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Comprehensive Evaluation of Inflammatory and Noninflammatory Sequelae of Ileal Pouch-Anal Anastomoses

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BACKGROUND AND AIMS: Ileal pouch-anal anastomosis (IPAA) improves quality of life (QOL) for ulcerative colitis patients who require surgery. Crohn's disease (CD) of the pouch, pouchitis, cuffitis, and irritable pouch syndrome (IPS) have an adverse impact on physical and psychological well-being, which can compromise the gain in QOL after the surgery. Their clinical, endoscopic, and histologic features have not been fully characterized. The aim of this study was to compare demographic, clinical, endoscopic, and histologic features between CD of the pouch, pouchitis, cuffitis, IPS, and normal pouches.

METHODS We enrolled 124 patients: normal pouches (N = 26), CD of the pouch (N = 23), pouchitis (N = 22), cuffitis (N = 21), and IPS (N = 32). Symptomatology, endoscopy, histology, and the Cleveland Global QOL and the Irritable Bowel Syndrome-QOL scores were compared among the groups.

RESULTS: Univariate analysis of demographic and clinical data showed a possible association between NSAID use and pouchitis, extraintestinal manifestation and cuffitis, and antidepressant use and IPS. There were no differences in the Pouchitis Disease Activity Index symptom scores between the disease groups, with an exception of bleeding, which occurred almost exclusively in cuffitis. Endoscopy was useful in discriminating between CD of the pouch, pouchitis, cuffitis, and normal pouches or IPS. Patients with diseased IPAA had worse QOL scores.

CONCLUSIONS: Symptoms largely overlapped among the disease groups of IPAA. Endoscopy is valuable for diagnosis. Inflammatory or noninflammatory sequelae of IPAA adversely affected patients' QOL.

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INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for patients with medically refractory ulcerative colitis (UC), UC with dysplasia, or familial adenomatous polyposis (1, 2). IPAA leads to improvement in health-related quality-of-life (QOL) scores in UC patients who require surgery (3–7), and offers a better QOL to patients compared to Brooke ileostomy and Kock pouch (7). The improvement in QOL is sustained for many years after IPAA surgery (8).

Inflammatory and noninflammatory sequelae in the pouch such as pouchitis, cuffitis, Crohn's disease (CD) of the pouch, and irritable pouch syndrome (IPS) can develop after surgery. Pouchitis has been a major focus for basic science and clinical investigation since it is the most common long-term inflammatory sequela after IPAA. The reported cumulative incidence of pouchitis ranges from 24% to 59% (1, 2, 9–12). Symptoms such as diarrhea, abdominal pain, and perianal or pelvic discomfort in patients with pouchitis and their poor functional status adversely affect QOL (13–15). Although the etiology and pathogenesis of pouchitis are not known, it is speculated that alterations in the microbial environment of the ileal pouch and host immune response in a genetically susceptible patient play a key role in the development of pouchitis.

With an increasing number of patients who have undergone IPAA over the last 25 yr, we often encounter patients whose symptoms are caused by inflammatory or noninflammatory conditions other than pouchitis. These disease entities

include CD of the pouch (16), cuffitis (17), and IPS (18) and account for a significant number of clinical visits at tertiary care centers. The clinical presentations, endoscopic and histologic features of CD of the pouch, cuffitis, and IPS have not been fully characterized. The degree to which these disease conditions affect patients' QOL has not been studied. There is little literature regarding how to best approach symptomatic patients with IPAA. It is important to distinguish pouchitis from CD of the pouch, cuffitis, and IPS, since treatment and prognoses differ. As we have shown in our previous study, symptom assessment alone is not reliable to make a diagnosis of pouchitis, and pouch endoscopy is critical (19). We hypothesized that symptom assessment alone would not be adequate to make a distinction between different disease conditions of IPAA, and these disease conditions would adversely affect patients' QOL.

The aim of this study was to compare demographic, clinical, endoscopic and histologic features, and QOL scores between CD of the pouch, pouchitis, cuffitis, IPS, and normal pouches.

METHODS

Study Patients

The Cleveland Clinic Foundation Institutional Review Board approved the study and written informed consent was obtained from the patients. From May 2002 to January 2004, 164 consecutive UC patients with IPAA were seen and 124 patients who met the inclusion criteria were enrolled in the study, including patients with CD of the pouch (N = 23), antibiotic-dependent or antibiotic-refractory pouchitis (N = 22), cuffitis (N = 21), IPS (N = 32), and normal pouches (N = 26). The patients were referred to the Pouchitis Clinic staffed by the primary investigator (BS) from primary care physicians, gastroenterologists, or colorectal surgeons in or outside the Cleveland Clinic. The patient populations consisted of (i) the disease groups (CD of the pouch, pouchitis, cuffitis, and IPS). All patients in the disease groups presented with symptoms; (ii) the healthy pouch group, in which patients had no symptoms and they came for their annual surveillance pouch endoscopy. None of the patients approached refused to participate in the study.

