

Bowel Cancer Characteristics in Patients with Regional Enteritis

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Abstract. We report 10 carcinomas in 8 patients with regional enteritis. Five of the cancers were in the ileum, 4 in the right colon, and 1 in the rectum. The visualized small bowel cancers appeared as benign strictures in small bowel involved by regional enteritis. Most were poorly differentiated. The colon cancers had a more typical radiographic appearance of malignancy. In some patients with small bowel cancer the malignancy was discovered only on histologic evaluation; the malignant nature of the lesion was not appreciated by radiography or gross examination at surgery.

Key words: Colon cancer – Small bowel cancer – Regional enteritis – Crohn's disease.

While carcinoma of the colon has long been recognized as a complication of ulcerative colitis, the increased risk of malignancy in patients with regional enteritis has only been established more recently. A number of clinical reports describing this association prompted us to investigate the radiographic findings to see what role radiology has in detecting the malignancy. The radiographic appearance of a small bowel or colon carcinoma in a setting of regional enteritis is of obvious significance. We could find only the report by Kerber and Frank that analyzed the radiographic findings in this association [1]. They reported the clinical and radiographic findings in 7 patients with re-

gional enteritis who developed a subsequent carcinoma. We add 10 carcinomas in 8 patients and discuss the spectrum of radiographic findings in these patients.

Methods

A retrospective search was made at the University of Rochester Medical Center to identify those patients with regional enteritis who subsequently developed a bowel carcinoma. The clinical history, physical findings, laboratory data, and available pathologic specimens were reviewed and the radiographic examinations analyzed. Particular attention was paid to the extent of bowel involvement by regional enteritis, the location of the subsequent carcinoma, and the indications for surgery. No effort was made to establish the incidence of carcinoma in these patients on a statistical basis.

Results

Ten bowel malignancies associated with regional enteritis were identified in 8 patients (Table 1). Radiographic studies of the gastrointestinal tract had been obtained prior to the diagnosis of cancer in all 8 patients. Six of the patients were men. The average age when regional enteritis was first diagnosed was 32 years, with a range of 18–44 years. The average age at cancer detection was 59 years, with a range of 51–70 years. The average duration between initial diagnosis of regional enteritis and the subsequent detection of the carcinoma was 27 years, with a range of 13–39 years. Of the 10 carcinomas identified, 5 were in the ileum, 4 in the right colon, and 1 in the rectum. All 10 malignancies were adenocarcinomas and most were poorly differentiated.

The resultant cancers were classified into 2 groups: those that occurred in the small bowel (Table 2) and those in the colon (Table 3).

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Table 1. Regional enteritis and cancer: summary of patient data

Patient	Sex	Onset of enteritis symptoms (age in years)	Interval to cancer diagnosis (years)	Site of enteritis	Site of cancer	Survival after cancer diagnosis
1	M	35	35	Ileum	Ileum	8 months
2	M	44	20	Ileum	Ileum	Alive, has metastases
3	F	38	15	Ileum	Rectum	3 years
4	M	32	30	Ileum	1. Ileum 2. Right colon	2 months
5	M	18	37	Ileum and colon	1. Ileum 2. cecum	2 years
6	M	38	13	Ileum and left colon	Ileum	Alive, has metastases
7	F	29	20	Transverse and left colon	Right colon	5 months
8	M	18	39	Pancolitis	Cecum	Has liver metastases 2 years after colectomy

Table 2. Regional enteritis and ileal cancer

Patient	Site of enteritis	Site of cancer	Radiographic appearance of ileal cancer	Comments
1	Ileum	Ileum	Smooth, benign-appearing stricture with partial small bowel obstruction	Proximal ileal resection showed regional enteritis and adenocarcinoma
2	Ileum	Ileum	Smooth, benign-appearing stricture	Cancer first detected at histology on resected ileum and ileovesical fistula
4	Ileum	Ileum and right colon	Ileal cancer in excluded segment not identified	Had previous exclusion ileocolostomy
5	Ileum and colon	Ileum and cecum	Ileal cancer not seen because of cecal obstruction	Ileal primary adenocarcinoma found at second resection
6	Ileum and left colon	Ileum	Smooth, benign-appearing stricture with partial obstruction	Distal ileal and right colic resection revealed regional enteritis and an adenocarcinoma

