Pouchitis – recurrence of the inflammatory bowel disease?

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Abstract

The incidence and characteristics of reservoir inflammation after restorative proctocolectomy for ulcerative colitis were studied in a series of 179 patients. The median follow up time was 27 months (range 6–80). Pouchitis occurred in 36 patients (20%) and nine of these (5%) developed a chronic, persisting pouchitis. There were no pouch failures as a result of pouchitis and no significant adverse effect on longterm functional outcome. The overall cumulative risk to develop pouchitis four years after surgery was 23%. The risk of pouchitis is unpredictable on clinical grounds except that there were significantly less patients with left sided colitis in the group who subsequently developed pouchitis. Morphological and histochemical studies showed a greater degree of colonic metaplasia in the pouch mucosa in patients with pouchitis and patients with a chronic pouchitis had the highest degree of changes. The results support the view that pouchitis is a novel manifestation of inflammatory bowel disease in ileal mucosa that has changed slowly to a colon like mucosa.

(Gut 1994; 35: 243–246)

A clinical entity called reservoir inflammation or pouchitis is a known complication of restorative proctocolectomy and collective experience has shown that pouchitis is the most common long-term complication associated with the procedure.^{1–4} Although most cases with pouchitis respond to antibiotic treatment, it can cause considerable functional disturbance to many patients and has even been the cause of pouch failure.⁴ Despite intensive studies the cause of pouchitis has remained unknown but many contributing factors, such as faecal stasis, bacterial invasion, and faecal bile acids have been postulated.^{5–7} There is increasing evidence, however, that colonic metaplasia eventually develops in the ileal reservoir mucosa and that pouchitis might be a novel manifestation of inflammatory bowel disease in a colon like small bowel mucosa.^{8–11} This study aimed at estimating the incidence and cumulative risk of pouchitis after restorative proctocolectomy for ulcerative colitis and at analysing possible clinical factors predicting its occurrence. Special attention was paid to histological and histochemical changes in the ileal reservoir mucosa in patients with and without pouchitis using mucosal morphometry and mucin staining.

Patients and methods

Altogether 181 patients with ulcerative colitis had restorative proctocolectomy between

January 1985 and July 1992 at our institution. Two patients died two and three months after surgery of unrelated causes and 179 patients with a mean age of 35.4 years (range 17–63) were followed up for at least six months with a functioning pouch. A permanent ileostomy had to be constructed during the study period in five patients because of anastomotic fistulas in two, poor anal function in two, and poor clinical condition (undiscovered adrenal insufficiency) in one patient. The median follow up time was 28 months (range 6–80). The original histopathological diagnosis was ulcerative colitis in all patients, but changed to indeterminate colitis in two cases after surgery.

A J shaped pouch from two 15 to 20 cm limbs of terminal ileum was constructed. A covering ileostomy was used in 61 patients while 113 patients initially had no ileostomy. Regular outpatient visits were arranged at three monthly intervals up to one year and after that on a non-routine basis in case there were any symptoms of pouchitis. Pouchitis was defined clinically with sudden increase in defecation frequency often associated with malaise but also requiring clear endoscopic and histological findings according to the criteria presented elsewhere.^{8,12} Faecal bacterial cultures were taken to check for any trace of specific enteropathogens (salmonella, etc). Only cases fulfilling all three diagnostic features (clinical symptoms, endoscopic inflammation, histological acute inflammation) were considered to have pouchitis. The treatment of pouchitis was usually with oral metronidazole (400 mg thrice daily) for 10 days, or, exceptionally, oral ciprofloxacin (250 mg twice daily) in patients who did not tolerate metronidazole. In patients with a persisting or chronic type of pouchitis systemic or local steroid treatment was used in combination with a low dose (400 mg once or twice daily) metronidazole for longer periods.

The determinants examined as possible predictive factors for pouchitis in this study included age, sex, duration of ulcerative colitis before surgery, the extent of the disease in the large bowel and its severity (whether fulminant or not) at the time of surgery, and the presence of extracolonic manifestations (iritis, arthritis, erythema nodosum, sclerosing cholangitis). The diagnosis of sclerosing cholangitis was based on raised serum alkaline phosphatase activities together with positive findings in endoscopic retrograde cholangiography and liver biopsy examinations.

HISTOLOGICAL AND HISTOCHEMICAL STUDIES

All patients with pouchitis had several biopsy specimens taken from the pouch mucosa from

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TABLE I Basic data of patients with and without pouchitis

	Pouchitis	Without pouchitis
Number	36	143
Sex		
Men	23 (63%)	79 (55%)
Women	13	64
Age (SD)	34.4 (9.8)	35.5 (9.0)
Duration of UC (years)	6.1 (4)	6.7 (6)
Extent of UC		
Left sided	1	32
Total colitis	35 (97%)	111 (78%)
Fulminancy	14 (38%)	36 (25%)
EIM	9 (25%)	20 (14%)

UC=ulcerative colitis; EIM=extraintestinal manifestation.

different areas and at least 5 cm from the anal anastomosis. The specimens were obtained in a quiescent phase after treatment of pouchitis and in cases with chronic pouchitis care was taken to biopsy only in those areas that seemed the most healthy. For comparison, similar specimens were taken from 30 other patients without pouchitis. In addition, control specimens of normal ileum were obtained from 10 patients 50 cm proximal to the pouch.

