Adenocarcinoma of the small intestine complicating Crohn's disease

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SUMMARY Adenocarcinoma of the small intestine is an uncommon complication of Crohn's disease. We report the clinical and pathological details of three cases diagnosed between 1968 and 1980 with a review of 58 cases from the literature. Of the 61 cases, 41 tumours occurred in the ileum, 18 in the jejunum, one in the duodenum and ileum, and one in the ileum and colon. Eighteen occurred in bypassed intestinal loops. The prognosis was poor: 44 patients (72%) had died with a mean interval of only 7.9 months from the diagnosis of cancer.

Adenocarcinoma of the small bowel complicating Crohn's disease was first described by Ginzburg *et al.*¹ in 1956. We have traced 58 examples of this association in the literature, the majority having been described as individual case reports. Individual case reports suggest an association between Crohn's disease and cancer, but neither of the two statistical studies of the cancer risk in Crohn's disease has shown an increased risk of cancer developing in the small intestine.^{2,3} We report three cases diagnosed in this unit between 1968 and 1980 with a review of the literature.

Case reports

CASE 1

R W, a man, was born on 11 January 1944. He presented at 14 years of age with abdominal pain and general malaise. Barium follow-through examination was reported as normal. Two years later when he was first seen in this unit a barium follow-through examination showed Crohn's disease of the ileum. He was treated with sulphasalazine and corticosteroids. An extensive jejunoileitis was found at laparotomy in 1964. No resection or bypass was performed. He was treated by vagotomy and pyloroplasty for duodenal ulcer in 1967 when Crohn's disease of the small intestine was still present, but the appearances had improved since 1964. At laparotomy in 1968 for subacute intestinal obstruction extensive malignant deposits were found throughout the peritoneum, pelvis, and liver. The resected small intestinal specimen showed multiple strictures and sacculations with superficial ulceration and fissures,

mucosal oedema, and fibrosis. There was an ulcerated lesion (3 × 2 cm) 3 cm from the distal end of the resected specimen. Histological examination showed

Fig. 1 Case 1. Histology showing anaplastic carcinoma. Haematoxylin and eosin.

an anaplastic carcinoma with signet ring cells (Fig. 1) extending through all layers to the peritoneal surface. He died in October 1968.

CASE 2

C P, a man, was born on 9 September 1924. He presented in 1969 with recurrent episodes of colicky abdominal pain and diarrhoea. Barium follow-through examination showed Crohn's disease of the terminal ileum. He refused surgical treatment and was lost to follow-up. He was readmitted as an emergency in 1979 with obstructive symptoms and a large tender mass in the right iliac fossa. At laparotomy a large abscess was found complicating extensive terminal ileal Crohn's disease with strictures and local enteroenteric fistulae. The abscess was drained and the macroscopic Crohn's disease was resected. The resected specimen showed extensive hose-pipe thickening and ulceration with lymphoid hyperplasia, micro-abscesses, oedema, fibrosis and one giant cell follicle, characteristic of Crohn's disease. Histological examination of the ulcerated lesion showed a moderately well-differentiated mucus-secreting adenocarcinoma extending through all layers of the ileal wall (Fig. 2). There was also evidence of mucosal dysplastic change. He died post-operatively of a massive pulmonary embolus.

Fig. 2 Case 2. Histology showing mucus-secreting adenocarcinoma. Haematoxylin and eosin.