CD of the pouch was diagnosed based on the presence of nonsurgery-related perianal fistulas, inflammation or ulcerations at the afferent limb or small bowel in the absence of nonsteroidal antiinflammatory drug (NSAID) use, or granulomas on histology. Pouchitis was defined by a Pouchitis Disease Activity Index (PDAI) $\geq$7 (20). Antibiotic-dependent pouchitis was defined as patients with $\geq$4 episodes per year or persistent symptoms requiring a long-term ($\geq$16 wk), continuous antibiotic therapy to stay in remission or frequent antibiotic therapy with probiotics as maintenance therapy (21). Antibiotic-refractory pouchitis was defined as failure to respond to a 2-wk course of single antibiotic (metronidazole 20 mg/kg/day or ciprofloxacin 500 mg b.i.d.) and the patient required $\geq$4-wk therapy with two antibiotics (metronidazole 10–15 mg/kg/day and ciprofloxacin 500 mg b.i.d.) or required oral or topical 5-aminosalicylate or corticosteroids or oral immunomodulators (21). Cuffitis was defined as inflammation of the rectal cuff with no more than minimal (PDAI endoscopic score $\leq$1) concurrent inflammation of the pouch. In patients with concurrent inflammation of the pouch and cuff, the patient was classified as having pouchitis if dominant inflammation was in the pouch, or cuffitis if dominant inflammation was in the cuff. Irritable pouch syndrome was defined as the presence of symptoms of abdominal pain, pelvic discomfort, and diarrhea in the absence of or minimal (PDAI endoscopic score $\leq$1) inflammation of the afferent limb, pouch, or cuff on endoscopy and histology (18). It was hard to identify patients having "completely" normal pouches with no prior history of pouchitis diagnosed based on symptoms with or without endoscopic evaluation. Therefore, currently asymptomatic patients with no endoscopic or histologic inflammation who had $\leq$3 episodes per year of pouchitis with symptoms responding to a 2-wk, single-agent antibiotic with last episode being at least 6 months prior were defined as having normal pouches.

Exclusion criteria were: (i) Antibiotic-responsive pouchitis, defined as currently symptomatic patients with a history of pouchitis ($\leq$3 episodes per year) responding to a 2-wk single-agent antibiotic (21); (ii) patients with equal degrees of inflammation on endoscopy and histology in the pouch as in the cuff who defied a clear classification of pouchitis or cuffitis; (iii) patients with a current diagnosis of IPS who had endoscopically diagnosed pouchitis or cuffitis within the prior 12-month period; (iv) patients with a pre-IPAA diagnosis of CD; and (v) patients with active pouch anastomotic leak, abscess, sepsis, or afferent limb syndrome.

Clinical, Endoscopic, and Histologic Evaluations

Demographic, clinical, endoscopic, and histologic data were collected. The 3-item, 18-point PDAI instrument was used to quantify symptoms and inflammation on endoscopy and histology, with the maximum score of each item being 6 points. Additional symptomatology in the 30 days prior to clinic visit, including obstructive symptoms (persistent bloating, nausea, vomiting, and difficulty in pouch evacuation), stool consistency, incontinence, food- or stress-associated symptom exacerbation, was documented. A GIF-160 upper endoscope (Olympus Optical, Tokyo, Japan) was used for evaluation of the afferent limb, pouch, and cuff, with the PDAI endoscopic scores (range 0–6 points) measured separately for each segment. Additional endoscopic features, including fistulas and strictures, were documented. The mucosal biopsies were taken from the areas with maximal inflammation in the afferent limb, pouch, and cuff, or from the posterior wall of the pouch if the pouch had a normal endoscopic

appearance. Based on the PDAI histology scores, (range 0–6 points), the gastrointestinal pathologist, blinded to demographic, clinical, endoscopic, and histologic data, assessed and graded inflammation of the biopsied specimens. Additional features of mucosal histopathology were documented, including dysplasia, granulomas, cytomegalovirus (CMV) infection, and pyloric gland metaplasia. For patients with antibiotic-refractory pouchitis and CD of the pouch, serum CMV DNA and stoll *Clostridium difficile* toxins A and B were assayed.

Assessment of QOL

The 3-item Cleveland Global Quality of Life (CGQL, scale 0–1.0, with 1.0 being the best) validated for IPAA patients (3), and the 34-item Irritable Bowel Syndrome–Quality of Life (IBS-QOL, scale 34–170, with 34 being the best) designed for patients with functional bowel disorders (22) were used to assess the health-related QOL. The IBS-QOL instrument has eight domains: (i) dysphoria; (ii) interference with activity; (iii) body image; (iv) health worry; (v) food avoidance; (vi) social reaction; (vii) sexuality; and (viii) relationship. The patients filled out all questionnaires in their clinic visits, before clinical and endoscopic evaluations, administered by a clinical nurse or medical assistant.

Correlation Analysis

We performed correlation analyses to assess associations between the PDAI symptom scores and CGQL and IBS-QOL scores, to see if patients' QOL scores were dependent on physical symptoms.

Statistical Analysis

Student t, Kruskal-Wallis, Dunn's, χ^2, and Pearson correlation tests were used for comparisons and correlation analysis. p-values < 0.05 were considered as statistically significant.