The specimens were studied by two pathologists (MT and AK), who were unaware of the clinical situation. Biopsy specimens were fixed in buffered neutral formalin and embedded in paraffin wax. Sections of formalin fixed paraffin wax were stained with haematoxylin and eosin for mucosal morphometry and high iron diamine alcian blue for mucin staining. Villous height, crypt depth, mucosa depth, villous atrophy, and the degree of acute and chronic inflammation together with dysplastic changes were separately studied according to the classification of De Silva *et al.*¹⁰ The degree of villous atrophy and acute and chronic inflammation were graded from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe). The villous index (relation between villous height and crypt depth) was used to describe the degree of colonic metaplasia. A blue colour (>90% of the surface area studied in microscopy) in mucin staining sections was defined as a predominantly small bowel type sialomucin and a brown colour (>90% of the surface area) as a predominantly colon type sulphomucin. If there was any other proportion of blue and brown colours, this was defined as a mixed pattern. For the purpose of study, the pattern of mucins was graded from 1 to 3 (1=predominantly sialomucin, 2=mixed mucins, 3=predominantly sulphomucin).

STATISTICAL ANALYSIS

Differences between the study groups and different parameters were assessed using the χ^2 and Fisher's exact test. The cumulative risk of overall pouchitis and chronic pouchitis were estimated by the Kaplan-Meier lifetable analysis and comparison of these risks was made with the log rank test.

Results

INCIDENCE AND CHARACTERISTICS OF POUCHITIS
Pouchitis occurred in 36 patients (20%) while 143 patients had no signs of pouchitis. Table I

TABLE II Occurrence of the first episode of pouchitis

	n	%
Within 6 months	19	52
Within 1 year	25	70
Within 2 years	33	91
Within 4 years	36	100

shows the basic differences between these two groups of patients. Patients with and without pouchitis did not differ significantly in age, sex, duration of colitis before surgery, severity of the disease activity or in the presence of extra-intestinal manifestations. Pouchitis patients, however, had a significantly lower incidence ($p<0.05$) of leftsided colitis than patients without pouchitis.

At the end of the follow up the 24 hour defecation frequency mean (SEM) was 5.2 (1.6) in patients with pouchitis and 5.1 (1.0) without pouchitis. None of the patients in either group had anal incontinence but mucus leakage or nocturnal evacuations, or both occurred in 13 (36%) and 42 (30%) of patients with and without pouchitis, respectively. About half of the first episodes occurred within six months after surgery and 90% occurred within two years (Table II). Single episode of pouchitis occurred in 13 patients (36%) and recurrent episodes (two or more pouchitis of short duration and responding well to treatment) in 14 patients (38%). Nine patients (26%), six men and three women with a mean age of 34.7 years, of 36 had a persisting or chronic pouchitis (non-responding inflammation needing longlasting treatment). Clinical signs of pouchitis gradually subsided in all of them despite persisting endoscopic and histological findings of pouchitis. Steroid treatment was successfully stopped in eight of these nine patients and all other treatment was stopped except loperamide in six patients. None of our patients with pouchitis required pouch excision and none had any clinical or histopathological signs of Crohn's colitis. The cumulative risk of developing pouchitis was 23% within four years after surgery (Figure) and 36% six years after surgery. The cumulative risk of developing chronic pouchitis was 5% four years after surgery (Figure) and 7% six years after surgery.

MUCOSAL MORPHOMETRY AND MUCIN STAINING

Table III summarises the results of mucosal morphometry and mucin staining. The degree of villous atrophy and acute and chronic inflammation was significantly greater in patients with pouchitis than in patients without pouchitis and in normal controls. Crypt hyperplasia (increased crypt depth) was significantly higher in patients with pouchitis but was similar between normal controls and patients without pouchitis. Villous index was lower in patients with pouchitis point-

TABLE III Mucosal morphometry and mucin staining in patients with and without pouchitis

	Controls (n=10)		Without pouchitis (n=30)		Pouchitis (n=36)
Villous atrophy	0	NS	0.5	p<0.05	1.9
Villous height	260 (210–360)	NS	241 (180–345)	NS	201 (90–320)
Crypt depth	164 (115–216)	NS	187 (120–300)	p<0.01	334 (160–490)
Mucosal depth	426 (375–610)	NS	498 (330–700)	p<0.05	572 (390–900)
Villous index	0.61	p<0.001	0.48	p<0.05	0.35
Acute inflammation	0	p<0.05	0.5	p<0.05	1.6
Chronic inflammation	0	p<0.05	0.6	p<0.05	2.0
Mucin type	1	NS	1.3	p<0.05	1.9

The values are mean (SEM) values in μ . Villous atrophy, acute, and chronic inflammation graded from 0–3. Mucin type graded from 1–3.

ing to a greater degree of colonic metaplasia in these patients. A significant change in mucin pattern towards a more colonic type of sulpho-mucin occurred in patients with pouchitis than in patients without pouchitis. Dysplasia was not found in any of the biopsy specimens.

