia; IPAA, ileal pouch-anal anastomosis; IBD, inflammatory bowel disease; LGD, low-grade dysplasia; PN, pouch neoplasia; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

Corresponding author at: College of Health Solutions, Arizona State University, Phoenix, AZ, Mail Code: 3020, 550 N. 3rd Street, United States. Tel.: +1 602 496 0789.
E-mail address: Keith.Lindor@asu.edu (K.D. Lindor).
1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease, characterized by progressive inflammation and fibrosis of the bile ducts which can lead to cirrhosis. PSC is associated with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC). Patients with PSC–UC have an increased risk of colorectal cancer compared to those with UC alone. Medical therapy is fundamental in the management of patients with IBD; however, colectomy is required in up to 30% of patients with UC. For patients with UC the surgical procedure of choice is typically a proctocolectomy with ileal pouch-anal anastomosis (IPAA).

The cumulative incidence for pouch neoplasia (PN) in a large IBD cohort was 0.9% and 1.3%, at 5 and 10 years, respectively. Thirty-eight patients (1.19%) had PN (dysplasia or cancer). Fifty cases of cancer arising in the ileoanal pouch have been reported to date. The majority consisted of adenocarcinoma (42/50; 84%), and less commonly, lymphoma (2/50; 4%), squamous cell carcinoma (3/50; 6%) and non-specific cancer (2/50; 4%) were reported. In clinical practice, many gastroenterologists believe that the presence of PSC could increase the risk of PN. Consequently, some recommend an annual pouchoscopy for individuals with PSC who have undergone an IPAA. However, evidence supporting this practice is limited by few studies on PN. Risk stratifying individuals who undergo an IPAA will be helpful in determining the intensity of pouch surveillance. Although PSC–UC patients are at an increased risk of colorectal neoplasia in an intact colon, the risk of PN is ill-defined. Consequently, we sought to describe the occurrence of pouch neoplasia in patients with PSC who underwent an IPAA at our institution.

2. Methods

2.1. Patient population

We identified patients with a confirmed diagnosis of PSC and IBD who underwent pouch surveillance between 1995 and 2012. This was done by utilizing a master computer system at Mayo Clinic Rochester and then manually reviewing the charts to confirm the diagnosis of PSC–IBD and confirm pouch surveillance during follow-up.

2.2. Primary sclerosing cholangitis

The diagnosis of PSC was confirmed based on laboratory data showing a cholestatic liver profile, and pathology or imaging tests (endoscopic retrograde cholangiopancreatography [ERCP] or magnetic resonance cholangiopancreatography [MRCP]) showing characteristic bile duct changes with multifocal strictures and segmental dilatations, following the exclusion of secondary causes of sclerosing cholangitis. The date of PSC diagnosis was defined as when a suspected case was first described in the medical record.

2.3. Inflammatory bowel disease

Diagnosis of IBD was made on the basis of clinical suspicion supported by appropriate macroscopic findings on sigmoidoscopy or colonoscopy, typical histological findings on biopsy, and negative stool examinations for infectious agents.

The date of IBD diagnosis was defined as when a diagnosis was first described in the patient's medical record and the diagnosis was then confirmed histologically at the Mayo Clinic. Pouchitis was diagnosed endoscopically when features of pouchitis (mucosal erythema, mucosal friability and loss of pseudo-colonic architecture) were present or biopsies showed inflammation in the lamina propria and hence pouchitis was mentioned on the pathology report. Recurrent pouchitis was the occurrence of pouchitis after successful medical management and remission of the pouchitis. This was determined by the recurrence of symptoms followed by endoscopic/histologic confirmation. Persistent pouchitis was defined as pouchitis not responding to medical management with persistent symptoms and histological changes.

2.4. Neoplasia

Neoplasia was defined as the presence of histologic evidence on endoscopic/surgical specimen of low-grade dysplasia (LGD), high-grade dysplasia (HGD), or colorectal cancer (CRC). The diagnosis of neoplasia was determined by 2 expert pathologists at the time of the original diagnosis. The grade of dysplasia was determined using the criteria from the Inflammatory Bowel Disease/Dysplasia Morphology Study Group.

