Crohn's Disease-Associated Carcinoma

A Poorly Recognized Complication of Inflammatory Bowel Disease

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We have reviewed eight cases of Crohn's disease associated carcinoma (CDAC) of the bowel treated at Saint Barnabas Medical Center since 1977. Five patients had colorectal carcinoma in areas of dysplasia within histologically recognizable Crohn's disease. One of the large bowel carcinomas was a diffusely infiltrating signet ring adenocarcinoma (linitis plastica), three were mucinous carcinomas, and one contained both cell types. Survival ranged from 4 to 55 months.

Three patients developed ileal carcinomas in areas of dysplasia within histologically recognizable Crohn's disease. One of the ileal cancers was a moderately differentiated adenocarcinoma; two were poorly differentiated adenocarcinomas. Survival ranged from 8 to 44 months.

The dysplastic changes seen in the bowel adjacent to the tumors in these patients were identical to the characteristic precancerous (dysplastic) changes well described in ulcerative colitis. The histopathologic changes seen in this high-risk group of patients are also similar to those of previously reported CDAC. Those patients with the more diffuse dysplastic changes might have been detected before the development of invasive cancer had they undergone periodic colonoscopic surveillance. One patient in the series with an asymptomatic lesion was, in fact, identified at surveillance colonoscopy. It would appear that Crohn's disease patients have a similar risk for carcinoma previously recognized in ulcerative colitis patients and that surveillance protocols should be developed for this group of patients.

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WHILE THERE APPEARS TO BE little doubt that Crohn's disease predisposes to gastrointestinal cancer, it has been difficult to accurately assess this risk for several reasons. Crohn's disease is a relatively new entity in the history of medicine, and the use of biopsies for the effective histopathologic differentiation between Crohn's colitis and ulcerative colitis has only been possible for about two decades. It is very likely that in the past many patients with Crohn's colitis had been clinically as well as pathologically diagnosed as having ulcerative colitis. The lack of biopsy-proved differentiation between the two similar diseases may have been responsible for the relative absence of prospective studies on the natural course of Crohn's disease.

In this paper, the history, pathology, and postoperative course of eight previously unreported cases of Crohn's disease-associated carcinomas (CDAC) of the small and large bowel were reviewed in an effort to determine which patients are at highest risk for malignant degeneration and to establish an effective surveillance program for individuals at risk.

Materials and Methods

We examined the records and pathologic material of eight patients operated on at Saint Barnabas Medical Center since 1976 who had histopathologically proved Crohn's disease and carcinoma in their operative specimens (Table 1). The diagnosis of Crohn's disease was made using the widely accepted pathologic criteria.[1] All patients were followed by the Saint Barnabas Medical Center Tumor Registry, through contact with the patients, and query of the patients' private physicians. The date of onset of Crohn's disease in each patient was determined as the time their physician initially diagnosed them as having ileitis, ulcerative colitis, or Crohn's disease. Dysplasia was determined by applying the criteria of the Inflammatory Bowel Disease Dysplasia Morphology Study Group.[2]

Cases Reports

Patient 1 was a 58-year-old man who developed symptoms of regional ileitis 5 months before admission. Laparotomy at another hospital 1 month before admission revealed findings (e.g. "fat wrapping") characteristic of Crohn's enteritis. No resection was done at that time. On

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TABLE 1. *Summary of Our Cases*

Patient	Onset of Crohn's	Age Cancer Detected	Crohn's Duration Preop	Primary Cancer Location	Cancer Cell Type	Lymph Nodes Involved	Dysplasia	Additional Treatment	Postop Survival
1	58 yrs.	58 yrs.	4 mos.	Ileum	Poorly differentiated adenocarcinoma	0/10	High Grade	None	15 mos.
2	27 yrs.	75 yrs.	48 yrs.	Ileum	Moderately differentiated adenocarcinoma	0/11	High Grade	Chemotherapy	8 mos.
3	27 yrs.	79 yrs.	1 mo.	Ileum	Poorly differentiated adenocarcinoma	1/12	High Grade	None	44 mos.
4	16 yrs.	37 yrs.	21 yrs.	Right colon	Mucinous	4/56	High Grade	Chemotherapy	22 mos.
5	22 yrs.	49 yrs.	27 yrs.	Rectum	Signet ring	19/21	High Grade Adenomatous	Radiation and chemotherapy	12 mos.
6	9 yrs.	26 yrs.	17 yrs.	Appendix	Mucinous and signet ring	7/87	High Grade	Chemotherapy	4 mos.
7	N/A	54 yrs.	None	Rectum	Mucinous	0/18	High Grade Adenomatous	Radiation	55 mos.
8	31 yrs.	72 yrs.	41 yrs.	Splenic Flexure	Mucinous	0/33	High Grade	None	Alive at 6 mos. NED

this first admission to SBMC, removal of the terminal ileum was performed for bowel obstruction. A 2-cm poorly differentiated adenocarcinoma, arising at the base of a "villous adenoma" in the terminal ileum, with extension to the serosal surface was found. The remainder of the specimen showed typical changes of advanced ileal Crohn's disease. Because of this unexpected finding, a wider resection of mesentery, ileum, and right colon was performed 2 weeks later. None of ten lymph nodes was positive for tumor. No further carcinoma was found. It was noted that the terminal ileum contained focal areas of high-grade dysplasia adjacent to the adenocarcinoma-containing "polyp". The foci of dysplasia had a prominent villous configuration that was responsible for the designation of "villous adenoma" (Figs. 1 and 2). No adjuvant therapy was used. The patient died 15 months after operation of diffuse carcinoma.

Patient 2 was a 75-year-old man admitted because of a distal small bowel obstruction. Forty-eight years before he had 122 cm of distal ileum removed for obstruction. Since that time, he had reported occasional episodes of crampy abdominal pain, each of which resolved spontaneously within two days. At operation, the terminal ileum and right colon were removed. Moderately differentiated adenocarcinoma of the terminal ileum invading the entire bowel wall was found. At least one liver metastasis was present. In addition to the invasive cancer, there were multiple areas of dysplasia and intramucosal carcinoma in the ileum superimposed on a background of active Crohn's disease. None of 11 lymph nodes was positive for tumor. He received CCNU and 5-FU chemotherapy. The patient died 8 months after operation with diffuse metastatic disease.

