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Association Between Pouchitis and Ulcerative Colitis–Related Gastroduodenitis After Restorative Proctocolectomy

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Background: Ulcerative colitis (UC)–related disorders, which include pouchitis and gastroduodenitis (GDUC), can develop even after restorative proctocolectomy (RPC). However, the etiology of and predictive factors for these disorders remain unclear.

Aim: We analyzed the incidence and associations between pouchitis and GDUC.

Methods: UC patients who underwent RPC at the Hyogo College of Medicine between 2009 and 2012 were included in this study. The postoperative results of examinations and the clinical courses were analyzed.

Results: A total of 122 patients examined by endoscopy after RPC out of 188 patients who underwent follow-up at the outpatient clinic were included. Pouchitis developed in 56 of 188 patients. The cumulative incidence of pouchitis was 32.1% at 5 years. GDUC was identified in 14 of 122 patients. In the Cox regression analyses, GDUC was selected as an independent predictive factor for pouchitis (hazard ratio, 2.32; $P = 0.025$).

Conclusion: An association between GDUC and pouchitis after RPC was found. However, this association should be evaluated in a further study because both complications might exist coincidentally as components of a systemic immune disorder, and the etiology of each complication should be determined.

Key words: Ulcerative colitis – Pouchitis – Gastro-duodenitis

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Restorative proctocolectomy (RPC) is a standard surgical procedure for ulcerative colitis (UC) that prevents frequent relapse, hospitalization, and the refractoriness of medical treatments. However, UC-related digestive disorders, which include pouchitis, gastroduodenitis, and enteritis, can develop even after an RPC is performed. Pouchitis is the most common complication. It occurs in up to 50% of patients after RPC and includes both acute and chronic types.[1–3] In our previous retrospective studies, the cumulative incidence of pouchitis was 10.7% at 10 years after RPC. In a retrospective analysis, 70% of pouchitis cases developed within 2 years.[4] Moreover, the prevalence of UC-related gastroduodenitis (GDUC) was 7.6% in 2007.[5] However, the association between pouchitis and gastroduodenitis remains unclear. Therefore, we evaluated endoscopic examinations conducted within 1 year after RPC and analyzed the incidence of and associations between pouchitis and GDUC.

Patients and Methods

Data collection

UC patients who underwent RPC at the Hyogo College of Medicine between January 2009 and December 2012 were included. We performed both upper and lower endoscopic examinations, regardless of symptoms, within 1 year after RPC for patients in this study. We reviewed the patient clinical records in our surgical database and evaluated the prevalence of and associations between GDUC and pouchitis. Additionally, to determine the cumulative rate of pouchitis development, the progression after RPC of patients who could be observed was prospectively evaluated in this observational study, and the predictors of pouchitis were assessed.

Surgical procedure

At our institution, the standard RPC procedures for UC include total proctocolectomy and ileal-J pouch anal anastomosis (IPAA). Patients who did not receive pouch reconstruction, including those who underwent a total colectomy or total proctocolectomy with end ileostomy, partial resection, ileorectal anastomosis, or ostomy creation alone, were not included in this study. All surgical procedures were performed by 2 certified surgeons.

Diagnosis

The diagnosis of pouchitis was based on clinical symptoms (increased stool frequency, bleeding, abdominal cramping, urgency, and fever) and endoscopic (edema, granularity, friability, a loss of vascular pattern, mucous exudates, and ulceration) and histologic (polymorphic infiltrate and area of ulceration) findings. The diagnosis was made using the Pouchitis Disease Activity Index (PDAI), which is a commonly used instrument for the measurement of disease severity in published clinical trials.[6] A PDAI score $\geq$7 suggests a diagnosis of pouchitis. Cases of secondary pouchitis triggered by cytomegalovirus or *Clostridium difficile* infection, radiation, or any other infectious enteritis were not included as pouchitis in this study.

Irritable pouch syndrome (IPS) was diagnosed in patients who were still symptomatic after IPAA and in those who did not satisfy the PDAI criteria, as previously described.[7]

GDUC was defined using previously reported endoscopic findings, including friable mucosa (erosive or ulcerative mucosa with contact or spontaneous bleeding), granular mucosa (multiple white spots with a faint red halo), or conditional, multiple aphthae (multiple white spots surrounded by a red halo, clinically excluding other disorders, such as Crohn disease) without a *Helicobacter pylori* infection.[5] Additionally, these conditions were defined by pathologic findings, such as severe mucosal inflammation with infiltration by neutrophils.

