*Gut*, 1980, **21**, 1010–1016

*Case reports*

# Adenocarcinoma of the upper small bowel complicating coeliac disease

G K T HOLMES,* G I DUNN, R COCKEL, AND V S BROOKES

*From the Derbyshire Royal Infirmary, Derby, Selly Oak Hospital, Birmingham and Queen Elizabeth Hospital, Birmingham*

SUMMARY Adenocarcinoma of the small intestine complicating coeliac disease is uncommon. Only 14 cases have been reported, and in only one of these was a jejunal biopsy carried out more than eight months before the diagnosis of malignancy. We describe four more patients with this association, all with long histories of coeliac disease, confirmed in three by jejunal biopsy over five years before the diagnosis of malignancy. Important presenting features of carcinoma were abdominal pain, anaemia, occult gastrointestinal bleeding, abdominal mass, and intestinal obstruction, and these were the main indications for operation. After resection of the tumour survival may be prolonged, as evidenced by one of our cases who remains well eight years after surgery.

An increased incidence of malignancy, usually in the form of lymphoma, has been observed in coeliac disease.[1] However, certain gastrointestinal carcinomas, notably those of the oesophagus and pharynx, have been found more commonly among coeliacs than in the general population.[1 2] It is perhaps surprising that there are so few reports of carcinoma occurring in the jejunum in coeliac disease, as this part of the bowel is characteristically abnormal in untreated patients and may show histological features of premalignancy.[3]

This paper (1) presents four new cases of this unusual association gathered from different clinics in Derby and Birmingham, (2) reviews the 14 patients previously reported, and (3) extracts those clinical features and investigations helpful in making the diagnosis of small bowel carcinoma in coeliac disease.

## Present series

Brief case histories of the four patients are set out below, and important details are summarised in Table 1.

CASE A

A young woman presented in her late 20s with steatorrhoea. She was treated with a low fat diet and remained symptom free on this regime until 1967, when at the age of 58 years she developed vomiting, flatulence, abdominal distension, and weight loss. She was anaemic with a haemoglobin of 9·9 g/dl. and had a faecal fat of 48 mmol/24 h. Jejunal biopsy was consistent with coeliac disease and she responded clinically to a gluten free diet.

She presented again in 1972, while still on a gluten free diet, with a three year history of flatulence, vomiting, and weight loss, and more recently colicky abdominal pain. A mass was palpable in the left upper quadrant and the haemoglobin was 8·6 g/dl. A barium follow-through examination showed obstruction of the upper small bowel. At laparotomy an obstructing tumour 12 cm below the duodenojejunal flexure was resected, along with an 18 cm segment of bowel. Histology revealed a primary adenocarcinoma of the jejunum with flat mucosa throughout the length of the resected specimen. No metastases were evident. The patient made a good postoperative recovery and remains well eight years later on a gluten free diet.

CASE B

A man first seen in 1964 at the age of 52 years with a 12 month history of rectal bleeding, was found to have stage 3 haemorrhoids and a haemoglobin of 6·9 g/dl. Barium meal and barium enema were

*Address for correspondence and reprints: Dr G K T Holmes, Derbyshire Royal Infirmary, London Road, Derby.