Patient 3 was a 79-year-old woman who was admitted for fever, diarrhea, and a palpable mass in the right lower quadrant. She had been diagnosed 1 month before as having regional ileitis on the basis of symptoms and barium studies. The distal ileum and right colon were resected. Poorly differentiated adenocarcinoma of the ileum invading through the entire bowel wall was present. It was noted that there were multiple areas of dysplasia and intramucosal carcinoma in the ileum superimposed on a background of active and advanced Crohn's disease. Of interest was the gross recognition of multiple polypoid, villiform elevations of mucosa in the gross specimen that corresponded with microscopic areas of high-grade dysplasia (Figs.3 and 4). One of 12 mesenteric lymph nodes contained tumor. Two years later an exploratory laparotomy was performed, and a 10-cm mesenteric mass consisting of metastatic tumor was resected. The patient received no adjuvant therapy and died 44 months after her initial resection with diffuse metastatic disease.

Patient 4 was a 37-year-old woman with a 21-year history of Crohn's colitis who was admitted for peritoneal signs, partial obstruction, and perforated viscus. She underwent a subtotal colectomy, Hartmann's pouch, and ileostomy. Mucinous adenocarcinoma of the proximal ascending colon arising from dysplastic colonic mucosa superimposed upon active Crohn's disease was found (Figs. 5 and 6). There was a metastasis to the appendix that had perforated. Four of 56 lymph nodes were positive for tumor. She received postoperative chemotherapy. Eight months after operation she returned with diffuse pelvic metastasis. She died after 22 months with metastatic disease.

Patient 5 was a 49-year-old man with a 27-year history of Crohn's ileitis and colitis who was diagnosed as having a benign rectal stricture since age 32 years. He was largely asymptomatic until several weeks before admission, when he noted diarrheal stools and partial bowel incontinence. Rectal biopsy of the stricture revealed poorly differentiated carcinoma. The biopsy included an area of adenomatous dysplasia histologically indistinguishable from a colonic adenoma (Fig.7). Barium studies revealed near-total obstructions at the terminal ileum and rectum. He received preoperative radiation and then underwent an en-bloc abdominal perineal resection of the sigmoid, rectum, anus, and prostate (Fig.8). A resection of the distal ileum and right colon was also performed. On microscopic examination, over 15 cm of diffusely infiltrating signet ring adenocarcinoma (linitis plastica) involved the rectum with multiple sites of mucosal involvement and mucosal inflammation (Fig.9). The terminal ileum was markedly fibrotic with typical inactive Crohn's disease. Nineteen of 21 lymph nodes were positive for tumor. He received postoperative radiation therapy and chemotherapy, but died 12 months later of metastatic disease.

Patient 6 was a 26-year-old woman with a 17-year history of Crohn's colitis. She had been asymptomatic for the past 7 years. She was admitted for weight loss, abdominal cramps, diarrhea, and a right lower quadrant abdominal mass. Random biopsies of the left colon showed changes consistent with quiescent Crohn's disease. Biopsies of the right colon showed marked epithelial dysplasia. A subtotal colectomy with ileostomy was performed. A combined signet ring and mucinous poorly differentiated adenocarcinoma invading the full thickness of the appendiceal

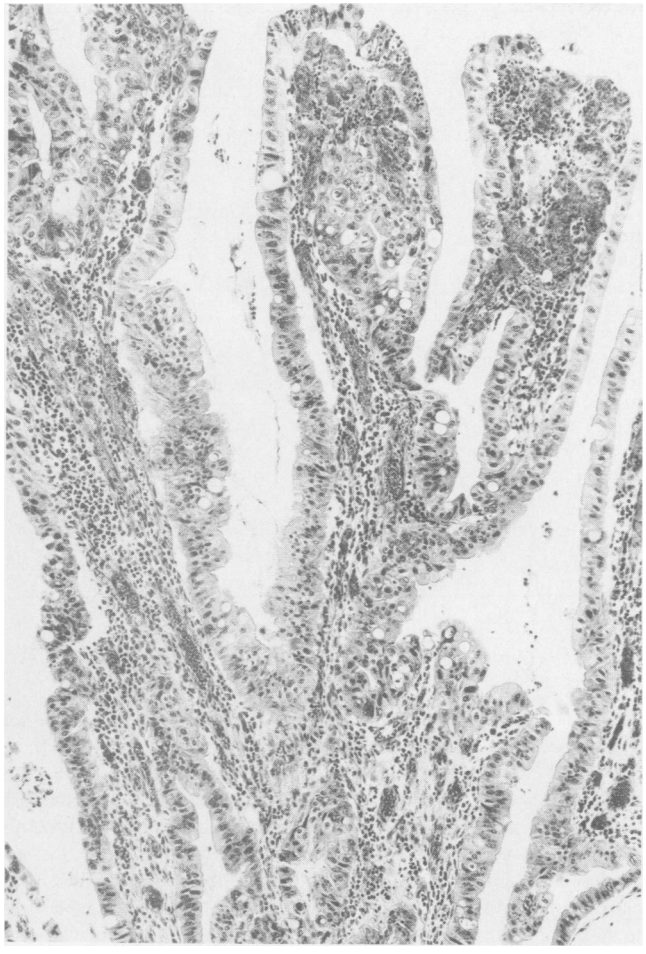


FIG. 1. Patient 1. Low-power photomicrograph of area of high-grade ileal dysplasia with villous pattern. Invasive adenocarcinoma was present deep to dysplastic mucosa. (Hematoxylin and Eosin × 130.)

wall and involving the mucosa of the cecum at the appendiceal base was found. Seven of 87 lymph nodes were positive for tumor. Chronic active Crohn's disease was present in the terminal ileum and right colon. The patient received postoperative chemotherapy but died after 4 months of diffuse metastatic disease.

Patient 7 was a 54-year-old woman with no antecedent history of inflammatory bowel disease who presented with a 3-month history of rectal bleeding and a three-week history of diarrhea and narrow stools. A mid-rectal polyp with intramucosal carcinoma was found as was an annular carcinoma of the rectosigmoid junction. Preoperative radiation was given prior to performance of a left hemicolectomy with removal of the proximal two thirds of the rectum. An end colostomy was fashioned and the rectal stump was oversewn. Typical changes of chronic active Crohn's disease with multiple areas of high-grade adenomatous dysplasia were noted in the portion of large bowel excised. Mucinous moderately differentiated adenocarcinoma extending to the muscularis was found at the rectosigmoid junction. None of 18 lymph nodes were positive for tumor. Postoperative radiation therapy was given. The patient died 55 months after surgery from recurrent carcinoma.

Patient 8 is a 72-year-old woman with a 41-year history of Crohn's colitis managed intermittently with Prednisone and Sulfasalidine. A surveillance colonoscopy done before admission revealed Crohn's disease and a carcinoma of the splenic flexure. Hypertension, well controlled by medications, was noted. A subtotal colectomy with ileoproctostomy was performed. Recovery was uneventful except for a brief episode of gastric bleeding that responded to H_2 blockers and antacids. The tumor was a 2.5-cm mucinous adenocarcinoma extending through the muscularis propria but not beyond subserosal fat. High-grade dysplasia was noted in the bowel adjacent to and overlying the tumor. She is now well, no longer takes steroids, and demonstrates no evidence of postoperative recurrence at 6 months.

