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Long-Term Prognosis of Crohn's Disease of the Pouch: A Single-Center Experience of 17 Years

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Abstract

Objective: Crohn's disease of the pouch is defined as the appearance of Crohn's disease complications such as fistula or stricture in an ulcerative colitis patient in the postoperative period, who had restorative proctocolectomy with ileal pouch anal anastomosis. The aim of this study is to investigate the long-term prognosis of Crohn's disease in the pouch patients.

Methods: A total of 1166 records of ulcerative colitis patients were examined, and 57 patients who underwent ileal pouch anal anastomosis were detected. We formed 2 control groups from ileal pouch anal anastomosis patients: patients with pouchitis (n = 12) and asymptomatic patients (control group, n = 17).

Results: Ten out of 28 patients with chronic pouchitis were grouped as Crohn's disease of the pouch. In this group, there were 6 patients with fistula, including 5 with perianal fistula and 1 with pouch–vagina fistula. In 2 patients, there was also concomitant stricture. Four patients had strictures without perinal fistula. In the perianal fistula group, all patients received tumor necrosis factor-alpha blocker treatment (5 infliximab and 1 adalimumab) combined with azathioprine in 5 of them. In the stricture group, 2 patients received azathioprine, 1 patient received infliximab combined with azathioprine, and 1 patient received infliximab monotherapy. In the fistula group, diverting ileostomy was performed in 3 patients; in only 1 patient, fistula flow stopped. During the follow-up period, none of the Crohn's disease of the pouch patients were in remission except 1 who had diverting ileostomy. Total remission rate in the pouchitis group was 33% (4/12).

Conclusion: Crohn's disease of the pouch is not an uncommon clinical entity with a frequency of 20% in the long term follow-up. Despite combined medical treatment, one-third of the patients ended with permanent end ileostomy due to pouch failure.

Keywords: Colonic pouch, restorative proctocolectomy, ileal pouch anal anastomosis, Crohn's disease of the pouch

Introduction

Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is a surgical treatment option for patients with ulcerative colitis (UC) who require colectomy due to chronic medical treatment-resistant UC to avoid a permanent ileostomy. A subset of UC patients who had IPAA can develop a form of chronic inflammatory condition like Crohn's disease (CD).[1] Chronic pouchitis, inflammation and/or strictures at the afferent limb (peripouch ileitis), perianal fistula, and/or stenosis in the pouch or at the anastomosis are the main components of this entity.[1-3] This condition was stated by different names like Crohn's disease of the pouch (CDP), Crohn's pouchitis, CD-like condition in ileal pouch, CD-like complications of the pouch, or post-IPAA CD.[2-4] There are no definitive diagnostic criteria for this condition, as it was mentioned in the meta-analysis of Barnes in most of the studies complications of CD such as the presence of fistula or stricture were used to define this condition.[1] Detection of granuloma was reported in 9.7%-12% of these patients.[5] Nevertheless, in some series, any patient had histopathological diagnosis of CD at the extirpated pouch.[6] The aim of this study is to investigate the long-term prognosis of patients who were diagnosed with CDP after IPAA.

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Material and Method

We investigated the files of UC patients who underwent IPAA between 2000 and 2017. Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (Date:03.05.2017, Number:166590). Due to the retrospective design of the study, informed consent was not taken. The main inclusion criterion was the histopathological diagnosis of UC in the resection specimen. The same pathologist reexamined resection specimens of all cases including control groups. All cases who had the histopathological diagnosis of indeterminate colitis (IC) or CD were excluded.

Crohn's disease of the pouch was defined as the detection of perianal fistula or stenosis in a chronic pouchitis patient who was unresponsive to conventional pouchitis treatment. Patients who have chronic pouchitis and afferent loop ileitis without fistula or

stenosis were investigated separately under the title of afferent loop ileitis. Two groups of UC patients who had IPAA were included as control groups—: the first control group (pouchitis group) consisted of UC patients who had chronic pouchitis and the second control group consisted of asymptomatic UC patients who had IPAA (control group). Isolated cuffitis patients were excluded from the study because the mechanism of inflammation in this group is accepted to be associated with the recurrence of mucosal activity of UC at the remnant mucosa. The definitions of 4 study groups are summarized in Table 1.

Statistical Analysis

Smoking habits, family history of CD, preoperative colonoscopy, radiological findings, treatment modalities, and outcome were recorded from patient files. We reviewed histopathological, endoscopic, and radiological findings of the preoperative period.