CASE 3

M R, a woman, was born on 8 January 1929. She presented in 1962 with anorexia, malaise, and loss of weight. At laparotomy there were a few enlarged soft mesenteric lymph nodes, but no other abnormality. Histological examination of the lymph nodes showed reactive hyperplasia only. A recent review of this material showed no evidence of Crohn's disease. She remained well until 1974 when she presented with general malaise, loss of weight, and vomiting. Barium follow-through examination showed multiple jejunal strictures but her symptoms resolved without specific treatment. In October 1980 she was first seen in this unit with a recurrence of her symptoms. At laparotomy there was evidence of Crohn's disease extending for some 90 cm from the duodenojejunal junction with multiple skip lesions in the distal jejunum. The proximal jejunal segment was resected. The resected specimen showed multiple strictures with ulceration, oedema, fibrosis, lymphoid hyperplasia, and giant cell follicles. A small carcinoma of the jejunum was found on careful inspection of the resected specimen. Histological examination showed a small papillary adenocarcinoma penetrating the muscularis propria (Fig. 3a). The adjacent mucosa showed severe dysplasia and an *in-situ* intramucosal carcinoma (Fig. 3b).

Review of literature

The published reports of 58 cases of carcinoma of the small intestine complicating Crohn's disease and the present series (61 cases in all) are summarised in Table 1. The case mentioned by Lear⁴⁷ and the two cases described by Marshak, cited by Floch *et al.*⁴⁸ have been excluded because there was insufficient clinical detail. We have also excluded one of the cases described by Farmer *et al.*²¹ as it was not clear whether the tumour arose in the small or large intestine. Greenstein *et al.*⁴⁸ recently reviewed their experience of cancer in inflammatory bowel disease and considered four cases of cancer complicating small intestinal Crohn's disease. These cases have been reported earlier by them and are included in this review under Greenstein *et al.*⁴² The reported cases of carcinoid tumour of the small bowel have also been excluded.

A summary of the available clinical information is shown in Table 2. The mean interval between the diagnosis of Crohn's disease and cancer was 18.2 years (range one week to 47 years). The mean age at diagnosis of cancer was 46.9 years (range 20–80 years). The cancers occurred predominantly in the ileum (41 cases); of the remainder, 18 cases occurred in the jejunum, one in the duodenum and ileum, and one in the ileum and colon. Eighteen cancers occurred in bypassed intestinal loops. The reported survival is shown in Table 2.