Discussion

Clinical Characteristics of Crohn's Disease-Associated Cancer (CDAC)

A literature review suggests the average age at the time of diagnosis of CDAC to be 49 years[3]; and a national survey of gastroenterologists[4] found the average age to be 46 years. This is 10 to 15 years younger than the average age for sporadically occurring bowel cancers. In the present series, the average age of diagnosis was 56 years. The average time from onset of Crohn's disease to the diagnosis of carcinoma has been reported to be 16 years.[4] Rate of

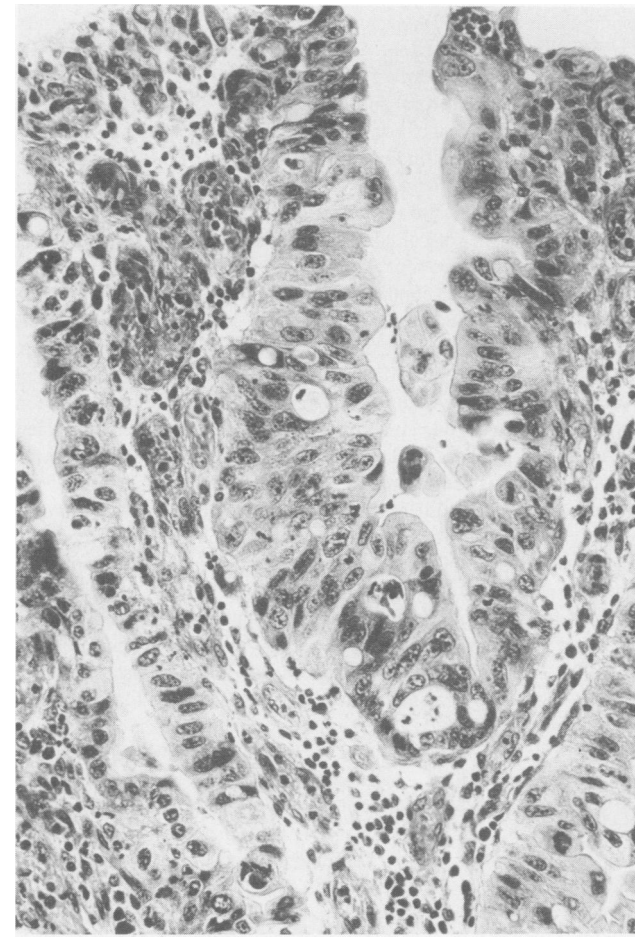


FIG. 2. Patient 1. Higher-power photomicrograph illustrating high-grade dysplasia of ileum. Note marked cellular pleomorphism, nuclear hyperchromasia, loss of polarity, and nuclear stratification. (Hematoxylin and Eosin × 335.)

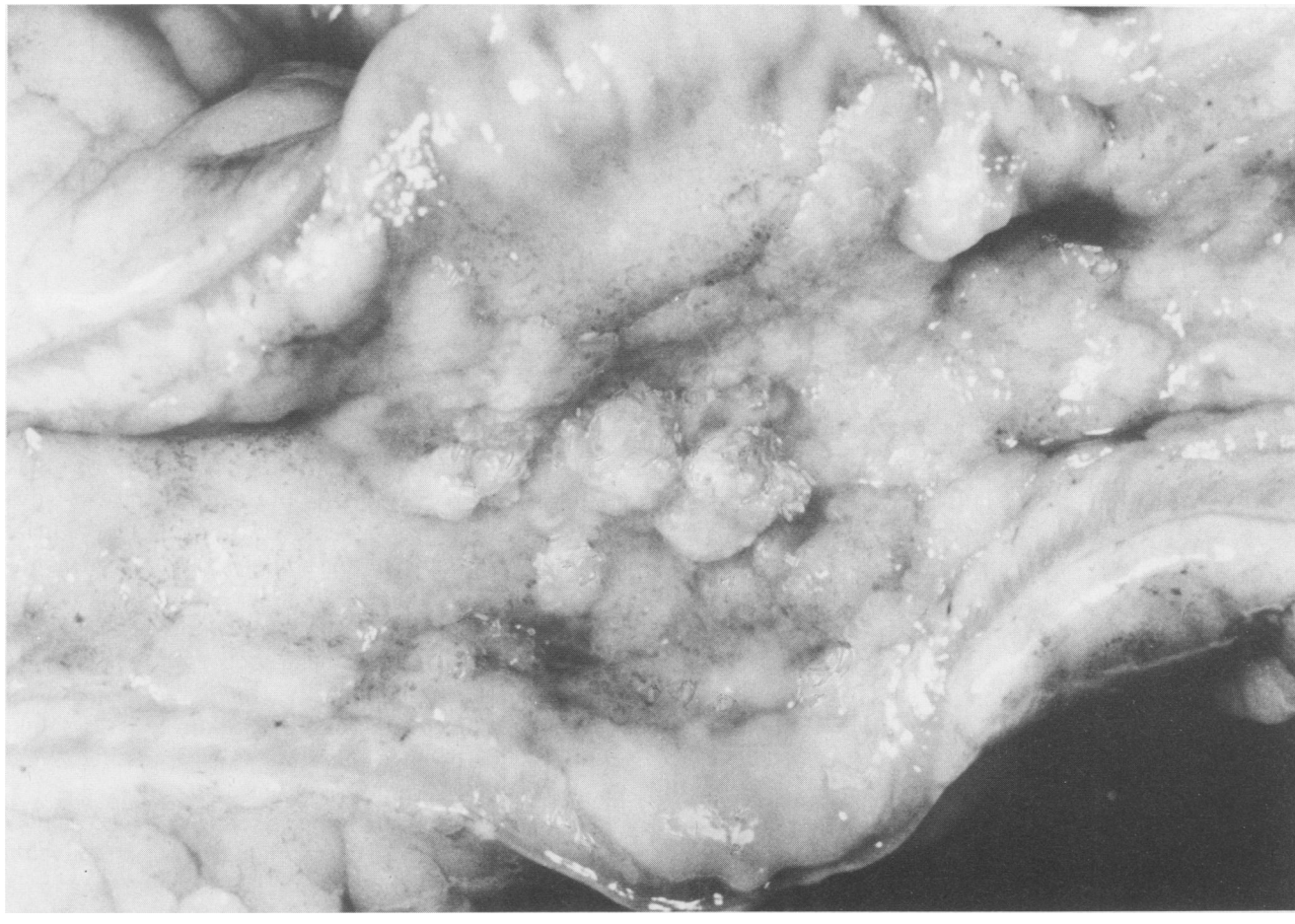


FIG. 3. Patient 3. Gross photograph of mucosal aspect of thickened ileal segment adjacent to invasive adenocarcinoma. Note prominent polypoid elevations of mucosa.

mortality from CDAC is over 80% in 2 years compared with a 50% 2-year mortality rate from cancer in ulcerative colitis.[5] In 30% of patients with CDAC, the diagnosis was made contemporaneously with the diagnosis of Crohn's disease.[6] CDAC has been noted to be multicentric in 20% of the cases.[4,8] The clinical characteristics of our series seem representative (Table 2).