Data about smoking rate, sex, disease extension (pancolitis or extensive colitis), the rate of ileal intubation, age at the diagnosis, age at the operation, disease duration time until the operation, symptoms appearance time after the operation, and follow-up time after the diagnosis were compared between CDP, pouchitis, afferent loop ileitis, and the control group. Data about the rate of having both pouchitis and cuffitis were compared between 3 groups (CD of the pouch, pouchitis, and afferent loop ileitis group). Pearson chi-square test, the Fisher's exact test, and the Kruskal–Wallis test were used for the comparison of parameters between groups.

Results

A total of 1166 records of UC patients were examined; we detected 57 patients who underwent IPAA operation. All patients were operated due to medical treatment refractory UC. Nine patients were excluded from this study for various reasons. In 2 patients, the histopathological diagnosis of the resection specimen was CD and IC. In 6 patients, we could not reach the resection specimen for reassessment and 1 patient was lost to follow-up after IPAA. In the remaining 48 patients, all have histopathological diagnosis of UC obtained from resection specimen. We excluded 3 patients with cuffitis. We divided resting 45 patients to 4 groups as it was mentioned in the methods.

A total of 10 patients with chronic pouchitis who have perianal fistula and/or stenosis at the pouch were grouped as CDP (10/48, 20.8%). Afferent loop ileitis group consisted of 6 patients (12.5 %). We grouped 12 patients including 7 patients with pouchitis and 5 patients with both pouchitis and cuffitis as pouchitis group. Seventeen asymptomatic UC patients who had IPAA were grouped as the control group (Figure 1).

Table 1. Definition of Study Groups

Group Name	Definition	N
Crohn's disease of the pouch	Chronic pouchitis with fistulizing or stenosing disease	10
Afferent loop ileitis	Chronic inflammation at the afferent loop with or without chronic pouchitis	6
Pouchitis	Chronic pouchitis without afferent loop ileitis, fistulizing disease, or stenosing disease	12
Control group	Asymptomatic ulcerative colitis patients who had restorative colectomy and ileal pouch anal anastomosis	17

The mean period of follow-up before proctocolectomy was 3.2 years (SD: 2.72, range of 1-11, median 2 years). Backwash ileitis was reported in 1 patient from the CDP group and 1 from the pouchitis group; there was no granuloma formation at the biopsy specimen obtained from terminal ileum in these 2 patients. In our reassessment of patient files, we detected some endoscopic findings, which can be associated with Crohn's colitis in 2 patients from the CLD group. In 1 patient, there were longitudinal ulcers at the sigmoid colon and in the second case there were some aftoid lesions besides pseudo polyps at some parts of the colon. In both patients, there was no sign of ileal inflammation at colonoscopy and at the abdominal computerized tomography study. In addition there was no sign of CD at the mucosal biopsy specimens obtained during colonoscopy. The rate of absence of ileal intubation during colonoscopy before the operation was 40% (4/10), 33.3% (4/12), and 11.8% (2/17) in the CDP group, pouchitis group, and control group, respectively. In the afferent loop ileitis group, all patients have had ileal intubation. Although the rate of absence of ileal intubation rate was higher in the CDP group numerically (40% against 20.6% in the rest of the group), there was no a statistically significant difference. In our retrospective reassessment of these patients without ileal intubation, we did not detect any sign of CD in their cross-sectional radiological examination in the preoperative period.

Crohn's Disease of the Pouch

All patients in the CDP group had chronic pouchitis that was refractory to antibiotics and Local 5-aminosalicylic acid (5-ASA) therapy. All patients have been examined by our surgical team to exclude surgical complications. None of these patients has had anastomotic leak or pelvic infection within the first year of the procedure. The main findings are summarized in Table 2.

There were 6 patients who had fistula (mean age: 41 ± 11.2), including 5 patients with perianal fistula (4 male and 1 female) and 1 patient with pouch–vaginal fistula. The mean time of the occurrence of the fistula after operation was 44 ± 13.5 (minimum 20, maximum 62, and median 45.5) months. All patients with fistula had also cuffitis. Five of them received combination of anti-tumor necrosis factor (TNF) agents and azathioprine therapy. One patient received only anti-TNF agent because azathioprine was stopped due to leukopenia. Five of them had also loose seton application during medical treatment. The patient who did not have seton treatment was the patient who had pouch–vaginal fistula. Three of them had diverting ileostomy due to debilitating fistulizing disease unresponsive to medical treatment. In 1 patient, fistula flow stopped after diverting ileostomy. Two patients had concomitant stricturing disease (Table 3).

