Refractory pouchitis: does it reflect underlying Crohn's disease?

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Abstract

Typical 'pouchitis' is a well recognised complication of ileal pouches in ulcerative colitis. Infrequently, a refractory pouchitis (RP) presents with certain clinical, endoscopic, and pathological features resembling Crohn's disease and is often ascribed to misdiagnosis of the initial colitis. To test that hypothesis and to identify risk factors for RP, this study reviewed cases of presumed ulcerative colitis with ileal pouches constructed at The Mount Sinai Hospital between 1973 and 1986. Twenty four cases with RP (16 Kock pouches and eight pelvic pouches) and 21 controls were compared for eight clinical variables. The original colectomy slides from 15 RP and 18 control cases were reviewed blindly, classified into five histological categories (corresponding to definite ulcerative colitis, definite Crohn's disease, and three indeterminate groups), and scored for 23 histological features. There were no significant clinical differences between RP and control cases except for more frequent extraintestinal manifestations (38% v 5%) and male preponderance (79% v 43%) in RP. There were also no significant differences between the distributions of RP cases and controls among the five histological categories or in the 23 histological features studied. Refractory pouchitis therefore does not seem to reflect underlying Crohn's disease, but may be linked to immunological mechanisms that are manifested clinically as extraintestinal complications.

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Florid active mucosal inflammation with disturbed bowel function, often called 'pouchitis', is a comparatively common complication of ileal reservoirs created after colectomy, usually for ulcerative colitis, occurring in roughly 20% of cases (range 7–42%).^{1–4}

Pouchitis usually responds well to treatment with antibiotics, but in a small subset of cases the inflammation is clinically severe, endoscopically atypical, and relatively refractory to conventional treatment. These cases seem to represent a distinct inflammatory condition, which we have termed 'refractory pouchitis' (RP). Because the endoscopic features of RP are not dissimilar to those of Crohn's ileitis, RP has often been attributed to underlying Crohn's disease, presumably 'misdiagnosed' as ulcerative colitis pre and perioperatively. To test the validity of this notion and to identify potential risk factors for RP, we reviewed our cases of RP at The Mount Sinai Hospital and compared the pathological features of their colectomy specimens as well as

TABLE I Endoscopic lesions in refractory pouchitis

Lesions	No of patients
Aphthous ulcers	6
Serpiginous ulcers	8
Ileitis proximal to reservoir	14
Cobblestone mucosa	4

their clinical features to those of a control group without RP.

Patients

All cases were selected from ileal pouches constructed between 1973 and 1986 at The Mount Sinai Hospital.

Refractory pouchitis – We selected 24 cases that were well known to their gastroenterologists and that fit the clinical, endoscopic, and pathological criteria for RP as adopted at an International Workshop on Pouchitis in London in January 1989,⁵ including clinical symptoms (bloody diarrhoea, malaise, or weight loss, or all three); resistance to treatment with antibiotics and steroids; and endoscopic features (serpiginous ulcerations, cobblestone mucosa, or ileitis proximal to the reservoir, or all three).^{6–8} Table I shows the frequency of each of the defining endoscopic lesions; in some cases, of course, more than one feature was present. Biopsies of the pouches of all these patients were reported as showing active chronic inflammation. The mean duration between pouch construction and onset of pouchitis was 22.3 months (range 2–72 months). Four of the 24 RP patients ultimately required pouch removal and conversion to a standard Brooke ileostomy.

Controls comprised 21 patients with ileal pouches constructed during the same period who had been followed up for a mean duration of 43 months (range 15–119 months) and who had had endoscopies that showed no evidence of active inflammation. Table II shows the distribution of Kock pouches (continent ileostomies) and pelvic pouches between RP cases and controls.

The medical records of all cases were reviewed for the following eight clinical features: sex, age at onset of colitis, age at colectomy, indications for colectomy, age at time of pouch construction, extraintestinal manifestations before colectomy,

TABLE II Distribution of pouches in the group

Type of pouch	RP (n=24)	Controls (n=21)
1 Kock	16	16
2 Ileoanal or pelvic	8	5

RP=refractory pouchitis.