Defining the Risk

Much of the literature on Crohn's disease and its relationship to carcinoma has segregated small and large bowel cancers instead of treating them as a potential final pathway of the inflammatory process inherent to Crohn's disease. The low prevalence of Crohn's disease, between 9 and 32 per 100,000 people,[9,10,11] noted in early epidemiologic studies must explain the limited amount of data available. More recently, it has been noted that the prevalence of Crohn's disease is rapidly increasing.[12] The increase may reflect a true rise in the prevalence of the disease, the inclusion of nonhospitalized patients in statistics, a greater awareness of the disease by clinicians and pathologists, or a combination of these factors.

Several difficulties arise when trying to accurately assess the risk of carcinoma in CDAC. Over 50% of the small bowel carcinomas in resected Crohn's diseased segments were unsuspected and incidentally found by the pathologist on sectioning.[13,14] This may indicate that a significant percentage of small and intramucosal Crohn's-associated small bowel carcinomas are overlooked. Over 50% of ileitis patients come to surgical resection,[15] and closely spaced serial sectioning of their specimens is rarely performed.[16] In addition, approximately 30% of the reported small bowel carcinomas in Crohn's disease occurred in patients who have bypassed loops.[14] These patients represent only a small percentage of surgically treated ileitis patients, most of whom have been managed by resection. It is possible that in resected patients, the excision removes small or intramucosal carcinomas. In CDAC of the large bowel, confusion with ulcerative colitis may well have resulted in an underestimation of the risk of carcinoma in Crohn's disease. The above difficulties not withstanding, the risk

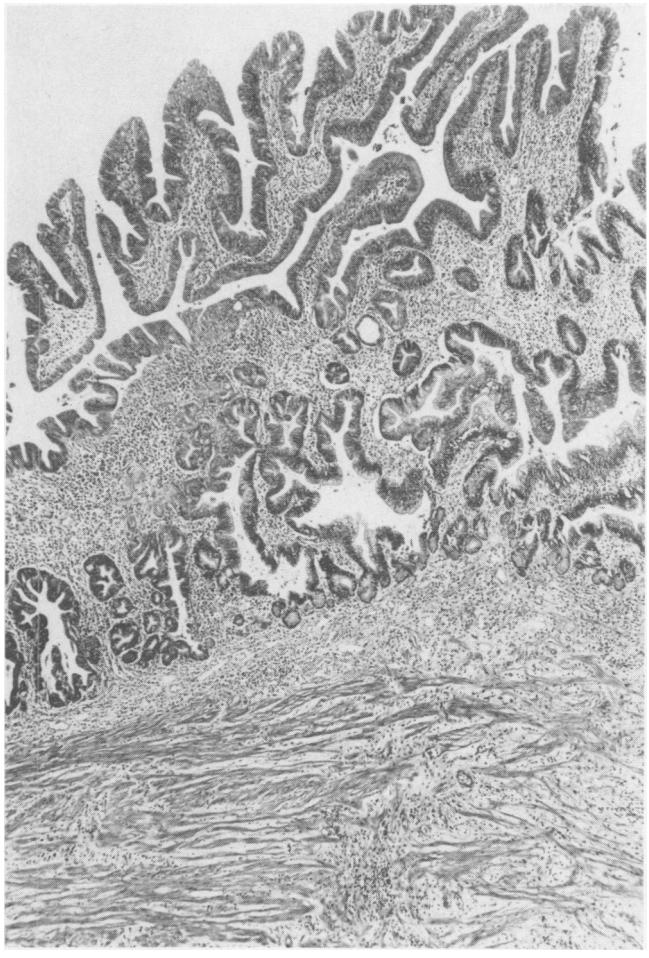


FIG. 4. Patient 3. Low-power photomicrograph of polypoid mucosa illustrated in Figure 3. Dysplastic surface shows prominent villiform configuration reminiscent of a villous adenoma. (Hematoxylin and Eosin × 53.)

of small and large bowel cancer in Crohn's disease is markedly elevated (Table 3).

The risk of colorectal cancer in the subset of Crohn's patients with colonic involvement is even higher (Table 4).

Pathology of Dysplasia and Crohn's Disease-Associated Carcinoma

The occurrence of adenocarcinoma and its association with dysplasia in patients with ulcerative colitis has been well established. The Inflammatory Bowel Disease Dysplasia Morphology Study Group organized by Riddell and Yardley[2] standardized the terminology and proposed a grading system for dysplasia. In their classification, dysplasia is described as "unequivocal neoplastic epithelial proliferation. It may be non-invasive (i.e., benign), but it also may be or may have the potential for becoming invasive. Not all features are necessarily present to the same degree in all dysplastic epithelia. *Low-grade* dysplasia has these changes in lesser intensity. *High-grade* dysplasia has these changes in greater intensity and includes carcinoma in situ."[2] It is through this standardized grading system that potential clinical applications exist.

Histologic features that characterize dysplasia may be both architectural and cytological. Architecturally, the pattern may mimic the appearance of an adenoma in patients without inflammatory bowel disease (Fig.7) and a villiform configuration is common (Figs. 1 and 4). The villiform lesions may occasionally also be recognized grossly as mucosal elevations (Fig.3). Cytologically, dysplasia is characterized by cellular pleomorphism, nuclear hyperchromasia, loss of polarity, and nuclear stratification (Figs. 2 and 5B).

The dysplasia seen in this series of patients as well as others recently reported with Crohn's disease-associated carcinomas is essentially identical to that described in patients with ulcerative colitis.[3,6,8,17] High-grade dysplasia was identified in all patients in our series (Table 1). It was present in both flat and villiform patterns. In two patients (5 and 7), the pattern was designated as "adenomatous" because of its close similarity to colonic adenomas.