Table 3. Regional enteritis and colon cancer

Patient	Site of enteritis	Site of cancer	Radiographic appearance of colon cancer	Comments
3	Ileum	Rectum	Polypoid and infiltrating cancer in nondiseased rectum	Rectal cancer discovered as incidental finding at ileal bypass evaluation
4	Ileum	Ileum and right colon	Constricting right colic cancer in normal-appearing bowel	Patient underwent right ileocollectomy
5	Ileum and colon	Ileum and cecum	Large cecal mass with obstruction at the ileocecal valve	Cecal carcinoma believed to be separate from the ileal cancer found at subsequent surgery
7	Transverse and left colon	Right colon	Typical infiltrating cancer in nondiseased right colon	Resection revealed an adenocarcinoma
8	Entire colon	Cecum	Large cecal mass	Patient was believed to have ulcerative colitis. Discovery of cecal mass led to total abdomino-perineal colectomy. Evaluation of the resected specimen changed the diagnosis to regional enteritis

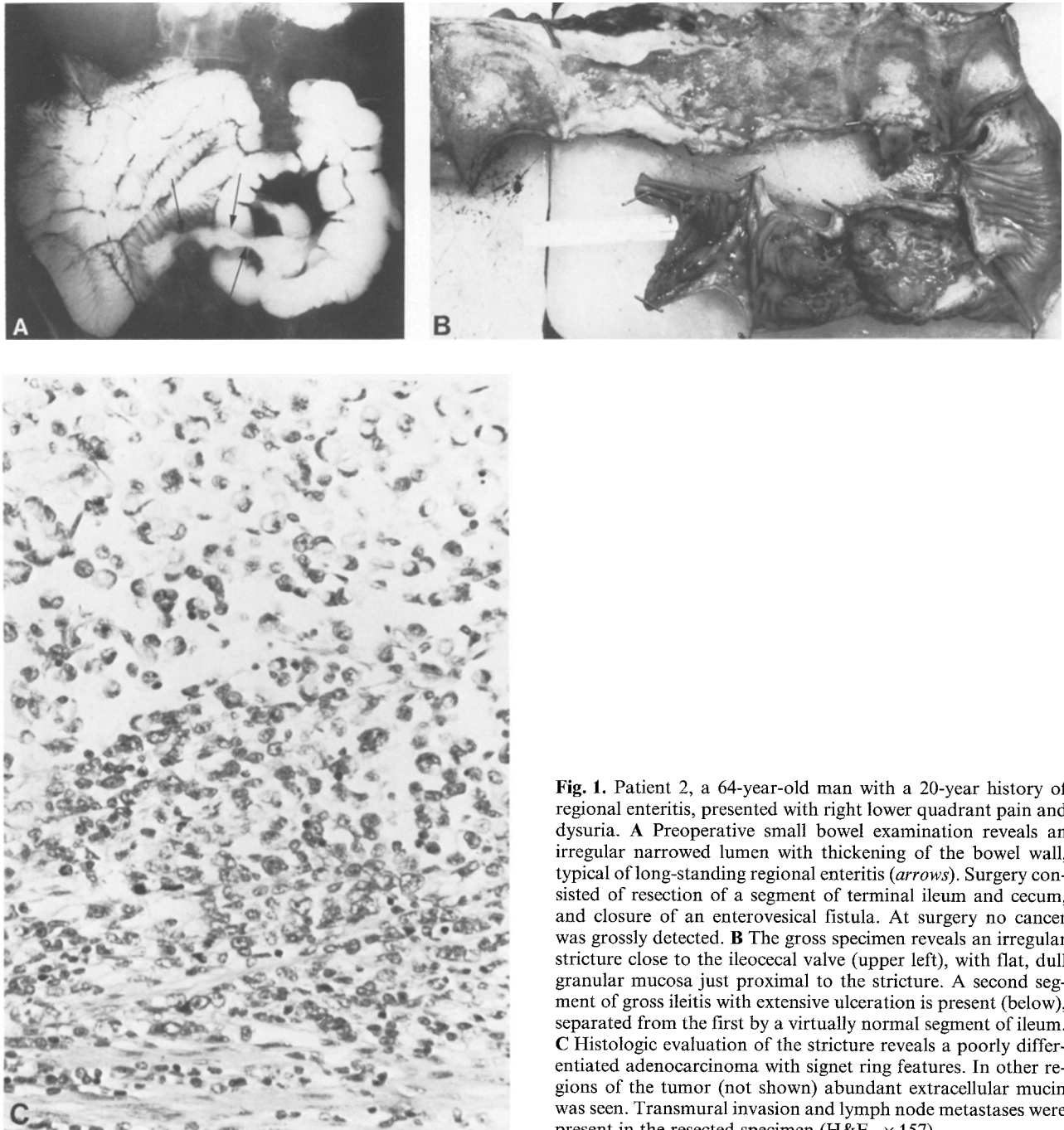


Fig. 1. Patient 2, a 64-year-old man with a 20-year history of regional enteritis, presented with right lower quadrant pain and dysuria. **A** Preoperative small bowel examination reveals an irregular narrowed lumen with thickening of the bowel wall, typical of long-standing regional enteritis (*arrows*). Surgery consisted of resection of a segment of terminal ileum and cecum, and closure of an enterovesical fistula. At surgery no cancer was grossly detected. **B** The gross specimen reveals an irregular stricture close to the ileocecal valve (upper left), with flat, dull granular mucosa just proximal to the stricture. A second segment of gross ileitis with extensive ulceration is present (below), separated from the first by a virtually normal segment of ileum. **C** Histologic evaluation of the stricture reveals a poorly differentiated adenocarcinoma with signet ring features. In other regions of the tumor (not shown) abundant extracellular mucin was seen. Transmural invasion and lymph node metastases were present in the resected specimen (H&E, $\times 157$).

Small Bowel Cancers

All 5 of the small bowel cancers occurred in ileal segments grossly involved by regional enteritis. Three of them (patients 1, 2, 6) were visualized by barium studies and all 3 appeared as smooth, benign-appearing strictures. In patients 1 and 6 a malignancy was suspected at surgery, while in patient 2 the carcinoma was first discovered at histopathologic study of the resected ileal segments.

The tumors developing in small bowel involved by regional enteritis tended to infiltrate intramurally, presenting with a narrowed lumen and thickened bowel wall; the overall radiographic impression in these patients was of severe, long-standing regional enteritis (Figs. 1, 2).

Patient 4 had an end-to-side ileotransverse colostomy performed $2\frac{1}{2}$ years previously. The patient continued to be symptomatic and developed melena. A barium enema revealed a constricting