TABLE III Histological classification of colectomy specimens

Category	Criteria
A	Definite UC; diffuse, continuous proctocolitis limited to mucosa and superficial submucosa.
B	Highly suggestive of UC, but focally evincing one of several histological features more commonly associated with CD than UC, for example, cleft like mucosal ulceration, neuronal hyperplasia, intramural lymphoid aggregates beneath intact mucosa, submucosal lymphangiectasia; also fulminant colitis, even if lacking any of these features.
C	Indeterminate colitis, with more than one, or increased prominence, of the histological features indicated for category B; also fulminant colitis with any one of these features.
D	Indeterminate colitis, suggestive of CD, with one or more histological features considered characteristic of CD, for example, skip segments, focality of inflammation, fissuring ulcerations, focal chronic ileitis with pseudopyloric metaplasia; no diagnostic granulomata.
E	Definite CD, with typical granulomata in an appropriate histological setting.

UC=ulcerative colitis, CD=Crohn's disease.

use of steroids before colectomy, and immediate postcolectomy complications.

Methods

Microscopic slides of 33 resection specimens were available for review (31 from The Mount Sinai Hospital and two from other hospitals), comprising 15 patients with RP and 18 controls. The specimens consisted of 21 total colectomies (several performed in two stages), 11 subtotal colectomies, and one second stage proctosigmoidectomy for which the corresponding colectomy specimen was not available. The original pathological diagnoses were either ulcerative colitis or indeterminate. The original macroscopic descriptions were reviewed to ensure that the available slides represented an adequate sampling of significant pathology. All slides were then reviewed by one pathologist (NH), who was aware that the cases comprised both RP and control groups but who had not seen the cases previously and had no knowledge of individual clinical histories or outcomes. An average of 15 sections (range 7–32) were available for both total and subtotal colectomies and six sections for the single proctosigmoidectomy, not counting sections of lymph nodes and stomas. Gross photographs of specimens were not examined, as they were not available for all cases.

Based on the microscopic review, each case

TABLE IV Individual histological features

Left to right gradient of chronic colitis (+/–)
Skipped segments (+/–)
Chronic ileitis (+/–)
Anal inflammation (+/–)
Microscopic focal inflammation (+/–)
Aphthous ulcers (+/–)
Sarcoid like granulomata (+/–)
Maximum depth of chronic inflammatory infiltrates beneath intact mucosa*
Fissures: frequency (0 to 3+), depth*
Ulcers: frequency (0 to 3+), depth*
Lymphoid aggregates: frequency (0 to 3+), depth*
Activity of mucosal inflammation (0 to 3+)
Thickening and splaying of muscularis mucosa (0 to 3+)
Paneth cell metaplasia (0 to 3+)
Neuronal hyperplasia (0 to 3+)
Mucus secretion (0 to 3+)
Hyperemia (0 to 3+)
Submucosal lymphangiectasia (0 to 3+)
Submucosal fibrosis (0 to 3+)
Submucosal fat (0 to 3+)
Submucosal vascularity (0 to 3+)
Follicular proctitis (0 to 3+)
Rectal crypt atrophy (0 to 3+)

*Maximum depths of fissures, ulcers, chronic inflammatory infiltrates, and lymphoid aggregates graded as follows: superficial, mid, or deep submucosa; superficial or deep muscularis propria; serosa.

TABLE V Precolectomy clinical features

	RP (n=24)	Kock (n=16)	Pelvic (n=8)	Controls (n=21)
Sex distribution (M:F)*	19:5	12:4	7:1	9:12
Mean age of patient (y)	36.7	36.9	36.3	37.5
Mean age of onset of UC (y)	19.6	17.7	23.5	19.5
Mean age at colectomy (y)	27.5	26.1	30.1	29.5
Mean duration between onset of UC and colectomy (y)	7.9	8.4	6.7	10.4
Mean age at time of pouch construction (y)	29.2	28.4	30.8	31.1
Use of steroids before colectomy	24	16	8	20
Presence of EIMs before colectomy*	9	6	3	1

*Statistically significant differences between RP and controls. RP=refractory pouchitis, UC=ulcerative colitis, EIMs=extraintestinal manifestations.

was assigned to one of five histological categories: cases representing definite ulcerative colitis were assigned to category A, cases representing definite Crohn's disease to category E, and cases containing overlapping features to indefinite categories B, C, or D, depending on the prominence and diagnostic significance of these features (Table III). Each case was also evaluated and graded for 23 individual histological features (Table IV), mostly those considered useful in the differential diagnosis of ulcerative colitis and Crohn's disease, but including others that were added in the search for histological features that might distinguish RP from controls.