RESULTS

Assessment of Risk Factors

Demographic data were compared between each of the disease groups with the normal pouch group. As compared to the normal pouch group, NSAID use was more common in patients with pouchitis; extraintestinal manifestations were more frequently presented in patients with cuffitis or IPS; and antidepressants were more often used in patients with IPS before they were diagnosed with the disease (Table 1). Figure 1 illustrated a possible causal role of NSAID use in pouchitis.

Table 1. Comparison of Demographic and Clinical Data: Diseased IPAA *versus* Normal Pouches

	Normal Pouch	Crohn's Disease of the Pouch	Pouchitis	Cuffitis	Irritable Pouch Syndrome
N	26	23	22	21	32
Age, median (25th, 75th)	42.0 (35.0, 53.0)	41.0 (27.0, 46.0)	52.0 (34.0, 58.0)	39.0 (32.0, 51.0)	48 (34.5, 57.0)
Male gender, n (%)	7 (26.9)	7 (30.4)	11 (50.0)	6 (28.6)	15 (46.9)
Duration of UC to date, years, median (25th, 75th)	11 (8.0, 17.0)	13.0 (10.0, 20.0)	13.5 (8.0, 25.0)	13.0 (6.0, 19.0)	10.5 (7.5, 19.5)
Duration of IPAA, years, median (25th, 75th)	5.0 (3.0, 8.0)	6.0 (3.0, 13.0)	3.5 (2.0, 8.0)	4.0 (3.0, 8.0)	4.5 (2.5, 7.5)
Pancolitis, n (%)	25 (96.2)	22 (95.7)	22 (100)	20 (95.2)	30 (93.8)
Fulminant colitis, n (%)	2 (7.7)	4 (17.4)	2 (9.09)	1 (4.8)	1 (3.1)
Indication for colectomy, n (%)					
Refractory/steroid-dependent	20 (76.9)	21 (91.3)	12 (54.6)	19 (90.5)	26 (81.3)
Dysplasia or cancer	6 (23.1)	2 (8.7)	10 (45.5)	2 (9.5)	6 (18.8)
J pouch, n (%)	23 (88.5)	21 (91.3)	21 (95.5)	20 (95.2)	31 (96.9)
2-stage IPAA, n (%)	22 (84.6)	18 (78.3)	18 (81.8)	14 (66.7)	28 (87.5)
NSAID use more often than monthly, n (%)	10 (38.5)	13 (56.5)	15 (68.2)†	6 (28.6)	13 (40.6)
Extraintestinal manifestations, n (%)					
Arthralgias	4 (15.4)	7 (30.4)	8 (36.4)	11 (52.4)†	13 (40.6)†
Primary sclerosing cholangitis	2 (7.7)	0	3 (13.6)	0	0
E. nodosum or P. gangrenosum	0	1 (4.4)	0	1 (4.8)	0
Iritis, uveitis, episcleritis	0	1 (4.4)	0	1 (4.8)	1 (3.1)
Current smoking, n (%)	1 (3.9)	4 (17.4)	1 (4.6)	0	2 (6.3)
Alcohol more often than weekly, n (%)	0	0	1 (4.6)	1 (4.8)	2 (6.3)
Family history of IBD,* n (%)	6 (23.1)	5 (21.7)	2 (9.1)	4 (19.1)	8 (25)
Long-term (≥6 months) use of Non-IBD related medicines, n (%)					
Antidepressants	4 (15.4)	3 (13.0)	7 (31.8)	7 (33.3)	14 (43.8)†
Antianxiety agents	2 (7.7)	1 (4.4)	2 (9.1)	3 (14.3)	9 (28.1)
Narcotics	2 (7.7)	1 (4.4)	4 (18.2)	3 (14.3)	9 (28.1)

*First-degree relatives.
†Risk factors identified in univariate analysis, $p < 0.05$.

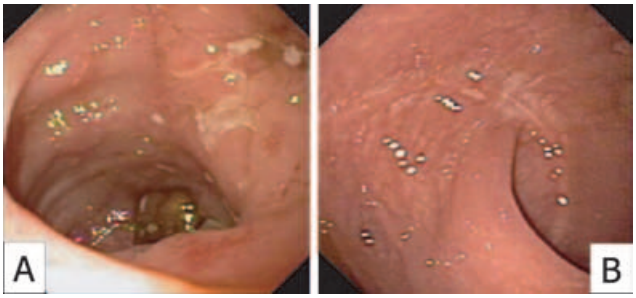

Figure 1. Endoscopic feature of NSAID-induced pouchitis (*A*) and resolution of inflammation after NSAID discontinued (*B*). A 29-yr-old female presented with antibiotic-refractory pouchitis, while taking ibuprofen on a daily basis. Pouch endoscopy showed inflammation of the afferent limb and pouch with edema, superficial ulcers, and aphthous ulcers. A repeat pouch endoscopy 4 wk after she stopped ibuprofen revealed complete healing of ulcers and resolution of inflammation of the pouch and afferent limb. Her symptoms of abdominal pain and diarrhea also resolved.

Clinical, Endoscopic, and Histologic Evaluations

Endoscopic spectra of CD of the pouch, pouchitis, and cuffitis are shown in Figures 2–4. The common endoscopic features shared by the CD of the pouch, pouchitis, and cuffitis groups were erythema, nodularity, granularity, ulceration, mucous exudates, and friability, which are all listed in the PDAI instrument.