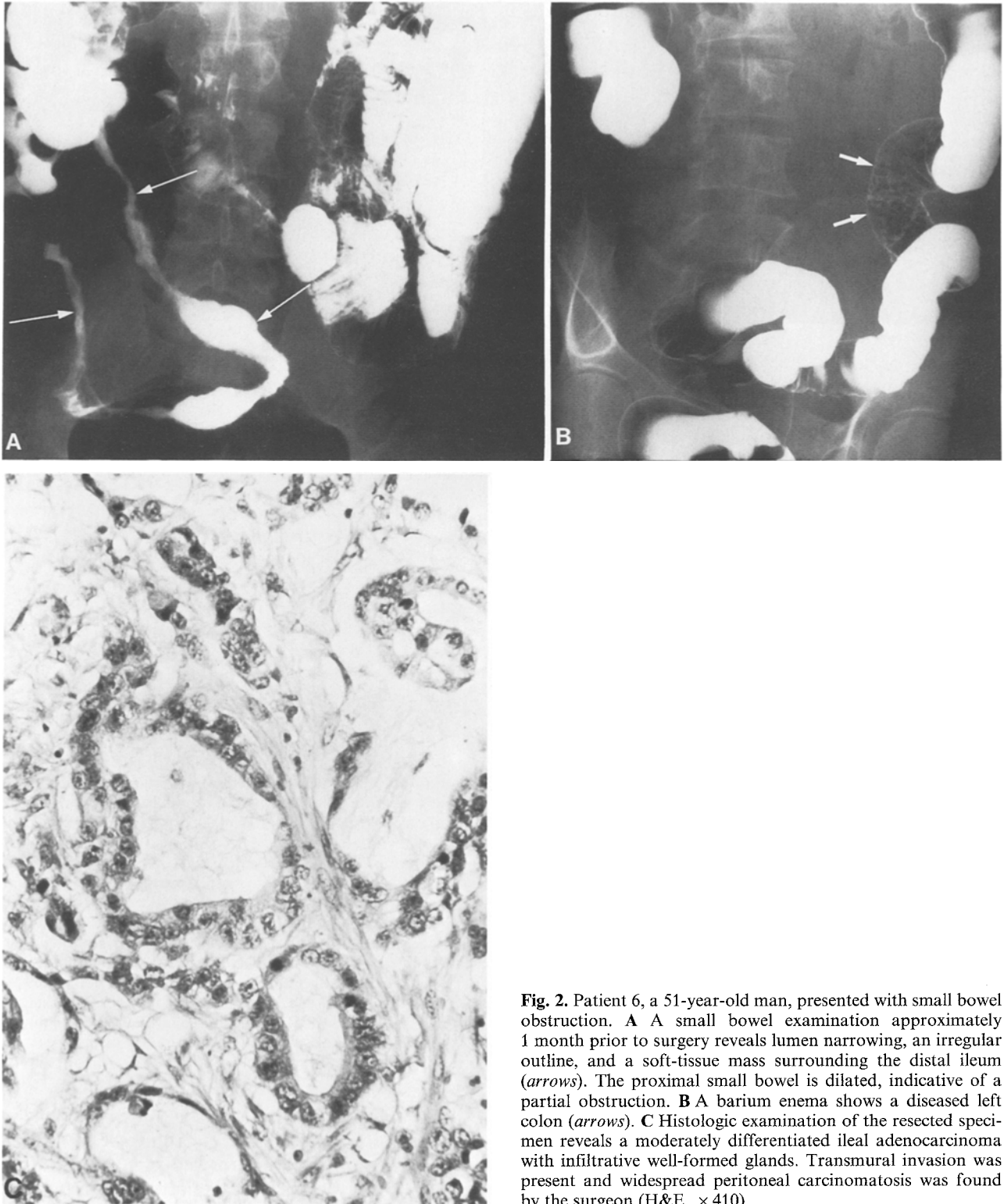


Fig. 2. Patient 6, a 51-year-old man, presented with small bowel obstruction. **A** A small bowel examination approximately 1 month prior to surgery reveals lumen narrowing, an irregular outline, and a soft-tissue mass surrounding the distal ileum (*arrows*). The proximal small bowel is dilated, indicative of a partial obstruction. **B** A barium enema shows a diseased left colon (*arrows*). **C** Histologic examination of the resected specimen reveals a moderately differentiated ileal adenocarcinoma with infiltrative well-formed glands. Transmurial invasion was present and widespread peritoneal carcinomatosis was found by the surgeon (H&E, $\times 410$).