Differences in the sex distribution and in the frequency of precolectomy extraintestinal manifestations were analysed by the χ^2 test and the remaining clinical variables by the Student *t* test. An association of each of the histological features with the presence or absence of pouchitis was sought by the χ^2 test.

Results

Table V shows the comparison of clinical features between RP cases and controls. There was no statistically significant difference between the two groups except for sex distribution and frequency of precolectomy extraintestinal manifestations. Refractory pouchitis patients showed a male preponderance of 79% *v* 43% in the control cases ($p<0.03$). They also had more prevalent precolectomy extraintestinal manifestations of 38% (9/24) *v* 5% (1/21) in the controls ($p<0.025$). These clinical profiles of RP cases did not differ significantly between Kock and pelvic pouches (Table V). Table VI shows the specific extraintestinal manifestations in the RP and control groups. In three of the RP cases, but in none of the controls, extraintestinal manifestations had provided the principal indication

TABLE VI Distribution of extraintestinal manifestations (EIMs)

EIMs	RP (n=24)	Controls (n=21)
Erythema nodosum alone	5	1
Erythema nodosum + arthritis	1	0
Pyoderma gangrenosum alone	1	0
Pyoderma gangrenosum + arthritis	1	0
Arthritis alone	1	0
Total	9	1

TABLE VII Indications for colectomy and perioperative features

	RP cases (n=21)	Controls (n=21)
Intractability	13	13
Bleeding	3	4
EIMs	3	0
Perforation	1	1
Dysplasia	1	1
Toxic megacolon	2	2
Growth failure	1	0
Emergency colectomy	5	4
Elective colectomy	19	17
Immediate postoperative complications	1	2

Abbreviations the same as in Table V.

TABLE VIII Histological classification of resected colons

Category	RP (n=15)	Controls (n=18)
A	6	7
B	3	2
C	2	3
D	2	3
E	2	3

for colectomy (Table VII); otherwise, the surgical indications were nearly identical between the two groups. It has been suggested that emergency colectomy and postoperative sepsis may predispose to the development of pouchitis.¹⁴ Our review of clinical features, however, found no increased incidence of pouchitis in cases that had had emergency colectomy or postoperative sepsis (Table VII).

As shown in Table VIII, the 13 cases that were judged histologically to be definite ulcerative colitis (category A) were distributed almost evenly between the RP and control groups. By the same token, five cases representing Crohn's disease (category E) by virtue of containing sarcoid like granulomata (evidently overlooked by the original pathologists), as well as 15 cases with varying degrees of overlapping histology (categories B, C, and D), were also distributed almost evenly between the two groups. Finally, there were no statistically significant associations of RP *v* control classification with any of the 23 individual histological features listed in Table IV, including the presence of chronic ileitis.

Discussion

Typical pouchitis has been reported in about 20% of ileal reservoirs, although incidences in different series range from 7–42%, with equal frequency in both pelvic and Kock pouches.^{1–3,9–17} By contrast, the syndrome that we have termed refractory pouchitis (RP) is comparatively rare. It may correspond to what the Lahey Clinic group has called 'chronic' pouchitis.¹⁸ Our cases of RP represent only about 3% of the ileal pouches constructed at The Mount Sinai Hospital during the 13 year period studied.