Obstructive complications were present in 6 (4 males and 2 females, mean age 45.8 ± 7.5 years) patients. The stenosis was in the cuff in 5 patients. In 1 patient, stenosis was at the afferent loop. In 2 patients, there was both cuff and afferent loop stricture. We applied balloon dilatation in 2 patients. In the patient with cuff stenosis, balloon dilatation was effective. In the patient who had both cuff and afferent loop stenosis, balloon dilatation of the afferent loop was not effective. Medical treatment of 10 patients with CDP is summarized in Table 4.

Afferent Loop Ileitis

There were 6 patients who had inflammation at the afferent loop; all of them had also pouchitis. Three patients had longitudinal ulcers, 2 had aftoid lesions, and 1 had superficial ulcers at the afferent loop. In addition, 3 of them had also longitudinal ulcers in the pouch. We summarized the findings of these patients in Supplementary Table 1.

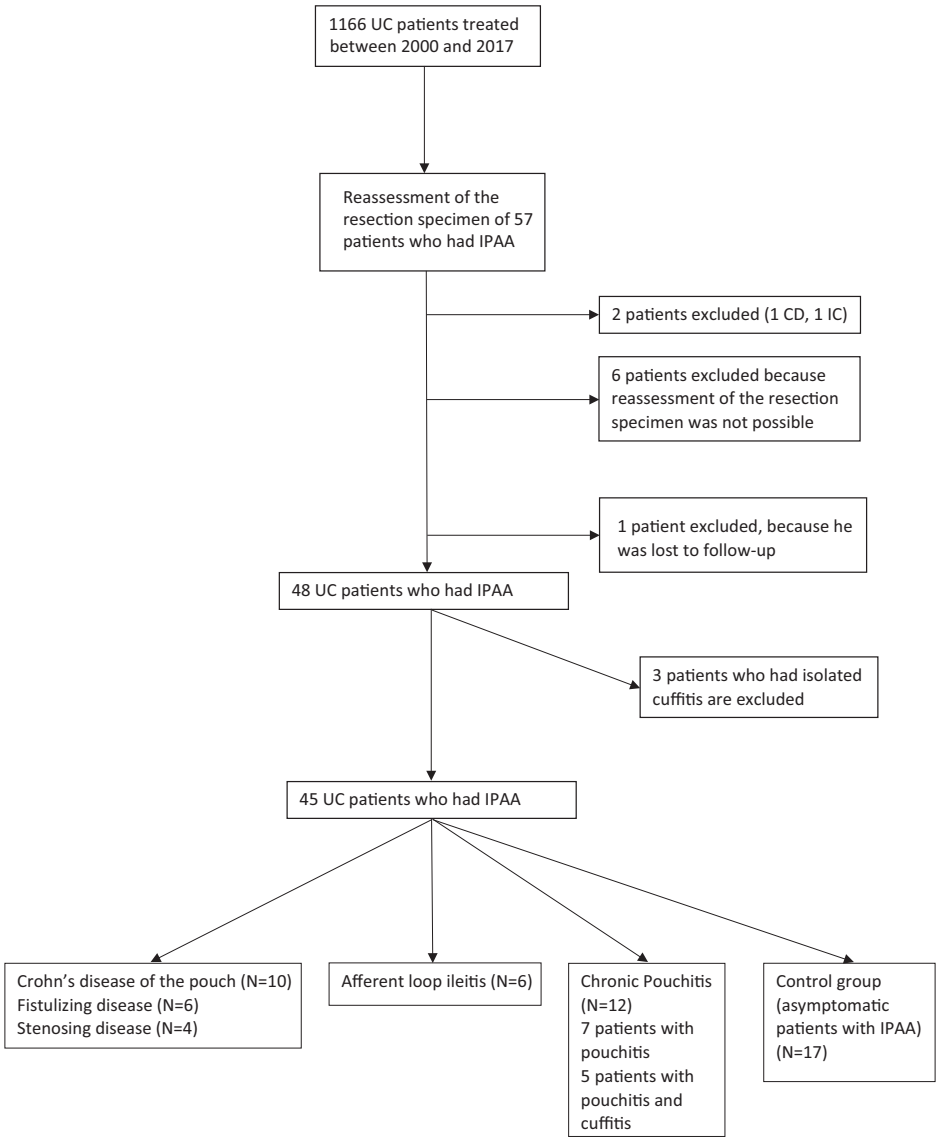

Figure 1. The flowchart of the patient selection and grouping. CD, Crohn's disease; IC, indeterminate colitis; IPAA, ileal pouch anal anastomosis; UC, ulcerative colitis.