The mean PDAI symptom scores and total PDAI scores were significantly higher in the disease groups than in the normal pouch group. The endoscopic and histologic inflammation of the afferent limb was a predominant feature of CD of the pouch. Endoscopic and histologic inflammation of the cuff was characteristic of cuffitis, which were also seen in some patients with CD of the pouch or pouchitis (Table 2).

Using the PDAI instrument, we found that there are no significant differences in total symptom scores among the disease groups. Bleeding is an exception, which occurred commonly in patients with cuffitis (20/21, 95.2%). The symptom items listed in PDAI, that is, abdominal pain, pelvic discomfort, and diarrhea had no discriminating role among the disease groups of IPAA (Table 2). Endoscopy was useful in discriminating between CD of the pouch, pouchitis, cuffitis, and normal pouches or IPS (Table 2). The role of histology items listed in PDAI was limited to confirm inflammation seen on endoscopy (Table 3).

Symptomatology in addition to the PDAI symptom scores was assessed. The majority of the symptoms overlapped in the disease groups. However, obstructive symptoms, such as constipation, constant nausea, and bloating, occurred in patients with CD of the pouch. Gas, incontinence, nocturnal symptoms, and liquid stools were rarely noted in the normal pouch group (Table 3).

Nonspecific histologic features, such as villous blunting, neutrophil and mononuclear cell infiltrations, and mucosal ulceration were often present in the CD of the pouch, pouchitis, and cuffitis groups. Granulomas were rarely (1/23, 4.3%) detected on mucosal biopsy in the CD of the pouch group. Pyloric gland metaplasia was occasionally seen in patients with CD of the pouch (4/23, 17.4%), pouchitis (1/22, 4.5%), or cuffitis (1/21, 4.5%) (Table 3). None of the 124 patients had CMV or dysplasia on biopsy histology. None of the patients with antibiotic-refractory pouchitis or CD of the pouch

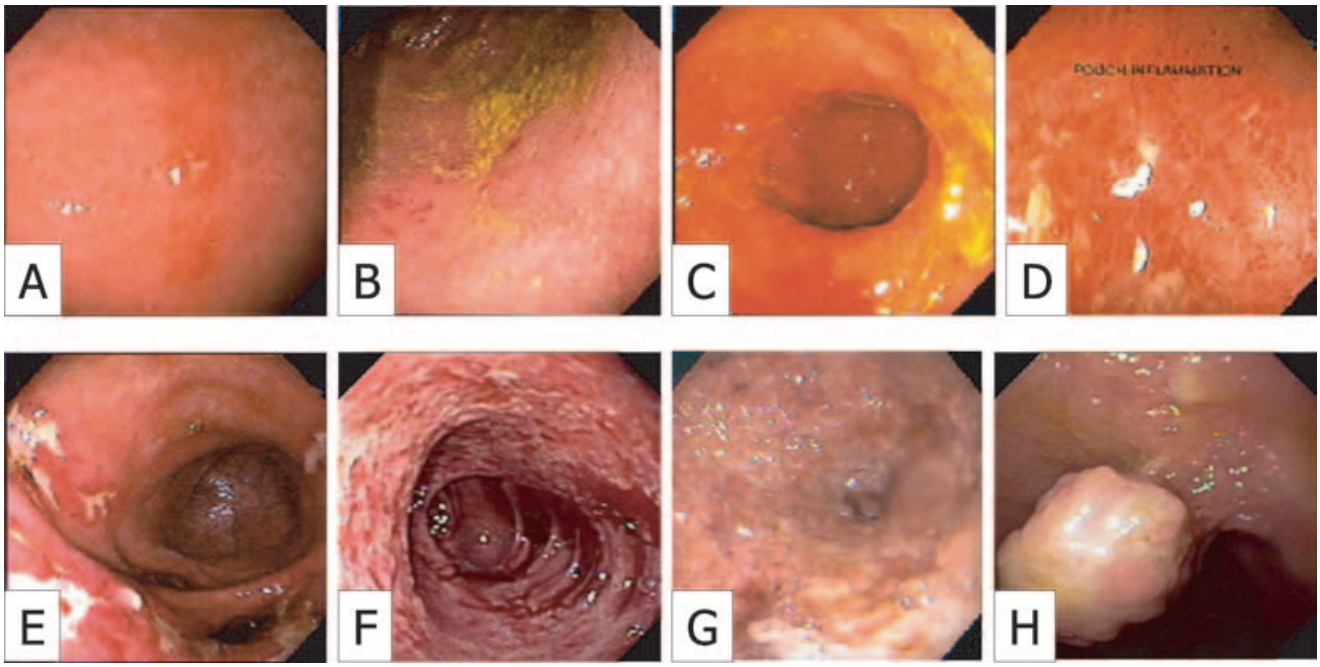

Figure 2. Endoscopic spectrum of pouchitis from mild to severe, with PDAI endoscopy scores ranging from 1 to 6 (*A–G*). A large pseudopolyp due to chronic antibiotic-refractory pouchitis (*H*).