TABLE 2. *Clinical Characteristics of Crohn's Disease-Associated Cancers*

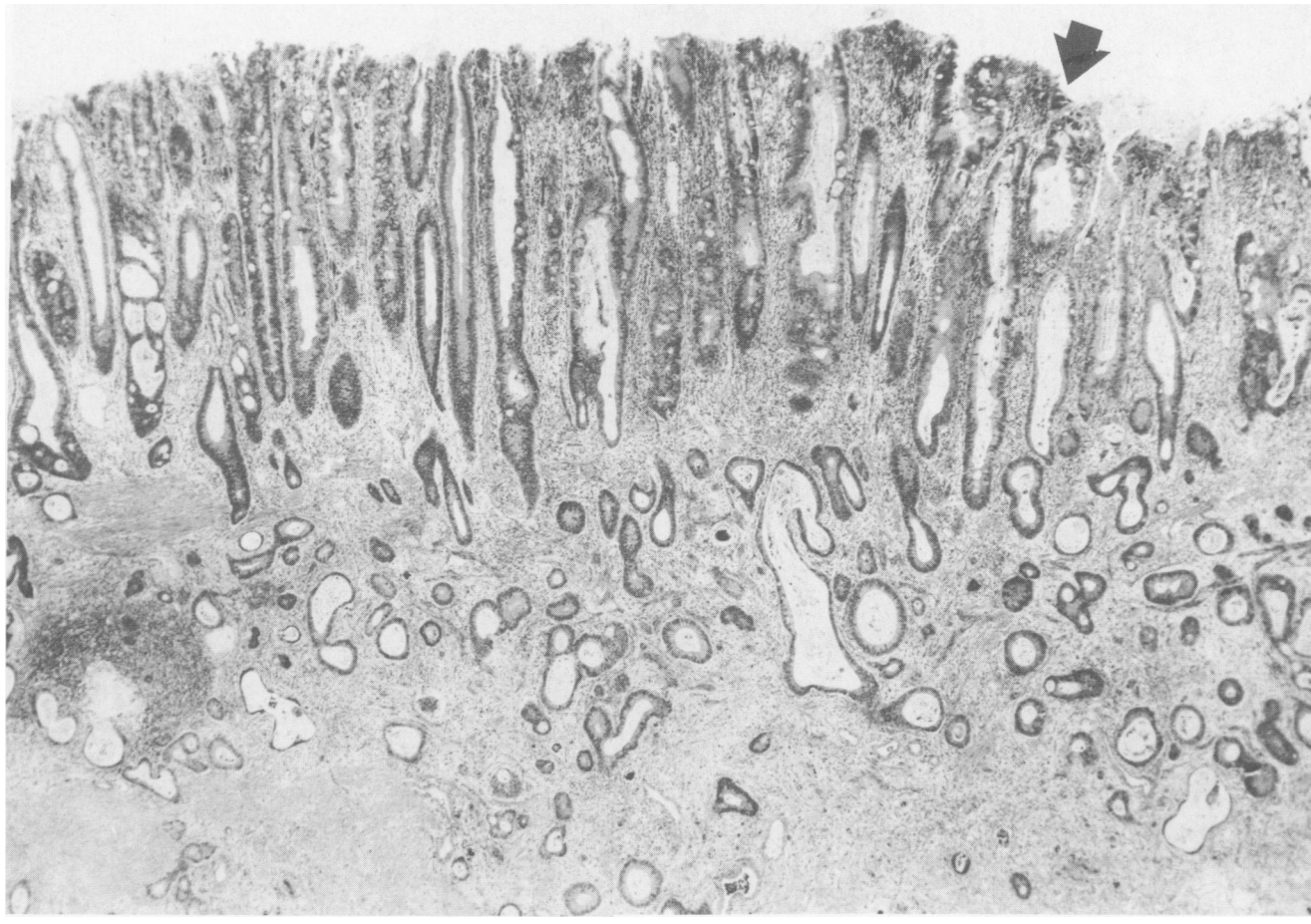
Characteristics	Literature	Present Series
Age at cancer diagnosis	49 years	56 years
Duration of Crohn's disease before cancer	16 years	19 years
2-year mortality	82%	71%*
Contemporaneous diagnosis of Crohn's disease and cancer	30%	38%
Multicentricity of carcinoma	20%	25%

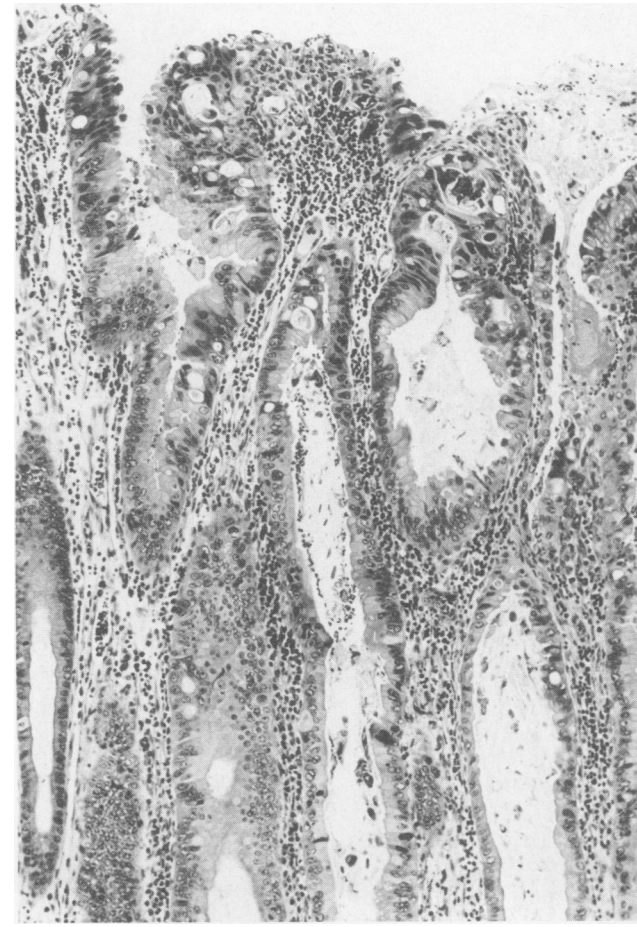
Patient 8 excluded (less than 2 years after operation).