Prognosis of Crohn's Disease of the Pouch

The mean appearance of complications after surgery was 24.8 ± 13.8 months (with a range of 7-57 months). A total of 3 patients had ileostomy (30%) due to intractable fistulizing disease. During the follow-up period with the mean of 109.5 ± 36.6 months, none of the 10 patients with CLD was in remission except 1 patient who had diverting ileostomy. We did not apply pouch excision and end ileostomy in any patient because they did not give consent. In 2 patients, endoscopic balloon dilation was applied due to stenosing disease; dilatation was effective in 1 of them. There was no mortality.

Table 2. Endoscopic and Clinical Findings of Patients with Crohn's Disease of the Pouch

Findings	n (%)
Fistulizing disease	6/10[a]
Stricture at the afferent loop	3/10[b]
Stricture at the cuff–pouch anastomosis	5/10[b]
Inflammation at the afferent loop	7/10

[a]Except 1 patient with pouch–vagina fistula, all patients had perianal fistulas.
[b]Two patients had both cuff and afferent loop stenosis and 1 patient had only afferent loop stricture; stricturing disease in the whole group was 60% (6/10).

Comparison Between Groups

Comparisons of groups revealed that the age at the time of operation in the CDP group was significantly less than that of the pouchitis group (Table 5). The mean time of the appearance of the first symptom after operation was not different in the CDP group from other groups, although it was significantly higher in the afferent loop ileitis group than the pouchitis group. The rate of having both pouchitis and cuffitis was not statistically significant within the 3 groups: 80% (8/10), 41.6% (5/12), and 83.3% (5/6) for the CDP group, pouchitis group, and afferent loop ileitis group, respectively.

There was no difference in smoking rate, sex, and disease extension (pancolitis or extensive colitis) between groups. There was 1

Table 3. Patients with Fistulizing Disease

Type of Fistula	Pouchitis	Cuffitis	Afferent Loop Ileitis	First Detection of the Fistula (Months)	Follow-Up Time (Months)	Active Fistula Discharge	Surgical and/or Endoscopic Treatment
TS	+	+	+	44	85	+	Seton treatment
PV	+	+[a]	+	62	84	+	None
IS	+	+	–	45	14	+	Seton treatment
IS	+	+	+	46	18	+	Seton treatment + ileostomy
IS	+	+	–	20	105	–	Seton treatment + ileostomy
TS	+	+[b]	+[b]	47	110	+	Seton treatment + ileostomy Endoscopic dilatation at the afferent loop before ileostomy

[a]Cuff stricture.
[b]Cuff and afferent loop stricture.
IS, intersphincteric; PV, pouch–vagina; TS, transsphincteric.

Table 4. Treatment Response in Patients with Crohn's Disease of the Pouch

	Treatment	Findings Which Resolved After Treatment	Findings Which Are Unresponsive to the Medical Treatment	First Appearance of the Complication after Operation (Months)	Follow-up Period After the Occurrence of the Complication (Months)
1	Azathioprine, budesonide, mesalazine, and mesalazine suppository	Pouchitis and stricture (cuff)[a]	Cuffitis and ileitis	31	27
2	Azathioprine, budesonide, mesalazine, and methylprednisolone	Pouchitis and ileitis	Cuffitis, stricture (cuff)	12	114
3	Azathioprine, budesonide, infliximab, mesalazine suppository, methylprednisolone, and ornidazole	Cuffitis	Pouchitis and stricture (afferent loop and cuff)	17	130
4	Budesonide, ciprofloxacin, infliximab, mesalazine, mesalazine suppository, mesalazine enema, and metronidazole	Pouchitis	Cuffitis, ileitis, and stricture (afferent loop)	7	90
5	Adalimumab, ciprofloxacin, and infliximab, metronidazole	Perianal abscess and perianal fistula (ileostomy)	Pouchitis and cuffitis	17	108
6	Amoxicillin–clavulanic acid, azathioprine, budesonide, ciprofloxacin, infliximab, mesalazine suppository, methylprednisolone, metronidazole, and moxifloxacin	None	Pouchitis, cuffitis, and perianal fistula	20	31
7	Adalimumab, azathioprine, mesalazine, methylprednisolone, metronidazole, and moxifloxacin	Ileitis and perianal abscess	Perianal fistula (ileostomy)	23	49
8	Amoxicillin–clavulanic acid, azathioprine, budesonide, and infliximab, metronidazole	Ileitis and abscess	Perianal fistula (ileostomy) and stricture (afferent loop and cuff)[1]	17	140
9	Adalimumab, azathioprine, ciprofloxacin, infliximab, mesalazine, mesalazine enema, mesalazine suppository, moxifloxacin, methylprednisolone, metronidazole, moxifloxacin, and rifaximin	Cuffitis, ileitis, and perianal abscess	Pouchitis and perianal fistula	11	118
10	Adalimumab, azathioprine, certolizumab pegol, ciprofloxacin, infliximab, and mesalazine	None	Pouchitis, cuffitis, ileitis, vaginal fistula, and stricture (cuff)	48	72