Received for publication 10 June 1980

Table 1 *Clinical details*

| *Case* | *Age (yr) and sex* | *Length of symptoms attributed to:* | | *Hb g/dl ing* | *GI bleed-* | *Ba FT* | *Jb* | *Jej hist at op.* | *GFD* | *Indications for op.* | *Site of tumour* | *Metastases* | *Outcome* | *Reference no.* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *malab-sorption (yr)* | *malig-nancy (m)* | | | | | | | | | | | |
| A | 68F | 40 | 24 | 8·6 | — | Obstruction below D-J flexure | Flat | Flat | 5 yr before op. responded | Intestinal obstruction, abdominal mass | 12 cm below D-J flexure | No | Well 7 yr after op. | Present series |
| B | 63M | 9 | 4d | 11·9 | — | Not done | Flat | PVA | 6 yr responded | Intestinal obstruction, abdominal mass | 10 cm below D-J flexure | Yes | Died 6 m after op. | Present series |
| C | 63M | 12 | 3 | 8·7 | — | — | Flat | Flat | GFD+ steroids. 10 yr responded | Abdominal mass | 15 cm below D-J flexure | No | Died 12 d after op. | Present series |
| D | 49F | 24 | 16 | 11·4 | — | Lesion second part of duodenum | Flat (duodenal) | Flat | Transient improvement | X-ray appearances | 2nd part of duodenum | Yes | Died 6 m after op. | Present series |
| 1 | 60M | 11 | 8 | 8·0 | Yes | Jejunal narrowing | No | Flat | No | Jejunal narrowing and GI bleeding | Prox. jejunum | Yes | — | 6 |
| 2 | 72M | 7m | 2 | 14·9 | No | Obstruction prox. jejunum | No | Flat | No | Intestinal obstruction | 144 cm below ligament of Treitz | No | Well 2 m after op. | 3 |
| 3 | 57M | — | — | — | — | — | — | Flat | — | Intestinal obstruction | Lower jejunum | — | — | 7 |
| 4 | 50M | 13m | 13 | — | No | Normal 5 m before operation | Flat | Abnormal villi | — | Intestinal obstruction | 70 cm below D-J flexure | Yes | — | 8 |
| 5 | 68M | 9 | 18 | 8·1 | Yes | Malabsorption pattern 5 m before operation | — | Flat | No | GI bleeding | Mid jejunum | No | — | 9 |
| 6 | 49F | 29 | 2 | — | — | Malabsorption pattern 2½ yr before operation | Flat | Flat | 4 yr before op. improved | Abdominal mass | Lower jejunumm | Yes | Well 9 m after after op. | 5 |
| 7 | 50M | 20m | 20 | 7 | Yes | Malabsorption pattern 20 m before operation | No | PVA | For 1 yr before op. some improvement | Abdominal pain | 10 cm below D-J flexure | No | Well 4 yr after op. | 10 |
| 8 | 65M | 8 | 5 | 11·1 | Yes | Neoplasm of jejunum | PVA | PVA | — | X-ray appearances | 8 cm below D-J flexure | Yes | Inoperable tumour. Died after palliative surgery | 10 |

Table 1 *Clinical details—continued*

| Case | Age (yr) and sex | Length of symptoms attributed to: Malabsorption (yr) | Length of symptoms attributed to: Malignancy (m) | Hb g/dl | GI bleeding | BaFT | Jb | Jej hist at op. | GFD | Indications for op. | Site of tumour | Metastases | Outcome | Reference no. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9 | 72F | 37 | 12 | — | — | Stricture upper jejunum | — | Flat | For 7 yr before operation improved | Obstructive features | 10 cm distal to D-J flexure | — | Well 2 yr after op. | 10 |
| 10 | 53M | — | 60 | — | — | — | — | Flat | — | Intestinal obstruction | Jejunum | — | — | 11 |
| 11 | 66M | 2 | 24 | 8·9 | Yes | Lesion in jejunum | Flat | Flat | 6 m responded only after surgery | X-ray appearances | Mid-jejunum | No | Well 3 m after op. | 12 |
| 12 | 37M | 7 | 5 | 10·4 | Yes | Dilated proximal jejunum | Flat | PVA | 7 yr before operation responded | X-ray appearances malignancy suspected | Just below D-J flexure | No | Well 2 yr after op. | 4 |
| 13 | 65M | 30 | 4 | 10 | Yes | Dilated loops of small bowel | Flat | — | 13 yr responded | No operation | 110 cm below ligament of Treitz | No | Died | 13 |
| 14 | 74M | 15m | 15 | 9·4 | Yes | Malabsorption pattern 3 m before operation | Flat | Flat | 2 m responded only after-surgery | GI bleeding from jejunal biopsy site | Proximal jejunum | No | Well 2 m after op. | 14 |

—, inadequate or no information provided; GFD, gluten free diet; JB, jejunal biopsy; PVA, partial villous atrophy
Information on four new cases A to D and 14 previously reported patients
1–14 with adenocarcinomas of the small bowel complicating coeliac disease.

normal at this time. He refused haemorrhoidectomy and after conservative management in hospital was discharged on iron. Two years later after another episode of rectal bleeding, his haemoglobin was 6·6 g/dl, but he also complained of 10 kg weight loss and episodes of diarrhoea during the preceding year. A barium follow-through showed appearances suggestive of malabsorption, and a jejunal biopsy confirmed the diagnosis of coeliac disease. He responded clinically to a gluten free diet. He did not attend for follow-up, but it is known that he remained well on a gluten free diet for six years, after which he reverted to a normal diet. He was next seen in April 1974 at the age of 62 years, when he underwent haemorrhoidectomy for severe prolapsed piles and presented again in September 1974 with frequent vomiting and a left-sided abdominal mass, which he himself had noticed. Laparotomy was performed and a jejunal tumour 10 cm from the duodenojejunal flexure was resected, which proved to be a primary adenocarcinoma. Metastases were found in lymph nodes and the peritoneal cavity. After operation he deteriorated and died six months later.