TABLE 3. *Relative Risk of Bowel Cancers with Crohn's Disease*

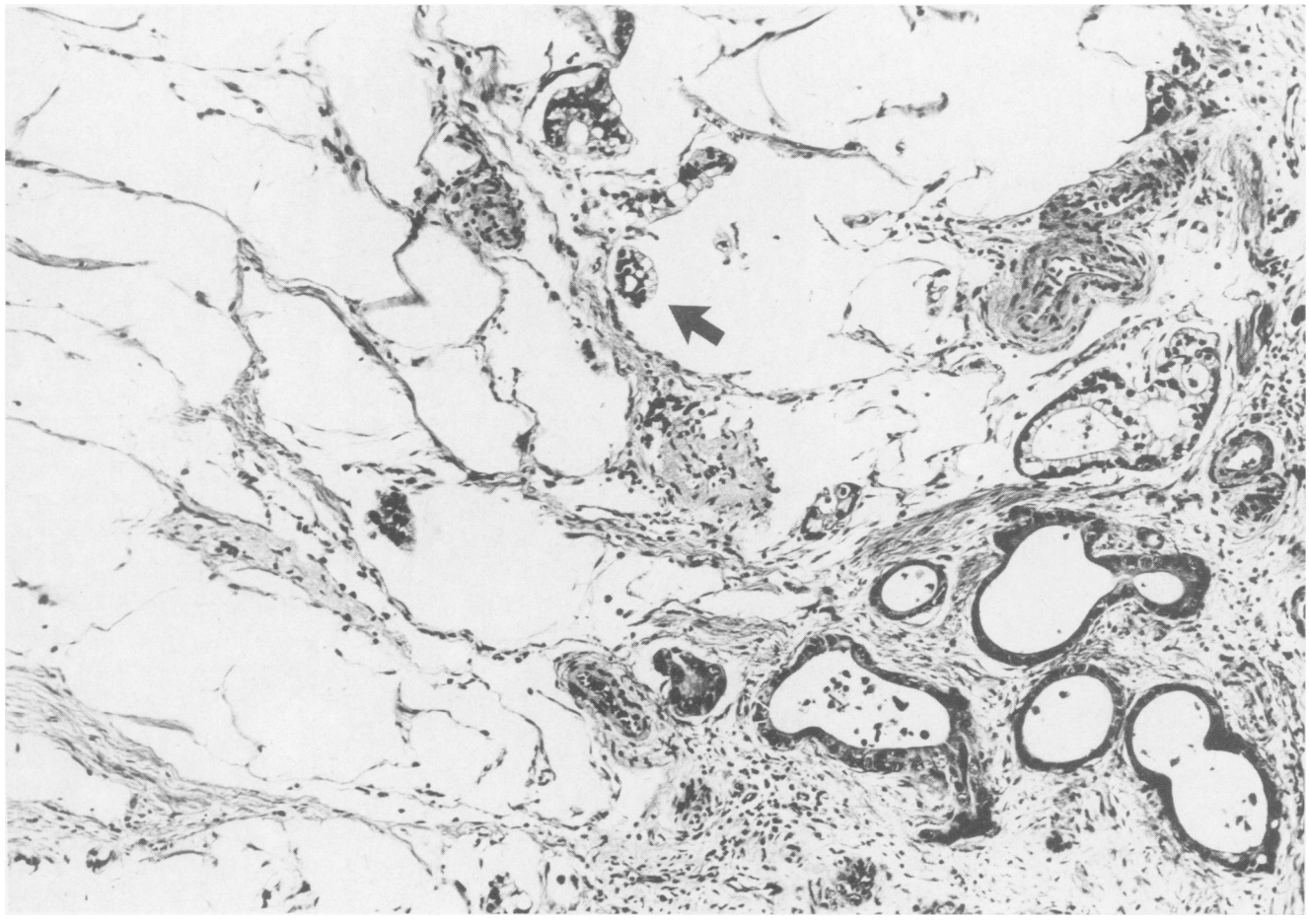
Location of Cancer	Risk of Crohn's Patients *vs.* General Population	Author	Method of Analysis
Small bowel	43 times	Korelitz[4]	Epidemiologic survey
Small bowel	100 times	Fresko[19]	Literature review
Small bowel	114 times	Greenstein[20]	Retrospective of hospitalized patients
Large bowel	6.4 times	Korelitz[4]	Epidemiologic survey
Large bowel	7 times	Greenstein[20]	Retrospective of hospitalized patients
Large bowel*	20 times	Weedon[21]	Retrospective

* (Study limited to patients with Crohn's disease onset before 22 years of age.)





FIGS. 5A and B. (A) Patient 4. Scanning-power photomicrograph showing invasive adenocarcinoma beneath a flat, dysplastic surface. (Hematoxylin and Eosin × 335.) (B) Patient 4. Higher-power photomicrograph of area noted (arrow) in 5A showing high-grade dysplasia in flat mucosa. (Hematoxylin and Eosin × 130.)