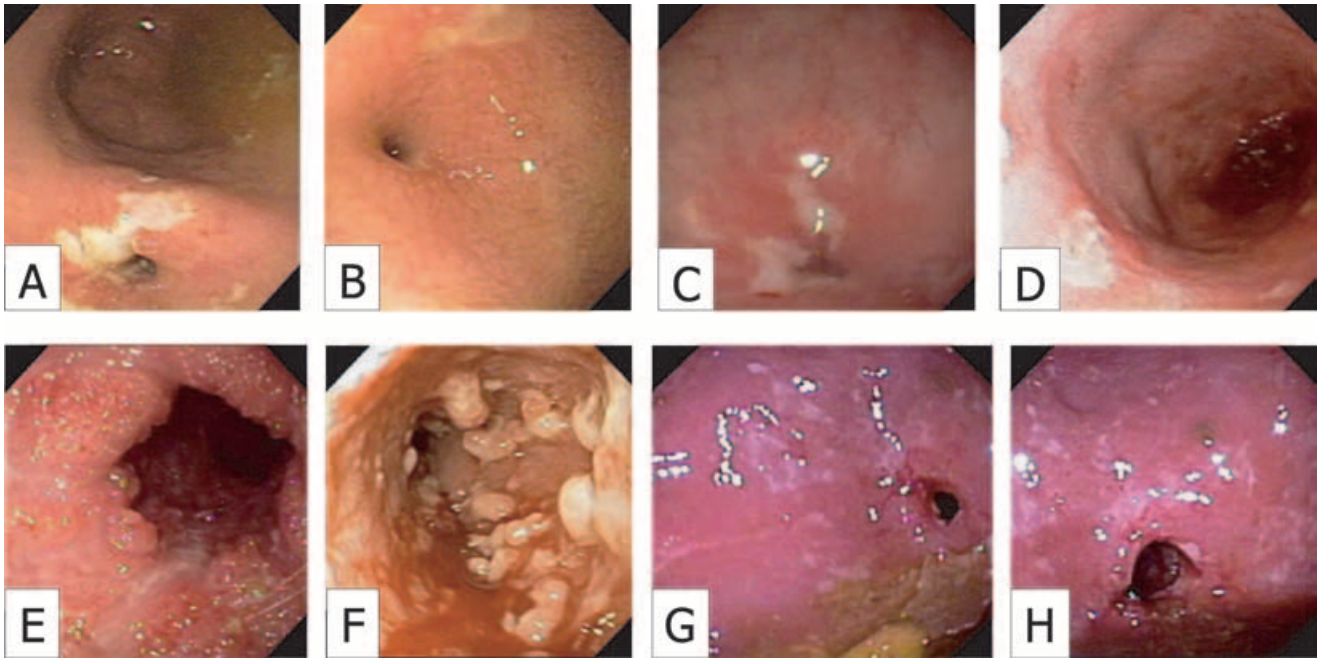

Figure 3. Endoscopic spectrum of Crohn's disease of the pouch. Pouch inlet strictures (*A*, *C*), pouch fistula (*B*), afferent limb ulcers (*D*), inflammation (*E*) and pseudopolyps (*F*), and inlet stricture before (*G*) and after (*H*) endoscopic dilation.

had positive serum CMV DNA or *Clostridium difficile* toxins in the stool.

Assessment of QOL

Patients with diseased IPAA have significantly worse CGQL and IBS-QOL scores than patients with normal pouches (Table 4). In addition, the IBS-QOL scores in the IPS group were significantly poorer than that of the pouchitis group ($p = 0.03$). Subanalysis was performed for the eight domains of IBS-QOL in the disease and normal control groups. Patients in the disease groups have significantly poorer scores in each domain of IBS-QOL than the patients with normal pouches ($p < 0.001$). Furthermore, the scores of body image and social reaction domains were significantly poorer in the IPS group than in the pouchitis group ($p < 0.03$).