Exclusion

Patients without pouch function (*i.e.*, patients who did not undergo ostomy closure during the RPC procedure) were not included in this study. Patients who had anastomotic leakage or a pelvic abscess after IPAA as an early surgical complication and required diversion with an ostomy or who required continuous corticosteroids or immunosuppressive agents due to secondary adrenal deficiency, arthritis or any other complication except pouchitis, were excluded. Patients with only cuffitis without pouchitis were not included in the analysis of the cumulative incidence of pouchitis.

Analysis of the predictors of pouchitis

Possible risk factors for the development of pouchitis included perioperative demographics and findings of IPS and GDUC on endoscopic examinations. The patient demographic variables collected before surgery included sex, age at the onset of UC $<$33 years, duration from the onset of UC to initial surgery $\geq$102 months, the extent of colitis, disease

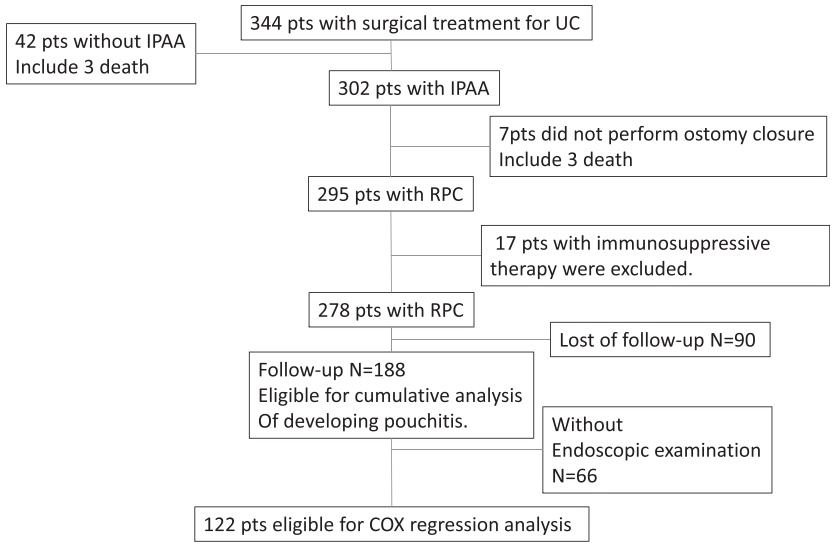

Fig. 1 The flowchart of patient selection. A total of 188 patients who underwent observation at the outpatient clinic and 122 patients who underwent endoscopic examinations were enrolled in the analysis.

severity of UC, preoperative immunosuppressive treatments, total prednisolone (PSL) dose ≥10,000 mg, preoperative PSL dose ≥20 mg, surgical indications, surgical timing, and active smoking after RPC. Moreover, the development of pouchitis, IPS, or GDUC with definitive endoscopic findings was also included as progression after RPC. These factors were analyzed using Cox regression analyses to determine their predictive significance. The total PSL dose was calculated based on previously administered steroid doses given since the initial diagnosis, and the values were converted to PSL equivalents. The cutoff values (age at the onset of UC <33 years, age at initial surgery <41 years, total PSL ≥10,000 mg, preoperative PSL ≥20 mg, and duration from the onset of UC to initial surgery ≥102 months) were defined based on the median values in this series. At our institution, the disease severity of patients with UC is primarily assessed based on the clinical features using the criteria of Truelove and Witts.[8]

Ethical considerations

All study protocols were approved by the Institutional Review Board at the Hyogo College of Medicine (No. 2088), and informed consent and agreement for the use of patient data were obtained before surgery.

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for all variables. Categoric variables were compared using a χ^2 test or Fisher exact test. Continuous variables are expressed as medians and ranges and were compared using the Mann-Whitney *U* test. The level of statistical significance was set at $P < 0.05$. Cox regression analyses of categoric data and of each individual factor were conducted. All variables with a value of $P < 0.2$ were entered into the multivariate analysis. The cumulative risk of pouchitis was estimated by Kaplan-Meier life table analysis. SPSS version 15.0 software (SPSS, Tokyo, Japan) was used to perform all analyses.