CASE C

A man presented at the age of 53 years with diarrhoea, muscle cramps, weight loss, and anorexia for 18 months. On examination he was pale with finger clubbing. Investigations showed anaemia, with a low serum folate and a megaloblastic marrow. Barium follow-through showed appearances of malabsorption and a jejunal biopsy was flat. He was started on a gluten free diet with vitamin supplements, but one month later still felt unwell and oral steroids were started after which his haemoglobin rose to 14 g/dl and he became symptom free. He lived in lodgings and had problems in adhering to a gluten free diet, requiring admission on several occasions for restabilisation, and each time responded quickly to gluten withdrawal and steroid therapy. In 1975 at the age of 63 years he became ill with weight loss and abdominal pain. On examination he had a right-sided abdominal mass and was

found to be anaemic. Laparotomy revealed a tumour 15 cm distal to the duodenojejunal flexure, which was an adenocarcinoma. No secondaries were found, but after operation he deteriorated and died 12 days later.

CASE D

This woman had been anaemic with haemoglobin as low as 8·4 g/dl during pregnancies in 1952 and 1954, for which she received iron and folate supplements. On admission with pneumonia in 1959 she was again anaemic, and improved only slightly on iron. In 1964 at the age of 36 years she was seen with a five year history of painful mouth ulceration and a shorter period of vague gastrointestinal symptoms, such as mild nausea and flatulence. On examination she was of small stature and had a smooth tongue. Investigations showed haemoglobin of 10·9 g/dl, a low serum folate of 1·7 ng/ml, but faecal fat excretion was normal and a jejunal biopsy was not performed. Folate supplements improved her mouth ulcers dramatically, and she did not attend for follow-up.

In May 1976 she complained of poor energy, muscle cramps, weight loss, and pale bulky stools which were difficult to flush away. She was found to be anaemic and steatorrhoea of 108 mmol/24 h was demonstrated. She could not be persuaded to swallow a Crosby capsule, but biopsy was obtained endoscopically from the duodenum. The mucosal appearances were characteristic of coeliac disease. Other abnormal features were a bilirubin of 40 μmol/l, a raised alkaline phosphatase, and raised transaminases. She was allowed home on a gluten free diet and appeared to respond, as at outpatients, one month later, bowel symptoms had improved, she was more energetic, and liver function tests were improved.

However, after another four weeks she again became unwell with deepening jaundice. A barium follow-through revealed a filling defect in the second part of the duodenum and on repeat endoscopy a lesion was seen, which had obviously been missed on the previous examination, which biopsy showed to be an adenocarcinoma. Laparotomy was performed and the tumour resected, but there were liver secondaries, and lymph nodes were involved. She deteriorated postoperatively and died six months later.

In summary, all had long histories of malabsorption ranging from nine to 40 years. Histological evidence of coeliac disease was obtained in three patients (cases A, B, and C) at least five years before the diagnosis of carcinoma. With regard to a gluten free diet, patients A and B responded satisfactorily for some years, patient D appeared to experience a transient improvement in symptoms, while patient C responded to gluten withdrawal and steroids. None of these patients had repeat jejunal biopsies performed while they were taking a gluten free diet.

## Review of reported cases

The 14 cases previously reported are reviewed in Table 1, 12 were male and two female, with an age range at the presentation of malignancy from 37 to 74 years (mean 60 years). Seven had long histories of malabsorption ranging from seven to 30 years, well before symptoms attributable to malignancy arose, while five had shorter histories of two years or less. In this latter group there was no history suggestive of coeliac disease before the development of symptoms attributable to malignancy in four of the patients, but three of these had biochemical evidence of malabsorption at presentation.