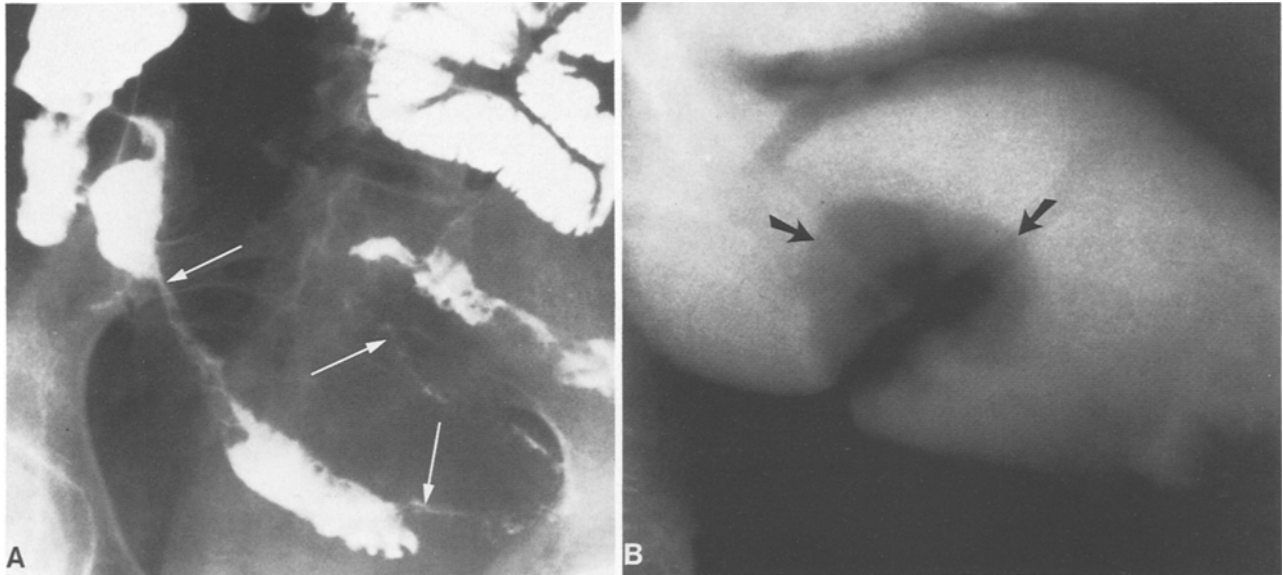


Fig. 3. Patient 3, a 53-year-old woman with a 15-year history of regional enteritis. **A** A small bowel examination reveals eccentric narrowing and a “cobblestone” appearance in the distal ileum (*arrows*). **B** Three years later the patient presented with a carcinoma of the rectum. The radiographic appearance on a barium enema is typical for a lobular polypoid cancer (*arrows*).

right colic cancer. There was no reflux into the bypassed terminal ileum and this segment could thus not be studied. The cancer in the excluded ileum was detected only at histologic examination of the resected specimen.