2.5. Data collection and analysis

Patient charts were manually reviewed for demographics and pertinent clinical data including dates of diagnosis of PSC and IBD, date of colectomy and surveillance of the ileoanal pouch following colectomy. Occurrence of PN was also recorded. Continuous variables were reported as median with range. Categorical variables were reported as unique count and percentage of the sample and were compared using Pearson chi-square test. The cumulative incidence of PN was determined using the 1-Kaplan–Meier method. Time to event analysis for the development of PN was determined using the Kaplan–Meier method. Patients who did not develop PN were censored at the time of their last surveillance pouchoscopy.
3. Results

The initial data search identified 101 patients with a suspected diagnosis of PSC and IBD who underwent colectomy. After manual review, 65 patients were included in the final analysis, and 36 patients were excluded due to absence of a confirmed diagnosis of PSC and/or absence of pouch surveillance during follow-up.

3.1. Demographics

Demographics and clinical data are summarized in Table 1.

3.2. Primary sclerosing cholangitis

The diagnosis of PSC was confirmed in all 65 patients. When looking at the histologic stage of PSC at baseline, 61 patients had stage 2 or higher (stage 2, 25 patients; stage 3, 25 patients; stage 4, 11 patients). The histologic stage of PSC at the time of colectomy (available in 43 patients) is shown in Fig. 1. Twenty-two patients (34.4%) were not staged at the time of colectomy. More than half of our patients (34 patients, 52.3%) had both intrahepatic and extrahepatic distribution of PSC, whereas 15 patients had only intrahepatic distribution, 7 patients had only extrahepatic distribution, and 9 patients had no clear distribution of PSC. Twenty patients (30.8%) underwent liver transplantation, and none of these transplanted patients developed recurrence of PSC after the transplant. Approximately half of the transplanted patients (11/20, 55%) underwent liver transplantation after their colectomy and IPAA.

Twenty-seven patients received low-dose (13–15 mg/kg/day) ursodeoxycholic acid (UDCA), 6 patients received high-dose (28–30 mg/kg/day) UDCA, and the remainder did not receive UDCA.

3.3. Inflammatory bowel disease

Sixty-four patients had a diagnosis of UC at the time of surgery and 1 patient had Crohn’s colitis. Twelve patients (18.4%) had backwash ileitis and 58 patients (89.2%) showed evidence of extensive colonic involvement. Thirty-nine patients (60%) had a history of neoplasia prior to colectomy, including 25 patients with unifocal LGD, 1 patient with unifocal HGD, 7 patients with CRC, 5 patients with multifocal LGD, and 1 patient with multifocal HGD.

3.4. Colectomy

All patients (by study definition) underwent colectomy with IPAA. The most common indication for colectomy was LGD in 27 patients followed by refractory UC in 26 patients. CRC was an indication for colectomy in 7 patients, 4 patients underwent colectomy for HGD, and 1 patient for bowel obstruction. Examination of the colectomy specimens showed that the majority of patients (50/65, 76.9%) had extensive colonic involvement, and 32 patients had moderately to severely active disease histologically. Colorectal neoplasia was evident in 33 colectomy specimens, with 10 patients showing evidence of CRC or multifocal HGD. All patients had IPAA, of which the majority (50 patients, 76.9%) were stapled anastomoses.

3.5. Pouch surveillance & development of pouch neoplasia

The median time from IPAA to the first pouch surveillance was 20 months (range, 1.6–172 months) and to the last pouch surveillance was 72 months (range, 3.6–248.4 months). Individual patients underwent a median
of 3 endoscopic surveillance procedures (range, 1–13 procedures) during the follow-up period.

Histologic evidence of pouchitis was present in all but one patient (64/65, 98.4%) and was persistent or recurrent in 55 patients (84.6%). Endoscopic evidence of pouchitis was present more than once in all 64 patients. However, no significant increase in the occurrence of PN was seen in patients with persistent pouchitis (pouchitis identified consistently on more than one pouch biopsy) as compared to patients with non-persistent pouchitis or no pouchitis (p = 0.46).

When surveying the pouch, 1 patient had unifocal LGD, 1 patient had multifocal HGD, and 1 patient had CRC in the pouch. Only the patient with CRC had the pouch surgically excised. The 5-year cumulative incidence of PN was 5.6% (95% CI, 1.8%–16.1%) (Fig. 2). None of the patients with PN had a prior history of colorectal neoplasia. The median interval between colectomy and development of PN was 1.8 years (range, 1.6–3.4 years). Features of PSC patients developing PN are shown in Table 2.