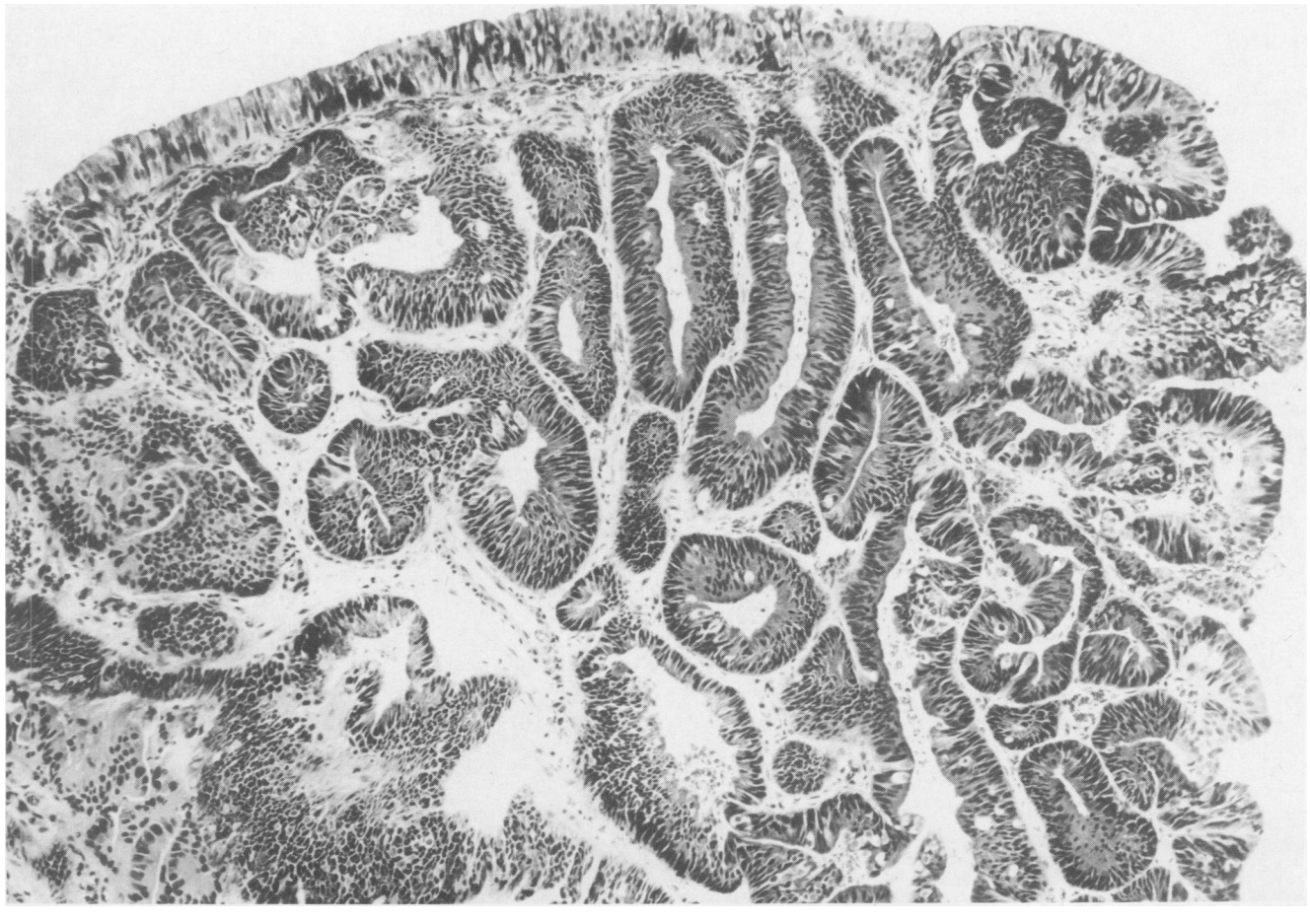


FIG. 6. Patient 4. Photomicrograph of mucinous adenocarcinoma deep to surface noted in Figures 5A and 5B. Most of tumor (clear area) consists of pools of mucin containing nests of tumor cells (arrow). (Hematoxylin and Eosin × 130.)

FIG. 7. Patient 5. Low-power photomicrograph of adenomatous dysplasia. Appearance simulates a colonic tubular adenoma. (Hematoxylin and Eosin × 130.)

The histopathologic types of colorectal carcinoma noted in our patients were significantly different from sporadically occurring lesions, an observation noted recently in another large series of CDAC.[6] Four of our five cases of colorectal carcinoma were of the mucinous (colloid) type (patient 6 had combined mucinous and signet ring carcinoma). Mucinous (colloid) carcinoma is defined as a tumor with greater than 60% of its volume composed of mucin. These lesions comprise from 9% to 15% of sporadic large bowel carcinomas and occur with increased frequency in association with ulcerative colitis and villous adenomas.[6] They have a worse prognosis than nonmucinous tumors, especially those arising in the rectum. Another unusual feature of our series was the occurrence of two cases of signet ring adenocarcinoma (linitis plastica) among five cases of colorectal cancer (patient 6 had combined mucinous and signet ring carcinoma). This is a very infrequent (less than 1%) variant of sporadic colorectal cancer and is usually advanced at the time of diagnosis.[18]

Surveillance

Given the dismal outlook for patients with CDAC, consideration of a proper surveillance protocol might permit identification of patients for selective prophylactic resections. The key issue would be to identify the subset of Crohn's patients who may be at risk. In 30% of patients who have a contemporaneous diagnosis of Crohn's disease and carcinoma, screening will not help. Of the remaining 70% of CDAC patients, one half will develop small bowel carcinoma.[4] Because the distal small bowel is not often accessible to colonoscopic biopsy, it is unlikely that adequate surveillance protocols will reduce the risks for this subset even though there is a close association with high-grade dysplasia. Thus, colonoscopic surveillance will only be applicable to a maximum of 50% of all Crohn's disease patients at risk. Recent studies of CDAC, including this series, have found virtually all the cancers to be associated with areas of high-grade dysplasia,[3,6,17,18] whereas thorough examination of 100 bowel specimens resected for non-cancer-associated Crohn's disease revealed only a 2% incidence of dysplasia; and, this dysplasia was only mild in character.[2] This strongly suggests that a colonoscopic biopsy that shows high-grade dysplasia should mandate a colectomy.

The more difficult question relates to who should undergo periodic colonoscopy with random biopsies. Excluding the patients who have simultaneous discovery of Crohn's disease and cancer, it is rare to have a CDAC occur sooner than 10 years after the clinically detected start of the inflammatory process. Therefore, ten years appears to be a good point at which to begin surveillance.

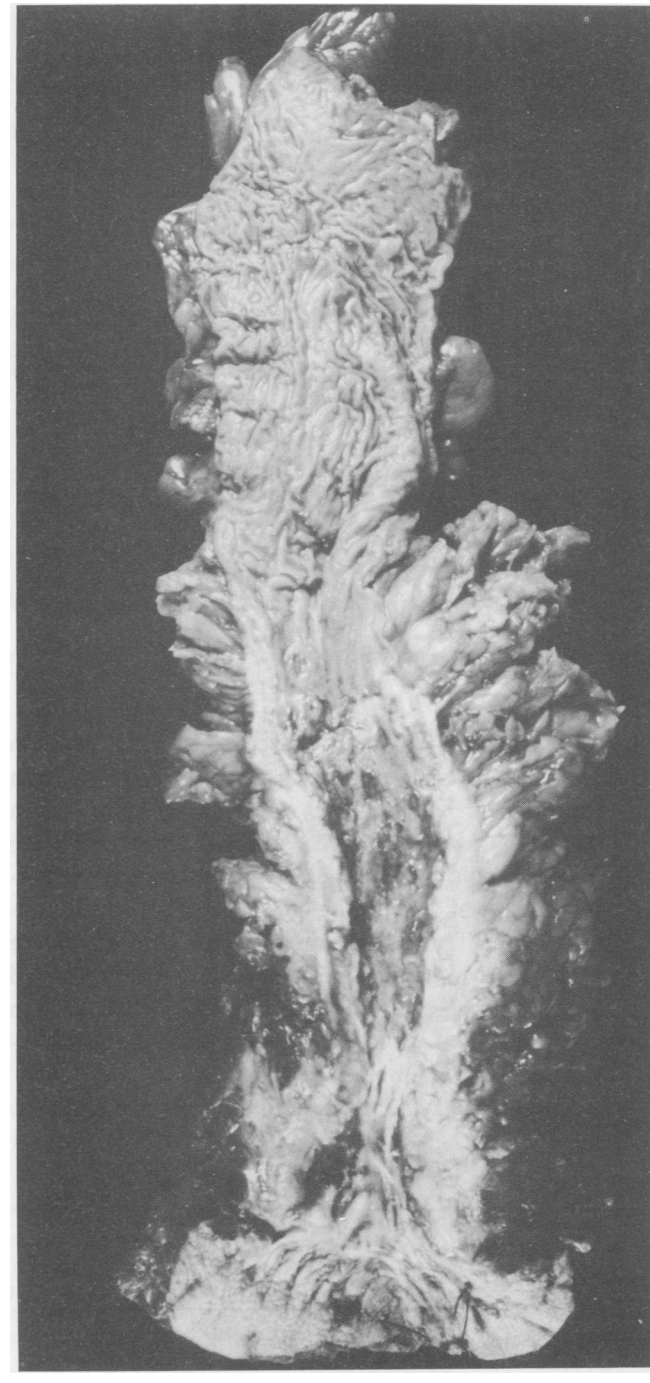


FIG. 8. Patient 5. Gross photograph of abdominal perineal resection specimen. The distal 15 cm contains a diffusely infiltrating signet ring (linitis plastica) adenocarcinoma.