Patient 5 presented with distal small bowel obstruction and a barium enema was performed to identify the site and nature of the obstruction. A large cecal mass was found obstructing the ileocecal valve. Subsequent resection revealed a second primary cancer in a diseased distal ileum.

Colon Cancers

All 5 of the colon cancers were visualized by barium studies (Table 3). Three of the cancers (patients 3, 4, and 7) occurred in nondiseased segments of bowel and all 3 had the typical irregular polypoid infiltrating appearance of a large colonic malignancy. There was an abrupt transition between normal and abnormal bowel (Fig. 3). The 2 cancers developing in diseased bowel (patients 5 and 8) were seen as large, intraluminal cecal masses in a setting of inflammatory bowel disease. A diagnosis of malignancy could be suggested with the barium examination.

Discussion

In both the small bowel and colon most of these cancers occur in segments of bowel involved by

regional enteritis. There may, however, also be an increased incidence of cancer in other segments of the gastrointestinal tract [2]. In general, the small bowel carcinomas occur more distally and colon carcinomas more proximally than corresponding *de novo* malignancies [3–8]. The small bowel malignancies likewise tend to occur at a younger age than those developing *de novo* (4–6, 8–10). There is a 3:1 male preponderance in these patients [8]. While some investigators believe that the colon cancers occur at a similar age to those arising *de novo* [3], others have found these cancers at a younger age [6, 11].

The latency period between the onset of regional enteritis and discovery of a carcinoma is usually long, with most cancers developing well into adulthood [4]. The latency period also appears to be longer with regional enteritis than with ulcerative colitis [12], although in rare instances the carcinoma is discovered during a first attack of enteritis [9, 13].

It is not understood why there is an increased incidence of cancer in patients with regional enteritis. Severe epithelial dysplasia is associated with an increased incidence of cancer in ulcerative colitis. The incidence of significant dysplasia in regional enteritis in randomly selected resected specimens appears to be low [14], although dysplasia occurs in close association with a carcinoma [11, 15, 16]. The immunosuppressive action of steroids in the induction of cancer in these patients should