[a]Balloon dilatation.

Table 5. Disease Duration Time, Age at the Diagnosis, and Age at the Time of Operation

	Crohn's Disease of the Pouch (n = 10)	Pouchitis (n = 12)	Afferent Loop Ileitis (n = 6)	Control (n = 17)	*P*
Age at the diagnosis, mean ± SD	24.8 ± 9.4	36.9 ± 13.9	37.5 ± 16.2	36 ± 8.5	.055
Age at the operation, mean ± SD	29.4 ± 8.9*	44.2 ± 13.1*	39 ± 15.8	40.5 ± 9.7	.037
Disease duration until operation, years	4.6 ± 3.8	7.3 ± 9	1.5 ± 1.5	4.5 ± 4.7	.227
Symptom appearance after operation (months)	20.8 ± 11.7	23.8 ± 34*	30 ± 5.1*	NA	.031
Follow-up period after operation, months	109.5 ± 36.6*	85 ± 43.8	77.6 ± 40.9	42.5 ± 25.6*	.001

*Difference between groups is statistically significant.

patient from the CDP group and 1 from the control group who had a first-degree relative with CD. We repeated our statistical analysis by combining the CDP group with the afferent loop ileitis group and compared with the control groups. We did not find any significant difference in the comparative results.

Discussion

Crohn's disease of the pouch is a type of chronic pouchitis characterized by manifestations of CD such as fistulas or stenosis that develops in an UC patient after IPAA. The incidence of CDP was reported as 3.3% and 6.9% in the first 2 studies published in 1991 about this entity.[7,8] In the meta-analysis of Barnes, the mean incidence of CDP was reported to be 10.3% (range from 3.1% to 21.3%); the incidence was found to be 12.4% if patients with IC were excluded.[1] In our series, the incidence of CDP is 20.8%. The cause of the large difference of the incidence of postoperatively diagnosed CD between studies is multifactorial. The diagnostic criteria of CDP are various among published studies, and preoperative assessments to exclude CD are not standard. Another important point for the incidence of CDP is the rate of IPAA operation performed in the study center. Data from the pre-anti-TNF blocker era include a large number of UC patients who were operated due to unresponsiveness to a limited number of medical treatment options. Because of that, the incidence of CDP might be low in a large case series from pre-TNF-antagonist era. For example, in the study of Cleveland clinic, the number of UC/IC patients was 2814 and the incidence of CDP was reported to be 3.1% between 1983 and 2007.[9] But for sure, the low incidence of the CDP in an experienced center is also related to the expertise of this center in choosing the right patient for IPAA. It was reported that the cumulative incidence of CDP was gradually increased from 7.5% at 5 years to 33% at 20 years postoperatively.[10] In our CDP group, the follow-up time was longer than the pouchitis group, but the difference was not significant. In our series, the age at the time of operation was less in the CDP group. Supporting this finding, CD patients who had pouch failure tend to be younger in Pellino's meta-analysis.[11]

Fistula after IPAA can be caused by complications of pouch surgery. In some patients, pouch–cuff anastomosis can show some inflammation due to suture complications or ischemia, and these factors can result in abscess formation. Spontaneous drainage of these abscesses may cause perianal fistulas. In general, postoperative surgical complications occur usually just a few weeks later after the operation.[2] None of our patients have had surgical complications, and the appearance of perianal fistula was at least 20 months later (with a mean of 44 months) after the operation. This long period before the appearance of perianal disease is against the possibility of the development of surgical complications. It is generally accepted that fistula which develops more than 1 year after pouch is more likely to be related to CDP and not to the surgical complication.[1-3] Diverting ileostomy due to intractable perianal fistulizing disease was required in 3 of 6 patients with fistulizing disease in our series. Although it was reported previously that infliximab was successful for fistula closure in CDP,[12-14] we did not obtain any response with combination therapy with TNF-alpha blocker and immunmodulator in our series. In the meta-analysis of Pellino, the rate of pouch fistula was reported to be 23.3% and 4.5% in CD and UC patients, respectively.[11] Fistula is the leading cause of pouch failure in CDP, and 30%-80% of patients with fistula will require diverting ostomy or pouch excision.[3]