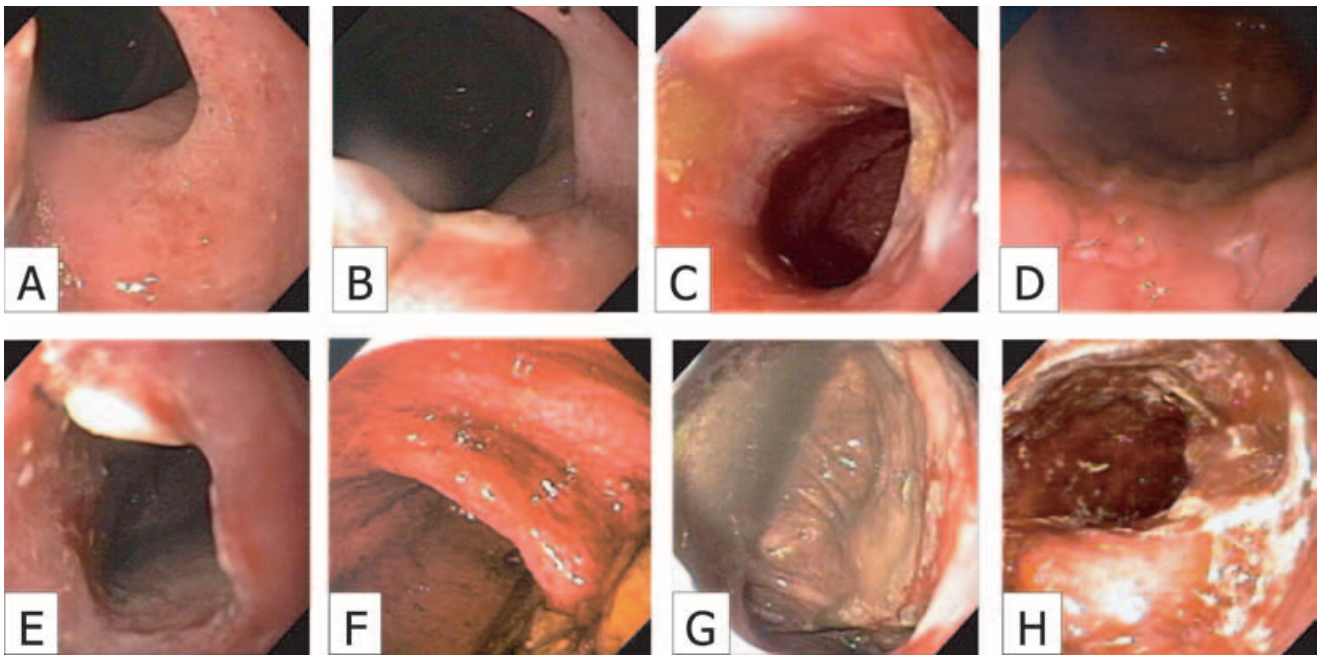

Figure 4. Endoscopic spectrum of cuffitis from mild to severe with PDAI endoscopy scores ranging from 1 to 6 (*A–H*).

Table 2. Symptomatology, Endoscopy, and Histology Using Pouchitis Disease Activity Index

Effect	Normal Median (25th, 75th)	Crohn's Disease of the Pouch Median (25th, 75th)	Pouchitis Median (25th, 75th)	Cuffitis Median (25th, 75th)	Irritable Pouch Syndrome Median (25th, 75th)	Kruskal-Wallis *p*-Values (Simultaneous Comparison)
N	26	23	22	21	32	
Total PDAI	1 (1, 2)	7 (5, 11)	8.5 (7, 11)	6 (5, 8)	5 (4, 5)	<0.001
Symptom	0 (0, 0)	3 (2, 4)	4 (3, 4)	4 (3, 5)	4 (3, 4)	<0.001
Endoscopy						
Afferent limb	0 (0, 0)	1 (0, 4)*	0 (0, 0)	0 (0, 0)	0 (0, 0)	<0.001
Pouch	0 (0, 0)	3 (1, 5)	3 (2, 6)	1 (0, 1)	0 (0, 1)	<0.001
Cuff	0 (0, 0)	0 (0, 2)	0 (0, 3)	4 (2, 4)†	0 (0, 0)	<0.001
Histology						
Afferent limb	1 (0, 1)	1 (0, 5)*	1 (0, 1)	0 (0, 0)	0 (0, 0)	<0.001
Pouch	1 (0, 1)	2 (1, 4)	2 (1, 2)	1 (0,1)	1 (0, 1)	<0.001
Cuff	0 (0, 1)	1 (1, 2)‡	0 (0, 1)	2 (1, 3)‡	0.5 (0,1)	<0.001

*CD of the pouch *versus* the rest groups, $p < 0.05$; †Cuffitis *versus* the rest groups, <0.001; ‡CD of the pouch and cuffitis *versus* the rest groups, $p < 0.01$.

Correlation Analysis

The CGQL and IBS-QOL scores in all five groups were correlated with correlation coefficients ranging from −0.38 to −0.64 ($p < 0.03$). In the CD of the pouch and pouchitis groups, patients' symptoms were correlated with CGQL and IBS-QOL scores. However, in the cuffitis and IPS groups, patients' symptom scores were not correlated with CGQL and IBS-QOL scores ($p > 0.05$) (Table 5), suggesting that additional factors may contribute to the patients' poorer QOL scores.

DISCUSSION

This study is the first of its kind to head-to-head compare demographic, clinical, endoscopic, histologic features, and QOL scores between inflammatory and noninflammatory sequelae of IPAA. There were no differences in the PDAI symptom scores between the disease groups, with an exception of bleeding, which occurred almost exclusively in cuffitis. Endoscopy was useful in discriminating between CD of the pouch, pouchitis, cuffitis, IPS, or normal pouches. Univariate analysis of demographic and clinical data showed possible association between NSAID use and pouchitis, extraintestinal manifestations and cuffitis, and antidepressant use and IPS. A multivariate analysis involving a larger number of patients in each study group is warranted to identify definite risk factors for these pouch diseases.