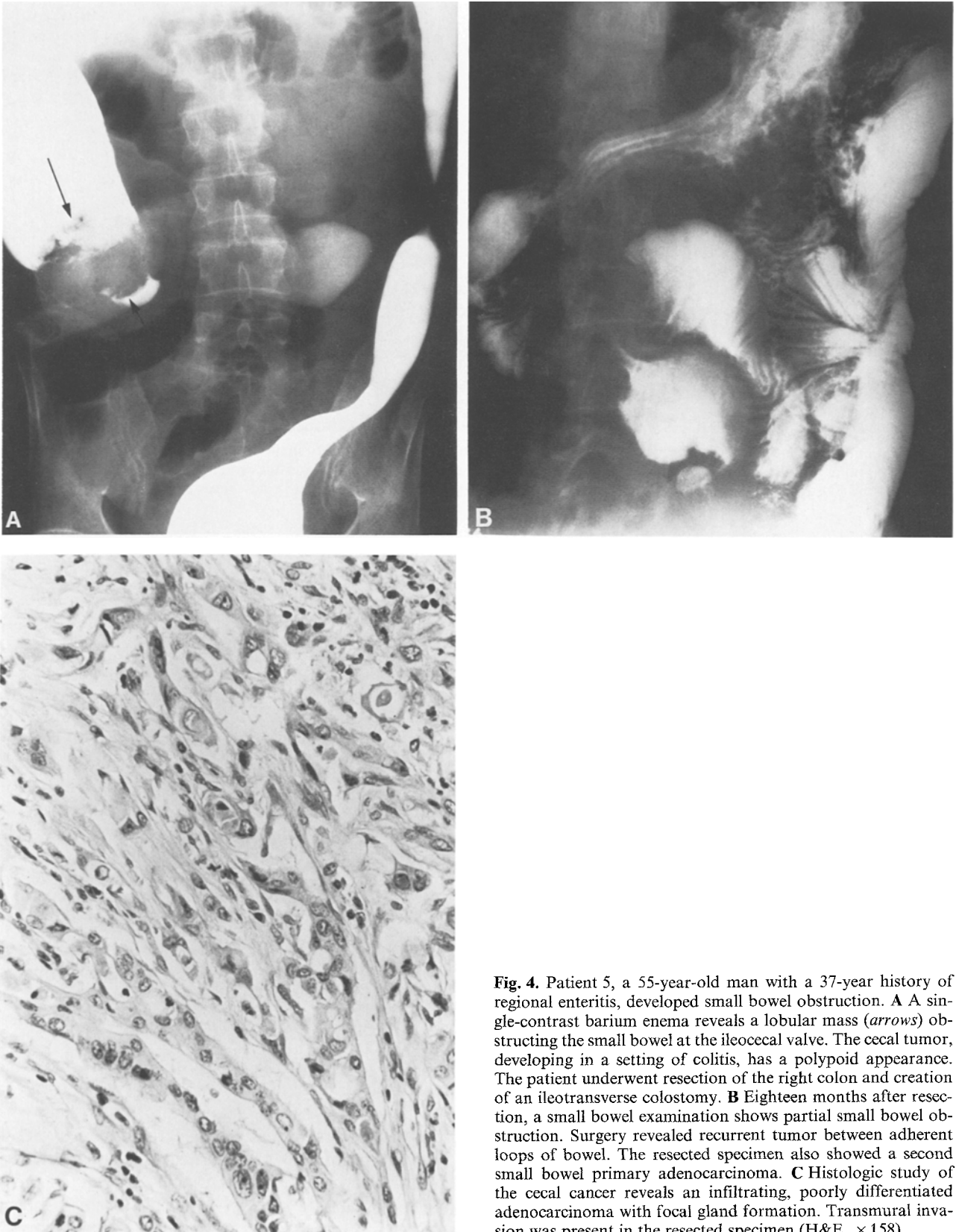


Fig. 4. Patient 5, a 55-year-old man with a 37-year history of regional enteritis, developed small bowel obstruction. **A** A single-contrast barium enema reveals a lobular mass (*arrows*) obstructing the small bowel at the ileocecal valve. The cecal tumor, developing in a setting of colitis, has a polypoid appearance. The patient underwent resection of the right colon and creation of an ileotransverse colostomy. **B** Eighteen months after resection, a small bowel examination shows partial small bowel obstruction. Surgery revealed recurrent tumor between adherent loops of bowel. The resected specimen also showed a second small bowel primary adenocarcinoma. **C** Histologic study of the cecal cancer reveals an infiltrating, poorly differentiated adenocarcinoma with focal gland formation. Transmural invasion was present in the resected specimen (H&E, $\times 158$).

also be considered. However, many of the reported patients have not had steroid therapy [17] and some other mechanisms must be postulated.

Three of our patients (1, 5, and 6) presented with obstruction, 2 with a benign-appearing ileal stricture and 1 with obstruction at the ileocecal valve (Fig. 4). Although obstruction secondary to regional enteritis is not uncommon, an obstruction developing after years of quiescence should raise suspicion of a malignancy [1].

A number of carcinomas have been reported in excluded loops of diseased bowel [4, 12, 18, 19]. These cancers can be either in excluded small bowel or colon [20]. Although some authors have suggested that a bypass per se may be carcinogenic [21], the fact that most patients with diseased small bowel and a carcinoma have not had a bypass argues against such an association [8]. Because of such exclusion, radiographic and colonoscopic evaluation is virtually impossible, thus leading to a delay in detection.

The radiographic appearance of cancer in a setting of regional enteritis can be discussed best by considering the small bowel and colon separately.

Small Bowel

Ginzburg et al. first reported in 1956 a carcinoma arising in small bowel involved by regional enteritis [22]. Of interest is that even in this patient with jejunal involvement the adenocarcinoma was first detected only on microscopic examination of the resected specimen. Since then numerous papers have described an association between regional enteritis and small bowel cancer, with many being case reports. The incidence may be higher than the literature indicates; the association of these 2 conditions has probably been ignored or overlooked in a number of patients.

Using the available prevalence rates of regional enteritis and carcinoma involving the same segment of small bowel, Darke et al. have estimated that the chance of the 2 diseases occurring separately in the same patient is less than $1:10^9$ [3]. The actual higher simultaneous incidence of the 2 conditions argues for a closer association than by chance alone [23].