Results

A total of 344 patients with UC were surgically treated during this study period. A flow chart of patient selection is shown in Fig. 1. A total of 302 patients underwent IPAA. The remaining patients included a patient who underwent low anterior resection, a patient who underwent ileorectal anastomosis, 11 patients who underwent only total colectomy with end ileostomy, and 29 patients who underwent total proctocolectomy. For the patients who underwent IPAA, hand-sewn IPAA and stapled IPAA were performed in 289 and 13 patients, respectively. The mortality rate was 6 of 344 patients (1.7%). Two patients who underwent only total colectomy, 1 patient who underwent total proctocolectomy, and 1 patient who underwent IPAA died due to sepsis. Two patients who underwent IPAA died due to postoperative bleeding and advanced cancer. Of the patients who underwent IPAA with ileostomy, 295 (286 with hand-sewn IPAA and 9 with stapled IPAA) underwent the

Table 1 Patient characteristics at initial surgery[a]

	Total patients, n = 188	Patients with pouchitis, n = 56	Patients without pouchitis, n = 132	*P* value
Sex (male:female)	111:77	31:25	80:52	0.61
Age at onset of UC, y	32.7 ± 14.5	30.3 ± 13.9	33.8 ± 14.6	0.13
Age at initial surgery, y	40.8 ± 14.8	37.8 ± 14.9	42.1 ± 14.6	0.07
Duration of colitis, mo	101.6 ± 93.6	95.0 ± 99.0	104.4 ± 91.5	0.53
Duration from initial surgery, mo	61.6 ± 14.4	63.3 ± 14.2	60.8 ± 14.5	0.28
Pan-colitis	152 (80.9)	46 (82.1)	106 (80.3)	0.77
Disease severity ≥ severe colitis	50 (26.6)	16 (28.6)	34 (25.8)	0.69
Active smoker	11 (5.9)	3 (5.4)	8 (6.1)	0.88
Preoperative EIMs	26 (13.8)	8 (14.3)	18 (13.6)	0.91
PSC	0 (0)	0 (0)	0 (0)	Not estimable
Preoperative treatments				
PSL use	147 (78.2)	45 (80.4)	102 (77.3)	0.64
Total given PSL, mg	10131.2 ± 10519.0	11407.9 ± 12830.1	9589.6 ± 9372.6	0.28
Preoperative PSL, mg/d	21.3 ± 20.2	23.2 ± 21.6	20.5 ± 19.7	0.41
Immunosuppressant use	101 (53.7)	30 (53.6)	71 (53.8)	0.98
Biologics use	20 (10.6)	7 (12.5)	13 (9.8)	0.78
Surgical indication				
Cancer, dysplasia/TMC, perforation/ refractory/massive bleeding/other	28/16/117/15/12	4/4/41/4/3	24/12/76/11/9	0.43
Urgent/emergent surgery	39 (20.7)	10 (17.9)	29 (22.0)	0.52

PSC, primary sclerosing cholangitis; TMC, toxic megacolon.

[a]Data are numbers with percentages in parentheses unless otherwise indicated. Continuous variables are indicated as mean ± SD.

complete RPC procedure with a final ostomy closure. A total of 17 patients, including 3 with arthritis, 3 with a diagnosis of Crohn disease after RPC, 2 with enteritis, 2 with cuffitis, 2 with adrenal deficiency, and 5 with re-ostomy creation due to pelvic abscess or stricture, were excluded. Of the remaining 278 patients, 188 patients attended consecutive follow-up at the outpatient clinic, including 122 patients who underwent endoscopic examinations within 1 year after RPC and 66 patients without examinations.

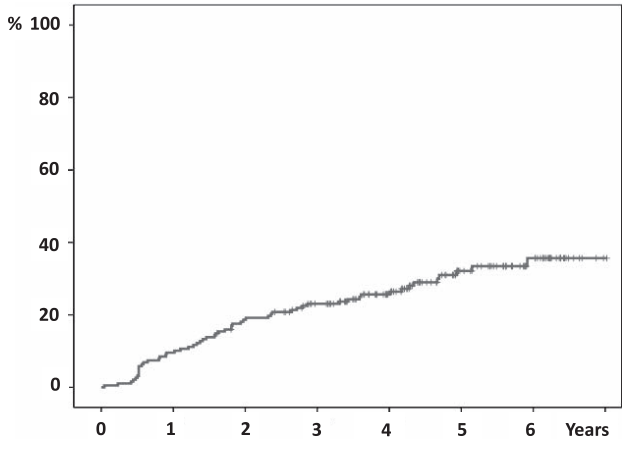

Fig. 2 The cumulative rate of pouchitis development in 188 patients was 32.1% at 5 years.

The patient characteristics are shown in Table 1. Preoperative extraintestinal manifestations (EIMs) were found in 26 patients, including 15 cases of arthritis, 9 cases of dermatitis, and 2 cases of both. Primary sclerosing cholangitis was not observed in this series.