In two patients, without any known episodes of pouchitis, morphometric studies showed extensive colonic metaplasia and predominantly sulphomucin in mucin staining was found in one. On the other hand, a very slight degree of metaplasia together with predominantly sialomucin was found in two patients who had single episodes of pouchitis. Table IV summarises the results of mucosal morphometry and mucin staining in patients with chronic and episodic pouchitis. There was a significantly greater degree of colonic metaplasia in patients with a chronic inflammation compared with patients who had single or recurrent episodes of pouchitis. Despite extensive metaplasia in two patients with chronic pouchitis who had predominantly sialomucin staining, others had either a mixed pattern or predominantly sulpho-mucin.

Discussion

Pouchitis remains the most common longterm problem after pouch surgery for colitis. Its frequency was 20% in this study and the cumulative incidence figures were 23 and 36% at four and six years even when strict diagnostic criteria were used. Previous variations in incidence figures^{1,2,4} have often been based more on clinical findings and on variable follow up time. Two types of inflammation occurred. Most patients with pouchitis had one or a few short term episodes of inflammation responding well to

treatment with metronidazole but about one quarter had a persisting pouchitis needing prolonged medical treatment. The cumulative risk of this chronic form of pouchitis was seven per cent at six years after surgery. None of our patients, however, has lost the pouch due to pouchitis and the longterm functional results have not differed from those in other pouch patients. In addition, dysplasia was not seen in mucosal biopsy specimens.

It was shown both morphologically and by mucin stainings that the pouch mucosa in pouch patients had a more pronounced colonic metaplasia than in patients without pouchitis. Furthermore, this metaplasia was of a higher degree in chronic pouchitis than in episodic pouchitis. Biopsy specimens from the pouches were systematically obtained from different areas and in patients with pouchitis after treatment rather than during the active attack to avoid interpretation bias, especially in mucin staining.¹⁰ Patients with chronic pouchitis, however, always had to some extent inflamed mucosa, which could explain why in two such patients predominantly sialomucin was found.

The gradual development of colonic metaplasia in ileal pouches together with a change from a small bowel type of sialomucin to colonic sulphomucin is already known from earlier studies.^{8–11} These changes have usually been greater in pouchitis than in reservoirs without inflammation but the findings have not been uniform. Thus, extensive metaplasia may occur in ‘normal’ pouches^{8,9,13} and similar changes have been found also in patients with familial polyposis after restorative surgery.⁹ It is reasonable to suppose that development of colonic metaplasia makes the ileal pouch vulnerable to pouchitis, but all patients with metaplastic and mucin changes do not necessarily develop clinical pouchitis.

There are only few studies evaluating the clinical predictors of pouchitis.^{2,3} One view is that chronic or recurrent forms of pouchitis are connected with indeterminate colitis, and the exact diagnosis may turn out to be Crohn’s disease.² Other studies have not found a relation between pouchitis and indeterminate colitis,¹⁴ and no cases of indeterminate or Crohn’s colitis occurred in our series. Lohmuller *et al*² showed that the risk of pouchitis in ulcerative colitis is far higher than in polyposis, and that the presence of extracolonic manifestations increases the risk of pouchitis. These manifestations were not a significant determinant of pouchitis in this study and the same applied to other factors studied making an exact prediction of the risk of pouchitis difficult or even impossible on clinical grounds.

The histological and histochemical findings of this study support the view that ileal pouch mucosa changes to colon like mucosa making recurrence of the original inflammatory bowel disease possible at least in some of the patients. Most patients with pouchitis are comparatively easy to treat, but some (5–7%) eventually have persistent pouchitis. Further development of dysplasia is possible in these patients with chronic pouchitis, and endoscopic surveillance of the pouches may be necessary.

TABLE IV Mucosal morphometry and mucin staining in patients with ‘episodic’ pouchitis and chronic pouchitis

	Chronic pouchitis (n=9)		Episodic pouchitis (n=27)
Villous atrophy	2.4	NS	1.7
Villous height	149 (90–180)	p<0.05	244 (120–320)
Crypt depth	403 (260–490)	p<0.05	297 (160–480)
Mucosal depth	651 (470–900)	p<0.05	528 (390–620)
Villous index	0.22	p<0.05	0.40
Acute inflammation	2.3	NS	1.4
Chronic inflammation	2.6	p<0.05	1.7
Mucin type	2.3	NS	1.6

The values are mean (SEM) values in μ . Villous atrophy, acute, and chronic inflammation graded from 0–3, mucin type from 1–3.

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