Table 1 Summary of literature review—clinical information

Authors	Case nos.	Sex	Interval from diagnosis of Crohn's to diagnosis of cancer (yr)	Age at diagnosis of cancer (yr)	Site of cancer	Bypass before cancer	Outcome
Ginzberg <i>et al.</i> 1956 ¹	1	M	19	30	Jejunum	No	Died 12/12
Kornfield <i>et al.</i> 1957 ⁴	2	F	8	36	Jejunum	No	Died 6/12
Bersac <i>et al.</i> 1958 ⁵	3	M	9	33	Duodenum/ ileum colon	No	Diagnosed at necropsy
Buchanan <i>et al.</i> 1959 ⁶	4	M	28	47	Ileum	No	Metastases at operation
Weingarten <i>et al.</i> 1959 ⁷	5	F	28	44	Jejunum	Yes	Died 3/12
Weingarten and Weiss 1960 ⁸	6	F	5	28	Jejunum	No	Died 1/12
Almond <i>et al.</i> 1960 ⁹	7	F	3	48	Ileum	No	Died 4/12
Steel and McNeely 1960 ¹⁰	8	M	14	38	Ileum	Yes	Necropsy
Zisk <i>et al.</i> 1960 ¹¹	9	F	1/52	61	Ileum	No	Died <1/12
	10	F	23	62	Ileum	Yes	Died 2 yr
Hoffert <i>et al.</i> 1963 ¹²	11	M	1	40	Ileum	No	Died 3 yr
Berman and Prior 1964 ¹³	12	M	25	51	Ileum	No	Not known
Cantwell <i>et al.</i> 1968 ¹⁴	13	M	31	60	Ileum	No	Died <1/12
Sheil <i>et al.</i> 1968 ¹⁵	14	F	5	40	Ileum	No	Metastases 16/12
Morovitz <i>et al.</i> 1968 ¹⁶	15	M	22	41	Ileum	No	Died 4/12
Magnes and DeBell 1969 ¹⁷	16	M	15	71	Ileum	No	Died 4/12
Tyers <i>et al.</i> 1969 ¹⁸	17	M	12	32	Jejunum	Yes	Died 10/52
Wyatt 1969 ¹⁹	18	M	7	33	Ileum	No	Died <1/12
Brown <i>et al.</i> 1970 ²⁰	19	F	25	55	Ileum	Yes	Died <1/12
Farmer <i>et al.</i> 1970 ²¹	20	F	7	61	Jejunum	No	Died 2/12
	21	M	9	43	Jejunum	Yes	Died 7/12
Goldman <i>et al.</i> 1970 ²²	22	F	11	21	Jejunum	Yes	Died 1/12
Shuman 1973 ²³	23	M	29	35	Ileum	Yes	Metastases
Papp and Pollard 1971 ²⁴	24	M	21	39	Jejunum	Yes	Died 1/12
Rha <i>et al.</i> 1971 ²⁵	25	M	5/12	38	Ileum	No	Died 12/12
Brun <i>et al.</i> 1971 ²⁶	26	M	29	80	Jejunum	No	Died 1/12
	27	M	16	76	Ileum	Yes	Necropsy
Ben-Asher 1971 ²⁷	28	M	5	49	Ileum	No	Necropsy
Schofield 1972 ²⁸	29	M	7	20+	Ileum	No	Died 2 yr
	30	M	4+	20	Ileum	Yes	Died few months
Beachey <i>et al.</i> 1973 ²⁹	31	M	20	51	Ileum	No	Died 8/12
	32	F	25	51	Ileum	No	Died 1/12
Darke <i>et al.</i> 1973 ³⁰	33	M	45	60	Ileum	No	Not known
Frank and Shorey 1973 ³¹	34	M	15	48	Ileum	No	Alive 3/12 post-op.
Saeed 1974 ³²	35	M	10	47	Ileum	No	Died 11/12
Crystal 1974 ³³	36	M	5/12	50	Ileum	No	Died 15/12
Savage <i>et al.</i> 1975 ³⁴	37	M	8	36	Ileum	No	Died 7/12
Lightdale <i>et al.</i> 1975 ³⁵	38	M	23	56	Ileum	No	Died 15/12
	39	M	25	53	Ileum	No	Alive 3 yr post-op.
	40	M	15	49	Ileum	No	Alive 11/12 at follow-up
Newman <i>et al.</i> 1975 ³⁶	41	M	20	67	Jejunum	No	Alive with metastatic disease
Flemming and Pollock 1975 ³⁷	42	F	1	56	Ileum	No	Alive and well 2 yr post-op.
Valdes-Dapena <i>et al.</i> 1976 ³⁸	43	M	30	48	Jejunum	Yes	Died 14/12
	44	M	20	64	Ileum	Yes	Died 3/12
	45	M	11	25	Jejunum	No	Died 1/12
	46	M	17	47	Jejunum	No	Died 10/12
Nesbit <i>et al.</i> 1976 ³⁹	47	M	35	69	Ileum	No	Died 6/12
	48	M	45	65	Ileum	Yes	Died 2/12
					+(colon)		
Burbige <i>et al.</i> 1977 ⁴⁰	49	M	20	43	Ileum	Yes	Alive at report
Westaby <i>et al.</i> 1977 ⁴¹	50	F	25	45	Jejunum	No	Alive with metastases at report
Greenstein <i>et al.</i> 1978 ⁴²	51	M	40	80	Ileum	Yes	Died 18/12
	52	F	25+	55	Ileum	Yes	Died 1/12
	53	M	32	51	Jejunum	Yes	Died
	54	M	19	40	Ileum	Yes	Died 12/12
Floch <i>et al.</i> 1978 ⁴³	55	M	32	53	Jejunum	No	Died 7/12
Maesgaard <i>et al.</i> 1979 ⁴⁴	56	M	5	64	Ileum	No	Alive 15/12
Smith <i>et al.</i> 1980 ⁴⁵	57	M	10	44	Ileum	No	Metastases
Heathcote <i>et al.</i> 1980 ⁴⁶	58	F	11½	33	Ileum	No	Alive 18/12 post-op.
Present series 1981	59	M	8	24	Jejunum	No	Died 3/12
1981	60	M	9	69	Ileum	No	Died 1/12
1981	61	F	6	51	Jejunum	No	Alive