Most of the reported malignancies of the small bowel have been in bowel segments involved by regional enteritis [8, 10]. In our study, these malignancies were indistinguishable radiographically from long-standing regional enteritis. In 2 of the patients described by Kerber and Frank, however, there was "shouldering," destruction, and a mass [1]. The radiographic appearance can therefore be

varied. A number of investigators have noted that some of the malignancies were not identified until the resected specimen was reviewed histologically [3, 4, 6, 10, 24]. In general, the small bowel malignancies tend to be poorly differentiated and are associated with a poor prognosis [1, 4, 5, 8, 25]. Similar to regional enteritis, occasionally these tumors can perforate [26]. Tumor growth along a fistula is not uncommon [1, 6].

Colon

A carcinoma of the ascending colon arising in bowel affected by regional enteritis was first described by Warren and Sommers in 1948 [27]. It is likely that previously many patients with regional enteritis limited to the colon were misdiagnosed as having ulcerative colitis. A cancer developing in such a setting would thus be associated with ulcerative colitis [2, 11]. It is estimated that the incidence of colon cancer in patients with regional enteritis involving either the small bowel or colon, or both, is approximately 4–20 times that seen in the general population [2, 21, 23, 28, 29]. The relative risk almost doubles in patients with extensive colonic disease [2]. It is striking that in some studies all of the colorectal cancers occurred in patients with regional enteritis involving the colon [28], although later reports contained occasional examples of cancer in grossly unaffected colon segments [30]. Some investigators predict that if patients with regional enteritis of the colon and ulcerative colitis are matched for similar anatomical extent and duration of involvement, the 2 disorders may show similar risks of colorectal cancer [31].

All of the colon cancers developing in our series were detected by radiographic examinations. Similar to the small bowel, however, these cancers can be missed not only with radiography but also with endoscopic examinations [11]. Some of the cancers occurring in diseased segments of colon described in the literature had infiltrated diffusely and had smooth borders [1]. In our study all were intraluminal with a discrete outline.

In this study, the colon tumors developing in nondiseased bowel segments had a typical appearance of carcinoma. The few published radiographic descriptions of colon cancer in *nondiseased* segments of bowel support the concept that these tumors tend to appear as more typical cancers [32]. It is tempting to speculate that these tumors develop fortuitously and were not related to the regional enteritis involving other bowel segments, although such proof is lacking.

Conclusion

Most small bowel carcinomas associated with regional enteritis occur in grossly diseased segments of bowel and present as infiltrating and constricting lesions that can be radiographically indistinguishable from long-standing regional enteritis. A suspicion of carcinoma should be entertained, however, if a quiescent period is followed by small bowel obstruction or other significant evidence of recurrence.

Colon cancers can develop at sites either grossly involved or not involved by regional enteritis. Many of these cancers can be detected by radiographic examinations. Although those cancers developing in grossly diseased bowel can appear as "benign" strictures, cancers in grossly nondiseased bowel tend to have the more typical appearance of a carcinoma.

