Differentiating Risk Factors for Acute and Chronic Pouchitis

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Background & Aims: **Pouchitis is the most common complication of ileal pouch anal anastomosis in patients with ulcerative colitis. In some cases the inflammation becomes chronic and requires long-term medical therapy. The clinical course and medical therapy are different between acute pouchitis and chronic pouchitis. The aim of this study was to determine if there are predictors of risk for acute vs. chronic pouchitis.** ***Methods:*** **Patients with acute pouchitis (N = 40) and patients with chronic pouchitis (N = 40) were matched with a control group who never had pouchitis (N = 40). Data were collected for multiple pre-, peri-, and postoperative factors and follow-up telephone calls were performed. Case-control univariable analyses and multivariate logistic regression were used to measure the association between covariates and pouchitis.** ***Results:*** **Multivariate logistic regression showed that extensive colonic disease (odds ratio [OR], 2.99; $P = .045$ for acute pouchitis; and OR, 4.61; $P = .010$ for chronic pouchitis) and extraintestinal manifestations (OR, 2.88; $P = .037$ for acute pouchitis; and OR, 2.69; $P = .047$ for chronic pouchitis) were associated with both acute and chronic pouchitis. Postoperative nonsteroidal anti-inflammatory drug (NSAID) use was associated with chronic pouchitis, but less so with acute pouchitis. Patients with fulminant colitis as an indication for surgery had a decreased risk for developing chronic pouchitis (OR, 0.22; $P = .036$), but no such association was seen for acute pouchitis.** ***Conclusions:*** **Extensive colonic disease and preoperative extraintestinal manifestations are associated with increased risk for both acute and chronic pouchitis. Fulminant colitis leading to colectomy is protective from development of chronic pouchitis. Postoperative use of NSAIDS is a risk factor for chronic pouchitis and possibly for acute pouchitis, and thus should be discouraged for patients who undergo ileal pouch anal anastomosis.**

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is the surgery of choice for the majority of patients with ulcerative colitis who require surgical intervention. The most common long-term complication of this surgery is pouchitis, a nonspecific inflammatory process of the ileoanal pouch.[1] The incidence of pouchitis varies with factors such as duration of follow-up evaluation, the diagnostic criteria used to define pouchitis, and the intensity of evaluation for pouch inflammation.[1,2] The reported 10-year cumulative incidence rates in patients with underlying ulcerative colitis vary between 15% and 50%.[1–4] In most cases, pouchitis is an acute process that responds rapidly to a short course of antibiotics.[1] However, in approximately 5% of patients, pouchitis can develop into a chronic problem requiring repeated courses of antibiotics over short periods of time or even chronic therapy with antibiotics or other agents.[1,2] In addition, patients with chronic pouchitis may be at higher risk for requiring pouch excision.

The cause of pouchitis is unclear but the disease occurs much more frequently in patients with underlying ulcerative colitis than those with familial adenomatous polyposis.[1,3] Risk factors for the development of pouchitis in ulcerative colitis have been reported in several studies, although there have been some conflicting results as well. Reported risk factors include primary sclerosing cholangitis,[4,5] other extraintestinal manifestations of inflammatory bowel disease,[5–7] young age at diagnosis of ulcerative colitis,[5] extensive colonic disease,[8,9] preoperative terminal ileal inflammation,[9] and the presence of perinuclear antineutrophil cytoplasmic antibodies.[10,11] On the other hand, one study showed that smoking was protective against the development of pouchitis.[12] Most of these studies evaluated patients who predominantly had acute pouchitis. Only a few studies have focused specifically on chronic pouchitis.[10,11] It is not known whether acute and chronic pouchitis represent different spectrums of the same disease, or whether they have the same underlying cause and the same risk factors. Determining risk factors for chronic pouchitis may be relatively more important given the chronicity of symptoms and frequent need for long-term medical therapy. Therefore, the aim of this study was to evaluate patients with

Abbreviations used in this paper: CI, confidence interval; IPAA, ileal pouch–anal anastomosis; OR, odds ratio.

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acute and chronic pouchitis to determine if there were different risk factors for these 2 groups.

Methods

Study Population

We performed 2 case-control studies evaluating a total of 120 patients with ulcerative colitis or indeterminate colitis who had undergone restorative proctocolectomy with IPAA. Patients with a course suggestive of Crohn's disease based on either colectomy pathology or postsurgical clinical course (development of perianal fistulas or inflammation in the small bowel proximal to the pouch detected by pouch endoscopy or radiographic studies) were excluded from the study.