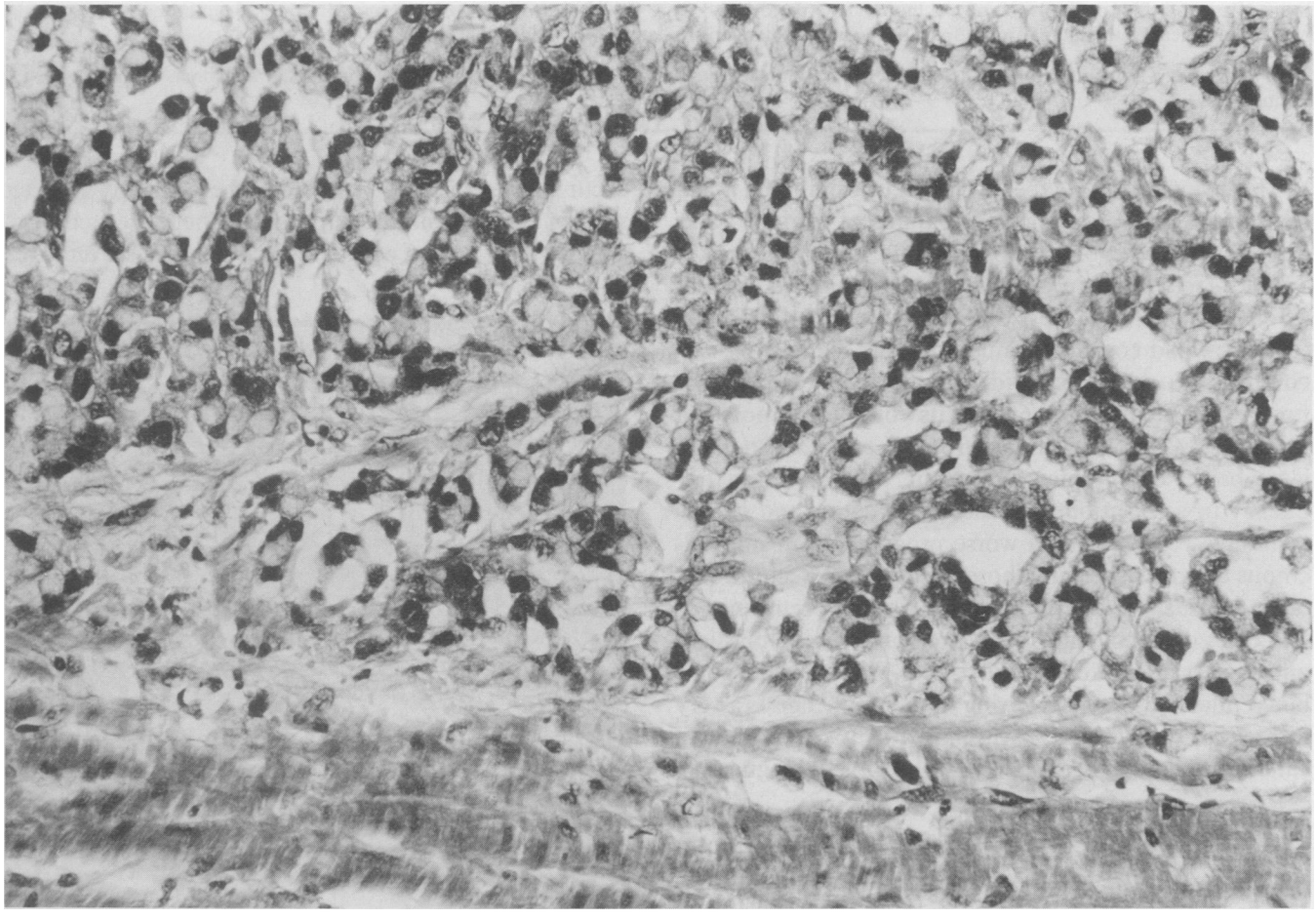


FIG. 9. Patient 5. Photomicrograph of rectal wall diffusely infiltrated by signet ring adenocarcinoma. (Hematoxylin and Eosin × 335.)

Any patient whose Crohn's disease had its onset prior to 22 years of age would seem to be a good candidate because the risk for colorectal cancer is at least as great as it is in a patient with universal ulcerative colitis. Crohn's disease patients with colonic involvement seem to have a tenfold greater risk of developing colon cancer than the general population. This risk is similar to left-sided ulcerative colitis patients. Moreover, the dismal 2-year survival noted among CDAC suggests a more virulent clinical course in these patients. This fact alone may justify the costs involved in the surveillance of this group.

The question of where to biopsy is easier to answer. Strictured areas and fistula sites have traditionally been labeled as carrying a high risk of neoplasia.[3,4] In addition, the typical skip area pattern of Crohn's disease mandates multiple random biopsies from cecum to distal rectum. As with ulcerative colitis patients undergoing surveillance, biopsies should be obtained from any unusual lesions, including plaques and nodular, thickened, or grossly villiform areas.[2]

While colonoscopic surveillance performed annually seems to be a reasonable frequency, there is no way to fully justify this until the results of surveillance programs can be reviewed. In the meantime, it should be noted that patient 8 of this series had a small carcinoma identified and completely excised as the result of a surveillance colonoscopy performed at a time when she was relatively asymptomatic.

TABLE 4. *Cancer Risks of Crohn's Colitis* Versus *Ulcerative Colitis*

Disease	Relative Risk of Colorectal Cancer *vs.* General Population
All Crohn's disease	6.4 times[4]
Crohn's disease involving colon	9.2 times[4]
Left-sided ulcerative colitis	8.6 times[20]
Universal ulcerative colitis	16.7 times[4]
Crohn's disease onset before 22 years	20 times[21]

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