Pouchitis developed in 56 patients (including 24 cases of acute pouchitis and 32 cases of chronic pouchitis) out of 188 patients who were followed until December 2015. The mean duration after RPC was 61.7 ± 14.4 months in these 188 patients. The cumulative rate of pouchitis development was 32.1% in 5 years (Fig. 2).

Finally, 122 patients were examined by both upper and lower endoscopy after RPC. The findings from the endoscopic examinations conducted within 1 year after RPC are shown in Table 2. IPS and GDUC were observed in 11 and 14 patients, respectively. Overall, pouchitis, including 21 acute and 25 chronic cases, was identified in 46 of 122 patients. Although GDUC was found in 9 of 46 patients (19.6%) with pouchitis and 5 of 76 patients (6.6%) without pouchitis, no significant difference was found ($P = 0.06$). EIMs developed after RPC in 9 of 122 patients, and no significant difference was observed regarding the presence of pouchitis ($P = 0.43$).

Regarding the analyses of predictors of pouchitis, the univariate analyses of the patient characteristics

Table 2 Postoperative complications[a]

	Total patients, n = 122	Patients with pouchitis, n = 46	Patients without pouchitis, n = 76	*P* value
Gastroduodenitis	14 (11.5)	9 (19.6)	5 (6.6)	0.06
Friable mucosa	6 (4.9)	2 (4.3)	4 (5.3)	0.84
Granular mucosa	8 (6.6)	4 (8.7)	4 (5.3)	0.72
Multiple aphthae	9 (7.4)	6 (13.0)	3 (3.9)	0.13
IPS	11 (9.0)	—	11 (14.5)	
EIMs after RPC	9 (7.4)	5 (10.9)	4 (5.3)	0.43

[a]Data represent numbers with percentages in parentheses unless otherwise indicated.

before RPC and the endoscopic findings after RPC are shown in Table 3. GDUC development was the only significant predictive factor for pouchitis in the univariate analysis. The results of the Cox regression analysis are shown in Table 3 and Fig. 3. GDUC was also a significant predictive factor for pouchitis in the multivariate analysis, with an HR of 2.75 ($P < 0.01$).

Discussion

In Japan, pouchitis is a major problem that occurs after RPC for patients with UC. Although the incidence of pouchitis in Japan was lower than that in Western countries prior to 2000, it is gradually increasing, along with the increased disease rate.[9,10] However, precise evaluations were not conducted in this study because of its retrospective design. Not all patients were routinely examined after RPC, including some patients with complaints, because of insurance limitations, cost limitations, or institutional limitations for performing the examinations at an outpatient clinic. Endoscopic examinations were typically performed on patients with symptoms. In this study, although the number of patients lost to follow-up was considerable, the incidence of pouchitis was similar to that in Western countries in a prospective observation.

Although the same RPC procedure used for UC is performed, pouchitis appears to be an unusual complication of familial adenomatous polyposis coli.[11,12] The alteration of bacterial flora, which can occur in patients after RPC, might contribute to the occurrence of pouchitis; however, in that case, pouchitis would be developed by an overwhelming majority of patients with UC.[13–15] Therefore, we predict that pouchitis might develop as part of a systemic immune disorder, similar to EIMs, includ-

Table 3 Risk factors for pouchitis

	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Male sex	1.13 (0.63–2.02)	0.68		
Active smoker	1.18 (0.58–2.39)	0.65		
Age at initial surgery <41 y	1.71 (0.95–3.10)	0.08	1.57 (0.79–3.16)	0.20
Age at onset of UC <33 y	1.65 (0.89–3.07)	0.11	1.17 (0.55–2.47)	0.69
Duration of colitis >102 mo	1.14 (0.63–2.06)	0.67		
Pan-colitis	1.09 (0.51–2.33)	0.83		
Disease severity ≥ severe colitis	1.39 (0.75–2.58)	0.29		
Preoperative EIMs	1.62 (0.81–3.26)	0.21		
Total given PSL dose ≥10,000 mg	1.53 (0.85–2.74)	0.16	1.56 (0.84–2.87)	0.16
Preoperative PSL ≥20 mg/d	1.17 (0.87–1.56)	0.3		
Immunosuppressant use	1.39 (0.71–2.74)	0.34		
Biologics use	1.05 (0.59–1.89)	0.86		
Surgical indications				
Cancer	0.97 (0.41–2.29)	0.95		
Refractory	1.01 (0.55–1.85)	0.99		
TMC/perforation/massive bleeding	1.12 (0.56–2.26)	0.75		
Urgent/emergent surgery	1.24 (0.83–1.86)	0.29		
EIMs after RPC	1.42 (0.51–3.97)	0.52		
Gastroduodenal lesions	2.65 (1.27–5.49)	0.009	2.32 (1.11–4.84)	0.025

TMC, toxic megacolon.