Fig. 3 Case 3. (a) Histology showing papillary adenocarcinoma. Haematoxylin and eosin. (b) Histology showing severe intestinal dysplasia. Haematoxylin and eosin.

Table 2 Data from reported cases

Total number of cases	61 (Male 45, Female 16)
Mean duration of Crohn's disease	18.2 yr (1/52–45 yr)
Mean age at diagnosis of cancer	46.9 yr (20–80 yr)
Site of tumour	
Jejunum	18 (30%)
Ileum	41 (67%)
Other	2 (3%)
Tumours in bypassed loops:	
Jejunal	6
Ileal	12
Outcome	
Dead	44 Mean survival 7.9 mth (1/7–3 yr)
Alive with metastatic disease	7
Alive and well without recorded metastases at follow-up	8 Mean interval 16 mth (3/12–3 yr)
Not known	2

The prognosis was poor. The mean interval between diagnosis of cancer and death was 7.9 months. No five year survivors have been reported.

Discussion

Small bowel carcinoma is a rare condition in the general population with an incidence of approximately 0.3/100,000 population/year.^{49 50} Crohn's disease is also uncommon, incidence 0.8 to 3.7/100,000 population/year,⁵¹ so that hospital series tend to be small in size (200–500 cases).^{2 3 15 30 52} It follows that, even in a large hospital series under long-term review, the number of observed cases of small bowel cancer will be insufficient to allow any definite statistical conclusions to be drawn as to the cancer risk.

In a study from this unit of 513 patients under long-term review between 1944 and 1976³ only one patient

with small bowel cancer was identified (case 1 of the present series). The other two reported cases were identified after the closing date for the statistical analysis. They would, however, not be eligible for inclusion in any future analysis, as they first presented to the unit with cancer complicating Crohn's disease. This constitutes selection for cancer, as the symptoms of cancer were the reason for referral.

A policy of surgical resection for persistent symptoms will further reduce the apparent cancer risk in the small intestine and prevent any statistical proof of an association between Crohn's disease and small bowel cancer. Moreover, the cancers that do occur are often small and can readily be overlooked unless a detailed histological search is made.

The different distribution of small bowel cancer in Crohn's disease, however, when compared with the general population supports the concept of an association. In Crohn's disease 67% of the small bowel cancers occur in the ileum, compared with 20.5%⁵³–30.5%⁵⁴ in the general population. The distribution of cancer of the colon in Crohn's disease also differs from the general population. In Crohn's disease the cancers are found predominantly in the right side of the colon, compared with the sigmoid colon and rectum in the general population.

Eight examples of multifocal cancers of the small intestine have been reported and dysplastic changes in the surrounding mucosa have been observed in 12 cases, lending additional support to the association between Crohn's disease and cancer.

Greenstein *et al.*⁴² described examples of small bowel cancer occurring in bypassed loops, suggesting that the risk of developing cancer is increased if macroscopically involved segments are left *in situ* for many years.

The prognosis of patients with small bowel cancer in Crohn's disease is poor, possibly because most tumours are diagnosed only at a late symptomatic stage. In the published reports 72% of cases were dead (mean survival 7.9 months from diagnosis of cancer). Only 15 patients were alive with an interval since diagnosis of cancer of 16 months. No five year survivors have been reported.

The possibility of malignant change in the small intestine should be considered in those few patients with longstanding macroscopic Crohn's disease, who develop recurrent symptoms after a prolonged period without symptoms.

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