The etiology and pathogenesis of inflammatory and noninflammatory sequelae of IPAA are largely unknown (2). Reported risk factors for pouchitis include extensive UC (1), backwash ileitis (23), extraintestinal manifestations

Table 3. Assessment of Additional Symptomatology, Endoscopy, and Histology

	Normal Pouch n (%)	Crohn's Disease of the Pouch n (%)	Pouchitis n (%)	Cuffitis n (%)	Irritable Pouch Syndrome n (%)	*p*-Values (Simultaneous Comparison)
N	26	23	22	21	32	
Symptoms						
Bleeding	0	0	1 (4.5)	20 (95.2)*	0	<0.001
Perianal symptoms	4 (15.4)	16 (69.6)	18 (81.8)	21 (100)	28 (87.5)	<0.001
Obstructive symptoms	0	6 (26.1)†	0	0	0	<0.001
Gas/bloating	2 (7.7)	9 (39.1)	13 (59.1)	14 (66.7)	27 (84.4)	<0.001
Fever	0	0	0	0	1 (3.1)	0.187
Incontinence	2 (7.7)	14 (60.9)	16 (72.7)	16 (76.2)	18 (56.3)	<0.001
Nocturnal symptoms	6 (23.1)	16 (69.6)	19 (86.4)	19 (90.5)	25 (78.1)	<0.001
Food/stress exacerbation	23 (88.5)	17 (73.9)	16 (72.7)	15 (71.4)	31 (96.9)	0.003
Postdefecation relieve	12 (44.4)	8 (34.8)	13 (59.1)	11 (52.4)	12 (37.5)	0.011
Liquid stools	0	7 (30.4)	7 (31.8)	6 (28.6)	20 (62.5)	<0.001
Daily antidiarrheal use	3 (11.5)	7 (30.4)	11 (50)	5 (23.8)	19 (59.4)	0.002
Weight loss >5% in 6 months	0	2 (8.7)	2 (9.1)	2 (9.5)	1 (3.1)	0.456
Endoscopy						
Fistula	0	5 (21.7)†	0	0	0	<0.001
Pouch inlet stricture	0	11 (47.8)†	0	0	0	<0.001
Pouch outlet stricture	0	4 (17.4)‡	1 (4.5)	3 (14.3)‡	00	<0.001
Histology						
Pyloric gland metaplasia	0	4 (17.4)	1 (4.5)	1 (4.5)	0	0.018
Granulomas	0	1 (4.3)	0	0	0	0.303

*Cuffitis *versus* the rest groups, $p < 0.001$; †CD of the pouch *versus* the rest groups, $p < 0.05$; ‡CD of the pouch and cuffitis *versus* normal and IPS, $p < 0.047$.

Table 4. Comparison of the Cleveland Global Quality of Life (CGQL) and Irritable Bowel Syndrome Quality of Life (IBS-QOL) Scores

Effect	Normal Median (25th, 75th)	Crohn's Disease of the Pouch Median (25th, 75th)	Pouchitis Median (25th, 75th)	Cuffitis Median (25th, 75th)	Irritable Pouch Syndrome Median (25th, 75th)	Kruskal-Wallis *p*-Values (Simultaneous Comparison)
N	26	23	22	21	32	
CGQL	0.87 (0.7, 0.9)	0.5 (0.4, 0.7)	0.58 (0.5, 0.7)	0.6 (0.5, 0.7)	0.6 (0.5, 0.8)	<0.001
IBS-QOL	50 (42.0, 73.0)	101 (78.0, 120.0)	87.5 (68.0,108.0)	100 (82.0, 108.0)	115 (85.5, 127.5)*	<0.001

*IPS *versus* Pouchitis, $p = 0.032$.

(especially primary sclerosing cholangitis) (11, 24, 25), and presence of perinuclear antineutrophil cytoplasmic antibody. There is inconsistency of the risk factors reported in the previous studies, which could be due to (i) diagnostic criteria used; (ii) stratification of pouchitis—acute *versus* chronic pouchitis or lumping both entities together; (iii) number of patients studied (type 2 errors in some studies); or (iv) duration of follow-up (12). In this study, the diagnosis of pouchitis was based on a combined assessment of symptom, endoscopy, and histology. In the category of pouchitis, only patients with antibiotic-dependent and antibiotic-refractory pouchitis were included, since these subtypes of pouchitis often pose a challenge for management. NSAID use was often reported in patients with pouchitis, suggesting that NSAID use may contribute to the development of the disease.

The true incidence of CD of the pouch in patients initially operated for UC is not known. Our group reported 74 patients (3.8%) with CD diagnosed based on pre- and postoperative pathology of colon specimens or ileal pouches in a large series of 1,965 patients with IPAA (26). CD of the pouch occurred under the following circumstances: (i) IPAA was intentionally performed in a select group of patients with Crohn's colitis without ileal or perianal diseases (27); (ii) CD was inadvertently found in colectomy specimens in postoperative histologic evaluation in patients with preoperative UC (28, 29); or (iii) *de novo* CD of the pouch developed weeks or years after IPAA (30). Risk factors for *de novo* CD of the pouch are yet to be identified.

Stapled IPAA without mucosectomy has preferably been used in our institution, since this technique is simpler and less likely to result in functional and septic complications than hand-sewn IPAA with mucosectomy (31–34). The stapled IPAA is performed close to the level of the anorectal ring without mucosectomy of the anal transition zone. To allow transanal insertion of the stapler head, it is usually necessary to leave a 1-cm to 2-cm strip of columnar cuff or anal transition zone mucosa that is at risk for developing symptomatic inflammation (cuffitis) or dysplasia (18, 35–37). Patients with cuffitis, which was considered as residual UC, were more likely to have extraintestinal manifestations in this series. Our recent trial of topical mesalamine in patients with cuffitis showed that the agent appeared effective in improving arthralgias as well as in relieving diarrhea, bleeding, and urgency (17).