References

- Kerber GW, Frank PH: Carcinoma of the small intestine and colon as a complication of Crohn's disease: radiologic manifestations. *Radiology* 150: 639-645, 1984
- Gyde SN, Prior P, Macartney JC, Thompson H, Waterhouse JAH, Allan RN: Malignancy in Crohn's disease. *Gut* 21: 1024-1029, 1980
- Darke SG, Parks AG, Grogono JL, Pollock DJ: Adenocarcinoma and Crohn's disease. A report of 2 cases and analysis of the literature. *Br J Surg* 60: 169-175, 1973
- Traube J, Simpson S, Riddell RH, Levin B, Kirsner JB: Crohn's disease and adenocarcinoma of the bowel. *Dig Dis Sci* 25: 939-944, 1980
- Floch HF, Slattery LR, Hazzi CG: Carcinoma of the small intestine in regional enteritis. Presentation of a case and review of the literature. *Am J Gastroenterol* 70: 520-527, 1978
- Lightdale CJ, Sternberg SS, Posner G, Sherlock P: Carcinoma complicating Crohn's disease. Report of seven cases and review of the literature. *Am J Med* 59: 262-268, 1975
- Zinkin LD, Brandwein C: Adenocarcinoma in Crohn's colitis. *Dis Colon Rectum* 23: 115-117, 1980
- Collier PE, Turowski P, Diamond DL: Small intestinal adenocarcinoma complicating regional enteritis. *Cancer* 55: 516-521, 1985
- Fresko D, Lazarus SS, Dotan J, Reingold M: Early presentation of carcinoma of the small bowel in Crohn's disease ("Crohn's carcinoma"). *Gastroenterology* 82: 783-789, 1982
- Frank JD, Shorey BA: Adenocarcinoma of the small bowel as a complication of Crohn's disease. *Gut* 14: 120-124, 1973
- Hamilton SR: Colorectal carcinoma in patients with Crohn's disease. *Gastroenterology* 89: 398-407, 1985
- Greenstein AJ, Janowitz HD: Cancer in Crohn's disease. The danger of the by-passed loop. *Am J Gastroenterol* 64: 122-124, 1975
- Perrett AD, Truelove SC, Massarella GR: Crohn's disease and carcinoma of the colon. *Br Med J* 2: 466-468, 1968
- Warren R, Barwick KW: Crohn's colitis with carcinoma and dysplasia. *Am J Surg Pathol* 7: 151-159, 1983
- Craft CF, Mendelsohn G, Cooper HS, Yardley JH: Colonic "precancer" in Crohn's disease. *Gastroenterology* 80: 578-584, 1981
- Simpson S, Traube J, Riddell R: The histologic appearance of dysplasia (precarcinomatous change) in Crohn's disease of the small and large intestine. *Gastroenterology* 81: 492-501, 1981
- Valdes-Dapena A, Rudolph I, Hidayat A, Roth JLA, Laucks RB: Adenocarcinoma of the small bowel in association with regional enteritis. *Cancer* 37: 2938-2947, 1976
- Greenstein AJ, Sachar D, Pucillo A, Kree I, Geller S, Janowitz HD, Aufses A Jr: Cancer in Crohn's disease after diversionary surgery. A report of seven carcinomas occurring in excluded bowel. *Am J Surg* 135: 86-90, 1978
- Victor DW Jr, Thompson H, Allan RN, Alexander-Williams J: Cancer complicating defunctioned Crohn's disease. *Clin Oncol* 8: 163-165, 1982
- Lavery IC, Jagelman DG: Cancer in the excluded rectum following surgery for inflammatory bowel disease. *Dis Colon Rectum* 25: 522-524, 1982
- Shorter RG: Risks of intestinal cancer in Crohn's disease. *Dis Colon Rectum* 26: 686-689, 1983
- Ginzburg L, Schneider KM, Dreizin DH, Levinson C: Carcinoma of the jejunum occurring in a case of regional enteritis. *Surgery* 39: 347-351, 1956
- Greenstein AJ, Sachar DB, Smith H, Janowitz HD, Aufses AH Jr: A comparison of cancer risk in Crohn's disease and ulcerative colitis. *Cancer* 48: 2742-2745, 1981
- Smith TR, Conradi H, Bernstein R, Greweldinger J: Adenocarcinoma arising in Crohn's disease: report of two cases. *Dis Colon Rectum* 23: 498-503, 1980
- Hawker PC, Gyde SN, Thompson H, Allan RN: Adenocarcinoma of the small intestine complicating Crohn's disease. *Gut* 23: 188-193, 1982
- Heathcote J, Knauer CM, Oakes D, Archibald RWR: Perforation of an adenocarcinoma of the small bowel affected by regional enteritis. *Gut* 21: 1093-1096, 1980
- Warren S, Sommers SC: Cicatrizing enteritis (regional ileitis) as a pathologic entity. *Am J Pathol* 24: 475-501, 1948
- Weedon DD, Shorter RG, Ilstrup DM, Huizenga KA, Taylor WF: Crohn's disease and cancer. *N Engl J Med* 289: 1099-1103, 1973
- Korelitz BI: Carcinoma of the intestinal tract in Crohn's disease: results of a survey conducted by the National Foundation for Ileitis and Colitis. *Am J Gastroenterol* 78: 44-46, 1983
- Greenstein AJ, Sachar DB, Smith H, Janowitz HD, Aufses AH Jr: Patterns of neoplasia in Crohn's disease and ulcerative colitis. *Cancer* 46: 403-407, 1980
- Sachar DB: New concepts of cancer. *Mt Sinai J Med* 50: 133-137, 1983
- Kim U, Aufses AH Jr, Kree I: Malignant tumors associated with granulomatous enterocolitis. *Am J Gastroenterol* 63: 66-70, 1975

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