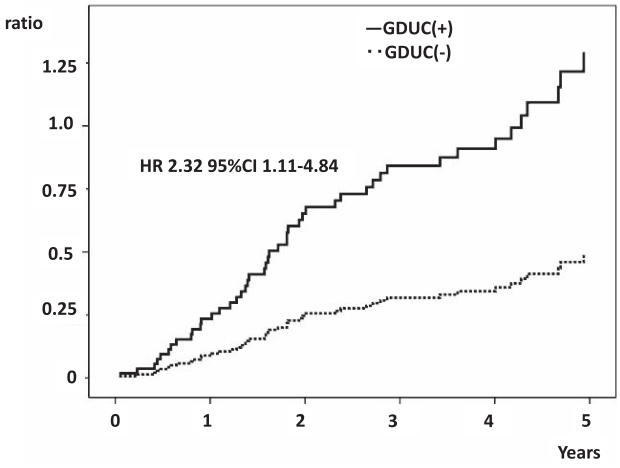

Fig. 3 The cumulative rate of pouchitis was distinct from that of complicated GDUC. The HR was 2.32 in patients with gastroduodenitis.

ing arthritis, pyoderma gangrenosum, and erythema nodosum. However, these EIMs, which occurred both before and after RPC, were not associated with the occurrence of pouchitis in this multivariate analysis. In previous reports, preoperative EIMs were frequently associated with the activity of colitis.[16] Therefore, EIMs could be a surgical indication. However, EIMs often developed even after an RPC was performed. Moreover, postoperative EIMs developed consecutively to pouchitis and were influenced by the severity of pouchitis in several patients in this series. This association between postoperative EIMs that develop after RPC in patients with pouchitis might be similar to the association between EIMs and colitis, although significant differences were not found. This finding should be evaluated in future studies because of the low occurrence of this complication after RPC.

We hypothesize that GDUC might be associated with the occurrence of pouchitis because similar organs are involved in the intestinal manifestations. This association was significant in our series. GDUC was the only independent predictive factor for pouchitis. However, the close association and similar etiology could not be explained in this study. Although the alteration of flora could lead to the development of pouchitis, this appears to be unrelated to the occurrence of GDUC because the flora might not influence the upper intestine. It remains unclear whether primary pouchitis could consecutively lead to a systemic immune disorder that includes GDUC, whether a primary systemic immune disorder could result in pouchitis and GDUC, or whether primary GDUC could lead to consecutive pouchitis.

From a treatment standpoint, pouchitis and GDUC might be independent phenomena. All patients with GDUC who received medical treatments that included 5-aminosalicylate, PSL, or biologics responded well, although 3 of 14 patients (21.4%) were treated with PSL, and 3 of 14 patients (21.4%) were treated with biologics as an immunosuppressive therapy. Moreover, after the remission of GDUC, no recurrences were found in patients who did not undergo maintenance therapy. However, 32 of 56 patients (57.1%) with pouchitis developed chronic pouchitis, including refractory, antibiotic-resistant, and antibody-dependent pouchitis.[17] More than half of the pouchitis patients required maintenance therapy, including immunosuppressive agents. However, although pouchitis is highly refractory, most patients responded to antibiotic therapy; only 5 of 32 (15.6%) required additional PSL use, and 2 of 32 (6.3%) required additional biologic therapy. Therefore, the treatment strategies of GDUC and pouchitis are quite different. We suspect that a correlation between pouchitis and GDUC existed before this study. Although differences in the treatments of pouchitis and GDUC, which both involve lesions classified as UC-related lesions, might exist, the etiology remains unknown.

One limitation of this study was its small sample size. Additionally, we analyzed only consenting patients. To precisely evaluate the incidence of and predictive factors for pouchitis, we should prospectively and consecutively analyze all patients who undergo RPC after surgery. However, such an analysis would be difficult because patients without multiple symptoms do not need to visit the outpatient clinic frequently. Patients who did not attend follow-up evaluations should not be discarded. If possible, all patients who undergo RPC should be prospectively examined in a future study to evaluate the actual incidence of pouchitis and GDUC and to clarify the predictive factors for these UC-related lesions.

An association between pouchitis and GDUC after RPC was observed. The existence of GDUC was identified as a predictive factor for pouchitis. However, pouchitis could not be predicted based on other background information. The etiology of pouchitis and GDUC should be determined in future studies to evaluate their predictive factors.

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