Irritable pouch syndrome is a newly described disease entity in patients with IPAA, with its symptoms overlapping with those seen in pouchitis and cuffitis (18). IPS shares clinical features with irritable bowel syndrome. Visceral hypersensitivity and psychological factors, which are important pathophysiological features of irritable bowel syndrome, may also play a role in the pathogenesis of IPS. Our recent study using an electronic barostat revealed a decreased threshold for perception of gas, urge to defecate, and pain in patients with IPS (indicating visceral hypersensitivity), while biomechanical properties of their pouches were similar to that in patients with healthy pouches (38). This, together with the evidence of large number of IPS patients on antidepressants at the time of the diagnosis as shown in this study, suggest that psychological factors may be part of the pathophysiology of the disease. Our anecdotal experience suggests that tricyclic antidepressants, which are commonly used in irritable bowel syndrome, appear to be effective in treating patients with IPS.

The distinction between CD of the pouch, pouchitis, cuffitis, and IPS is important, since treatment and prognosis are different for each entity. Although none of symptoms was

Table 5. Correlation between PDAI Symptoms Scores and Quality-of-Life Scores

Cohort	Pair	N	Correlation Coefficient (95% CI)	*p*-Values
Normal pouch	CGQL *versus* symptoms	26	−0.47 (−0.84, −0.10)	0.015
	IBS-QOL *versus* symptoms	26	0.49 (0.12, 0.86)	0.011
Crohn's disease of the pouch	CGQL *versus* symptoms	23	−0.49 (−0.89, −0.09)	0.018
	IBS-QOL *versus* symptoms	23	0.72 (0.41, 1.00)	<0.001
Pouchitis	CGQL *versus* symptoms	22	−0.32 (−0.76, 0.12)	0.14
	IBS-QOL *versus* symptoms	22	0.52 (0.12, 0.92)	0.013
Cuffitis	CGQL *versus* symptoms	21	−0.12 (−0.59, 0.36)	0.62
	IBS-QOL *versus* symptoms	21	0.29 (−0.17, 0.75)	0.2
Irritable pouch syndrome	CGQL *versus* symptoms	32	−0.08 (−0.46, 0.29)	0.65
	IBS-QOL *versus* symptoms	32	−0.12 (−0.49, 0.25)	0.5

diagnostic for any of the disease conditions of IPAA, bleeding was almost exclusively seen in patients with cuffitis, while obstructive symptoms, afferent limb disease, pouch inlet strictures, and fistulae were characteristic of CD of the pouch. The majority of these features could be assessed with careful endoscopy. Our previous study (19) has demonstrated that symptom assessment alone is not reliable for the diagnosis of pouchitis. The same is true for cuffitis and CD of the pouch. Endoscopic evaluation provides a valuable tool for the diagnosis of CD of the pouch, pouchitis, and cuffitis. Endoscopy is also useful for the diagnosis of IPS, since IPS is currently a diagnosis of exclusion. In addition, endoscopy could render treatment of certain structural diseases of the pouch, such as endoscopic balloon dilatation of pouch inlet or outlet strictures (39).

Histology evaluation is an important component for the evaluation of IPAA patients with symptoms. However, inflammation graded by histology does not correlate with patients' symptoms or endoscopy (19). A more important role of histology would be the evaluation for disease-specific features, such as dysplasia, granulomas, CMV infection, or pyloric gland metaplasia. Although specific for CD, granulomas were rarely detected in patients with CD of the pouch. Pyloric gland metaplasia, more often seen in CD, was also detected in pouchitis or cuffitis in this series.

Ileal pouch-anal anastomosis has greatly improved QOL of UC patients who require surgery (3–7). Patients with pouchitis had poorer QOL scores than patients with normal pouches (14, 15). In addition, we also showed that patients with CD of the pouch, cuffitis, and IPS similarly had poor QOL scores, as measured by the previously validated CGQL and IBS-QOL. These disease conditions of IPAA have an adverse impact on physical and psychological well-being, which can compromise the gain in QOL by the "curative" IPAA surgery. Multiple factors could contribute to their poor QOL. Although symptoms and endoscopic and histologic inflammation could directly contribute to the poor QOL scores, symptom scores do not necessarily correlate with QOL scores, especially in patients with cuffitis or IPS. These results suggest that additional factors, such as cognitive function, socioeconomic status, education, coping strategies, social support, personality, may play a role. The information can be useful to tailor appropriate management for a particular patient with a diseased IPAA.

In summary, symptoms largely overlapped among the disease groups of IPAA, although bleeding (cuffitis) or obstructive symptoms (CD of the pouch) may suggest a diagnosis. Endoscopic evaluation is valuable for diagnosis. Patients with diseased IPAA have significantly worse QOL scores compared to the patients with normal pouches. This may provide guidance for patients, gastroenterologists, and colorectal surgeons when they make decision for IPAA surgery and for the diagnosis and management of inflammatory and noninflammatory sequelae after IPAA.

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