4. Discussion

Our study shows that the occurrence of PN in patients with PSC–IBD who have undergone IPAA is relatively low. Only one patient out of 65 (1.5%) developed CRC and two patients (3%) developed LGD or HGD. The 5-year cumulative incidence of pouch neoplasia was 5.6% (95% CI, 1.8%–16.1%). This finding calls into question the practice of annual pouchoscopy to detect PN in all PSC patients.
Cases of PN following IPAA in patients with UC have been reported extensively throughout the literature. Our findings are similar to those described in other studies examining the risk of pouch neoplasia in IPAA patients with only IBD. For example, in two large systematically case-control studies, the risk of neoplasia in patients with UC and IPAA is small. Kariv et al. also concluded that the risk of neoplasia is not eliminated by colectomy or mucosectomy. Moreover, Derikx et al. identified that incidence of pouch neoplasia in patients with IBD without a history of colorectal neoplasia is relatively low. However, they also concluded that prior dysplasia or colon cancer in this subset of patients is associated with a significant increase in risk (4 fold versus 25 fold, respectively) of developing pouch neoplasia.

One of the first cases of adenocarcinoma developing in an ileoanal pouch in a patient with a liver transplant for PSC was reported by Walker and Radley in 2006. However, there are limited data describing the incidence of PN in a large cohort of PSC patients. The only other study looking at pouch neoplasia in IBD-PSC-IPAA patients was published by Stahlberg et al., which proposed that an increased risk for neoplastic transformation seems to be present in this subgroup of patients; our study clarifies that this risk is minimal.

Identifying risk factors for PN and risk stratifying patients is important to guide screening practices. A recent study by Rahman et al. described an increased incidence of pouch mucosal atrophy, pouchitis and pouch dysplasia in patients with UC and associated PSC when compared to patients without PSC. Banasiewicz et al. concluded that patients with pouchitis are at elevated risk of dysplasia and hence require surveillance of the pouch. Another group recommended surveillance pouchoscopies in patients with UC who have a prior history of dysplasia or carcinoma, type C ileal mucosa and PSC due to increased risk of dysplasia and cancer in the ileal mucosa in the reservoir and below the IPAA. In contrast, we could not detect a markedly increased incidence of PN in a PSC-UC cohort when compared to the incidence in patients with UC alone despite the fact that nearly all patients included had histologic evidence of pouchitis. However, making direct comparisons across studies can be challenging. The small number of events prevented us from examining which risk factors could influence the development of PN in PSC patients.

Our study is important as it highlights the risk of PN in a relatively large cohort of individuals with a rare disease (PSC-IBD patients who underwent an IPAA). The primary limitations of this study are that it was done at a single referral center, with limited follow-up (median 6 years) and hence few events were detected and finally the lack of a control group (IBD non-PSC). Future studies should focus on longer duration of follow-up and multicenter collaboration in order to better determine the natural history and epidemiology of PN in PSC-IBD patients. Such long-term studies will be useful in providing guidance regarding the optimal pouchoscopy surveillance strategy following an IPAA in PSC patients.

In conclusion, the development of neoplasia in the ileoanal pouch following colectomy in patients with PSC-IBD is uncommon despite the presence of chronic pouchitis. Previous studies recommending surveillance every 1 to 3 years have failed to identify dysplasia prior to cancer and hence the value of this strategy is unclear. More studies are needed to define an optimal surveillance strategy.

Author contributions

Dr. Imam was involved in study concept and design, statistical analysis and interpretation of data, and drafting the manuscript. Dr. Eaton was involved in study concept and design, collection of data and revision of the manuscript. Dr. Puckett was involved in the collection of data. Dr. Talwalkar, Dr. Loftus, Ms. Gossard and Dr. Lindor were involved in the critical revision of the manuscript.

Writing assistance

None.

Potential conflict of interest disclosures

None.

Grant support

None.

References


<table>
<thead>
<tr>
<th>Table 2 Features of PSC patients developing PN.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; PN, pouch neoplasia; UC, ulcerative colitis; LGD, low-grade dysplasia; HGD, high-grade dysplasia; CRC, colorectal cancer.