In our series, there is no pouch excision or pouch revision because none of our patients accepted to have a permanent ileostomy and the excision of the pouch. It is difficult to convince a patient to have another surgical operation like pouch excision If this operation also has some risks like surgical wound infection or perianal fistulas.[15]

Although it is known that the prognosis of the pouch surgery is worse than UC, CD is not a contradiction to perform IPAA. It is mentioned in European Crohn's and Colitis Organisation (ECCO) and European Society of Colo-Proctology (ESCP) guidelines that the candidate CD patient should be carefully selected before IPAA; the most important rule is that they should not have perianal disease or ileitis.[16] In a meta-analysis, the rate of pouch failure was reported to be 31.6% in patients who had postoperative CD diagnosis, whereas it was 12.1% and 5.7% in patients who had preoperative diagnosis of CD and in UC, respectively.[11] The same meta-analysis showed also that pouch fistulae and pouch stricture were also more common in postoperatively diagnosed CD.[11] According to these findings, we can say that patients who had CD diagnosis after IPAA have worse prognosis than preoperatively diagnosed CD patients. This difference can be related to strict selection criteria applied to an already known CD patient before performing IPAA operation.[11]

In this study, we gave our results of CDP and afferent loop ileitis groups separately. Nevertheless, we did not find any difference when we combined these 2 groups and compared with pouchitis and control groups. To classify a patient with IPAA who has mucosal inflammation resembling CD in the absence of fistula and stricture can be challenging. We reported in this study 6 patients who had afferent loop ileitis and pouchitis without stricture or fistula. Four of these patients had longitudinal ulcers in the pouch and in the afferent loop or in both locations. We argue that afferent loop ileitis patients also can be classified as CDP. To use the term of CDP in this context is not incorrect because afferent loop is anatomically associated with pouch and cuff.

Conclusion

The diagnosis of CDP is about 20% in the long-term follow-up of IPAA patients. Despite combination of anti-TNF and immunomodulatory therapy, mucosal remission and fistula healing could not be achieved in any patient, and more than one-third of patients ended with pouch failure.

Current Knowledge

Crohn's disease of the pouch is defined as the occurrence of signs of CD such as fistula or stricture in an UC patient who had restorative proctocolectomy with ileal pouch anal anastomosis.

What Is New?

- Fistula formation is the most debilitating complication of this entity.
- Complications of CDP is refractory to combination therapy of TNF-alpha blockers and immunmodulator.
- Pouch failure can occur in one-third of these patients due to fistula and/or stenosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (Date:03.05.2017, Number:166590).

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Supplementary Table 1. Patients with Afferent Loop Ileitis

Case	Cuffitis	Pouch	Afferent loop	Treatment	Findings which resolved after treatment	Findings which are unresponsive to the medical treatment	First appearance of the complication after operation (months)	Follow-up period after the occurrence of the complication (months)
1	+	Longitudinal ulcers and star-like ulcers	Longitudinal ulcers	Adalimumab, ciprofloxacin, infliximab, mesalazine, mesalazine suppository, mesalazine enema, methylprednisolone, metronidazole	Cuffitis, pouchitis	Ileitis	33	100
2	-	Nonspecific pouchitis	Longitudinal ulcers	Azathioprine, budesonide, ciprofloxacin, infliximab, mesalazine, metronidazole	None	Pouchitis, ileitis	32	36
3	+	Nonspecific pouchitis	Aftoid lesions	Azathioprine, budesonide, ciprofloxacin, mesalazine suppository, mesalazine enema, metronidazole	Pouchitis, cuffitis	Ileitis	23	10
4	+	Longitudinal ulcers	Superficial ulcers	Azathioprine, budesonide, ciprofloxacin, mesalazine suppository, metronidazole	Cuffitis	Pouchitis, ileitis	57	45
5	+	Longitudinal ulcers and star-like ulcers	Longitudinal ulcers	Azathioprine, budesonide enema, mesalazine, mesalazine suppository	Cuffitis, ileitis	Pouchitis	14	26
6	+	Aftoid lesions	Aftoid lesions	Azathioprine, methylprednisolone, mesalazine, mesalazine suppository	None	Cuffitis, ileitis, pouchitis	36	3