The mean interval from reservoir surgery to onset of pouchitis in our series was 22 months (range 2–72 months). This figure conforms closely to the experience of others. Zuccaro *et al*¹⁹ reported a mean interval of 25 months (range 3–54 months) and Lohmuller *et al*²⁰ reported a mean interval of 17 months (range 2 days–93 months). There may in fact be some differences in these time intervals and in other patho-

genetic factors between Kock pouches and pelvic pouches, but in view of the general clinical similarities between the RP syndromes in these two forms of pouch (Table V), we have felt justified in combining them for the purposes of our analysis.

Because the endoscopic findings in RP often include serpiginous ulcerations, fissures, and ileitis proximal to the pouch, the syndrome has often been attributed to underlying Crohn's disease, the diagnosis of which had presumably been 'missed' both clinically and pathologically up to and including the time of colectomy. There has been no systematic study, however, to discover if this assumption is correct. We therefore sought clinical and pathological features that might test this concept and help us identify risk factors for the development of RP.

The only distinguishing clinical features we could identify in the RP group were male preponderance and an increased frequency of extraintestinal manifestations. We are not aware that a male preponderance has been previously seen in association with any form of pouchitis. Lohmuller *et al*²⁰ reported that among 671 patients with chronic ulcerative colitis, if preoperative extraintestinal manifestations had been present, pouchitis occurred in 39% of cases, but in only 26% if no extraintestinal manifestations had been present. They also showed by lifetable analysis that the risk of pouchitis at 5 years was 44% if preoperative extraintestinal manifestations had been present *v* 33% if they had been absent. Similarly Becker *et al*²¹ reported that if their ulcerative colitis patients had preoperative extraintestinal manifestations, 39% developed pouchitis *v* only 19% among those patients who had not had preoperative extraintestinal manifestations. Indeed, severe systemic manifestations have been reported in the course of pouch ileitis itself.²²

Blind pathological review of the colectomy specimens showed no correlation between histological category and the presence or absence of RP. For example, colectomy specimens were classified as definite ulcerative colitis (Group A) as frequently in RP as in controls (40% and 39%, respectively). This lack of significant difference between the proportions of RP cases and controls held true for the other histological categories as well, including even patients with definite Crohn's disease (Group E) (RP 13%, control 17%). Our findings are supported by the Mayo Clinic report of no increased incidence of pouchitis in cases of histologically indeterminate colitis compared with cases of more classic ulcerative colitis.²³

Our review also attempted to discern any correlation between RP and individual histological features, primarily those considered to be indicators of classic Crohn's disease, but we found no such associations. For example, the same proportions of RP and control patients had histological evidence of ileitis on review of their surgical specimens (20% and 17%, respectively). This particular finding supports the finding, based on radiological studies, that the presence of backwash ileitis did not predispose to an increased incidence of pouchitis.²⁴

It should be emphasised that even the five

cases classified pathologically as Group E were not histologically compelling examples of classic Crohn's disease apart from the presence of typical granulomata. Granulomata themselves were comparatively infrequent, and other histological features characteristic of Crohn's disease were less conspicuous than usual. Therefore, we are not implying that patients with classic Crohn's disease are necessarily good candidates for reservoir surgery, nor does the recent experience of The Cleveland Clinic support such a view.²⁵ We are suggesting, however, that the postoperative development of RP is not *prima facie* evidence for a 'missed' diagnosis of Crohn's disease before and including the time of colectomy.

The cause of RP may be linked to the still unelucidated immunological mechanisms in inflammatory bowel disease that are clinically manifested as extraintestinal complications. Perhaps an immunologically vulnerable subset of inflammatory bowel disease patients, Crohn's disease and ulcerative colitis alike, are prone to develop refractory pouchitis under the influence of certain mechanical, vascular, bacteriological or biochemical factors, or all four that may arise in an ileal reservoir.²⁶⁻²⁹ This concept may explain why the inflammatory changes manifested in the clinical syndrome of 'pouchitis' are seen almost exclusively in patients who have had colectomy for inflammatory bowel disease rather than for familial polyposis.¹⁹

Whatever the pathophysiological basis of RP may be, however, it is worthy of serious study as a 'human experimental model' of inflammatory bowel disease,³⁰ rather than cavalier dismissal as simply a 'misdiagnosis' of Crohn's disease.

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