Cases consisted of patients with acute pouchitis (N = 40) and chronic pouchitis (N = 40) as defined later. The control group consisted of asymptomatic IPAA patients who have never had pouchitis (N = 40). Patients were matched as closely as possible by date of surgery and by sex.

Patients were identified from 2 sources. The first source was the outpatient clinical practice at the Center for Inflammatory Bowel Disease at the Cleveland Clinic Foundation. The second source was the Cleveland Clinic Ileal Pouch Registry. This registry is a prospectively maintained database that includes information on over 2800 patients who have undergone IPAA at the Cleveland Clinic Foundation since 1987. Patients are evaluated with standardized yearly questionnaires and receive a screening pouch endoscopy every 1–2 years. Patients who met the definitions listed later were selected randomly from this registry.

The study was approved by the Cleveland Clinic Foundation Institutional Review Board.

Definitions of Pouchitis

All patients classified as having either acute or chronic pouchitis were required to have typical symptoms of pouchitis and at least one abnormal pouch endoscopy during one of these symptomatic episodes. Typical symptoms were defined as increased number and looser consistency of bowel movements compared with baseline, rectal bleeding, urgency, incontinence, and/or abdominal or pelvic cramps.

Acute pouchitis was defined as: (1) 3 or fewer episodes of pouchitis per year, (2) symptoms lasting less than 4 weeks at a time with each episode, (3) symptoms responding to short courses ($\leq$14 days) of antibiotics, and (4) at least one pouch endoscopy showing endoscopic and histologic inflammation of the pouch during one of these episodes of pouchitis.

Chronic pouchitis was defined as the presence of 1 or more of the following criteria: (1) 4 or more episodes of pouchitis per year, (2) active symptoms lasting continuously for more than 4 weeks despite antibiotic therapy, or (3) chronic antibiotic or anti-inflammatory therapy to control symptoms of pouchitis. In addition, we required at least 1 pouch endoscopy showing endoscopic and histologic inflammation of the pouch during an episode of pouchitis.

Data Collection

Detailed information regarding preoperative, perioperative, and postoperative factors was obtained by review of medical records. Telephone interviews then were conducted with all patients to confirm the number of episodes of pouchitis and to ascertain demographic data, smoking history, and use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Preoperative factors that we evaluated were as follows: (1) age at diagnosis of ulcerative colitis; (2) family history of inflammatory bowel disease; (3) use of immunomodulators (not including corticosteroids) to control disease; (4) presence of extraintestinal manifestations including arthralgias related to disease activity, peripheral arthritis, ankylosing spondylitis, ocular manifestations including scleritis, episcleritis, or uveitis, skin involvement including erythema nodosum and pyoderma gangrenosum, and primary sclerosing cholangitis; and (5) maximal extent of disease involvement. Because the overall numbers for each extraintestinal manifestation were relatively small, we combined all of these manifestations into one group and performed an analysis as to presence of any extraintestinal manifestation vs. no extraintestinal manifestation. The determination of extent of disease was based on maximal macroscopic extent and was classified as either extensive (disease extending proximal to the splenic flexure) or left sided (disease up to or distal to the splenic flexure).

Perioperative factors that we evaluated were as follows: (1) duration of disease before surgery; (2) indication for surgery; (3) terminal ileal inflammation (backwash ileitis) as determined by colectomy pathology; and (4) number of surgeries at time of ileostomy closure. Indication for surgery was classified as medically refractory disease (chronic disease failing to respond to standard outpatient therapy of ulcerative colitis including 5-aminosalicylic acid agents, corticosteroids, and immunomodulators), fulminant colitis (defined as severe colitis requiring hospitalization and failing to respond to intravenous corticosteroids), and dysplasia/cancer. The number of surgeries at time of ileostomy closure was classified as 1-, 2-, or 3-stage surgery. Of note, only 3 patients in all of the study groups had a 1-stage proctocolectomy with IPAA so we analyzed 1- or 2-stage vs 3-stage surgeries.

Postoperative factors that we evaluated were as follows: (1) use of NSAIDs after colectomy as assessed during the past 1 year before the telephone interview was conducted, (2) pouchitis course and response to treatment, and (3) smoking history at time of follow-up evaluation. The use of NSAIDs was classified if study patients used either over-the-counter or prescription NSAIDs including aspirin at least once per week for a period of at least 6 months. Smoking status was classified as current smoker, ex-smoker (quit for at least 6 months before the telephone interview), or never smoker.

Statistical Analysis

Two case-control studies, one comparing acute pouchitis with the control group and one comparing chronic pouchi-