Histological evidence of coeliac disease was obtained by peroral jejunal biopsy before the diagnosis of carcinoma in only six patients in the series. These specimens were obtained at a maximum of eight months before the diagnosis of malignancy, with one exception where a biopsy was done seven years before a carcinoma became evident.[4] In one patient a characteristic flat biopsy was obtained after resection of the tumour.[5] In the majority of patients histological diagnosis was made on specimens of small bowel resected at operation and case reports comment that these were flat throughout their length, or at sites well removed from the tumour.

FEATURES AT PRESENTATION

An analysis of presentation in the 14 reported cases together with our own four patients is shown in Table 2. Anaemia occurred in 12 patients and was often associated with occult gastrointestinal blood loss. Intestinal obstruction was a common presentation and an abdominal mass was found in four individuals.

In investigating these cases, nine barium follow-through examinations were performed, all of which were helpful in leading to the diagnosis of malignancy. In eight the lesion itself was seen as a constant

Table 2 *Numbers of patients with various presentations*

| *Presentation* | *No. of patients* |
|---|---|
| Anorexia | 7 |
| Vomiting | 10 |
| Diarrhoea | 4 |
| Weight loss | 11 |
| Abdominal pain | 5 |
| Anaemia | 12 |
| Intestinal obstruction | 7 |
| Abdominal mass | 4 |
| GI blood loss | 8 |

narrowing of the small bowel and, in one, dilated loops suggesting intestinal obstruction were present.

INDICATIONS FOR OPERATION

Of the 18 patients, 17 came to surgery. Intestinal obstruction and abdominal masses were the indications for operation in the majority, while gastrointestinal haemorrhage, abdominal pain, and radiographic appearances accounted for the remainder.

## Discussion

While malignancy not uncommonly complicates coeliac disease[1 15], it is surprising that the mucosa of the upper small bowel, which is severely abnormal in untreated patients and with histological features of premalignancy,[3 5] should so rarely be the site of carcinoma. In a review of malignancy occurring among a large series of patients with coeliac disease reported from one unit and followed for many years, no examples of small intestinal carcinoma were encountered.[1] However, whether those cases which have been reported represent a significant increase over the very small numbers expected to arise in the general population is at present undetermined.

In the general population the incidence of small bowel cancer is low in contrast with the stomach and colon. Several explanations have been put forward. It has been suggested that the mucosa of the small bowel may be less exposed to carcinogens than elsewhere in the gut because of the fluid nature of the intestinal contents and rapid small intestinal transit.[16] Other factors of importance may be the relative sterility of this part of the bowel and possibly protective immunological mechanisms.[17] These factors may also be important in protecting the jejunal mucosa in coeliac disease, and, in addition, the increased turnover of the epithelial cells which occurs may be advantageous by rapidly eliminating malignant or potentially malignant cells before they become established. From the literature survey only patients with histological evidence of coeliac disease have been considered.[18] A patient with long-standing steatorrhoea who developed an adenocarcinoma at the duodenojejunal flexure has been reported,[19] was almost certainly a coeliac, but, as there was no histological confirmation of the diagnosis, he has not been included in Table 1. A carcinoma of the ileum has also been reported,[8] but has been dismissed because only the upper small bowel is considered here.

Consideration must be given to those patients without histories of malabsorption, or with only short histories before the diagnosis of malignancy. Should such patients be accepted as coeliacs with complicating carcinoma, or is malignancy responsible for the histological change in the jejunal mucosa? Absence of a history consistent with coeliac disease does not invalidate the diagnosis, as it is well established from family studies that asymptomatic patients with a flat mucosa do occur.[20] Biopsy studies in malignant conditions do not lend any support to the view that cancer produces a flat mucosa.[21–23] Furthermore, malignancy may arise in patients in histological remission after gluten withdrawal without the mucosal appearances deteriorating.[24] While it may be argued that mucosal distortion might occur in the immediate vicinity of the tumour, most case reports comment that in resected specimens the mucosa was flat in areas remote from the growth. Thus, there are strong grounds for accepting these patients as coeliacs whose disease has been complicated by malignancy. There can be less controversy over patients with long histories of malabsorption, especially those who had biopsies several years before malignancy was diagnosed, which applied to three of our new cases. Follow-up jejunal biopsies were not obtained from our patients after gluten withdrawal. Histological appearances during treatment with a gluten free diet would have been of considerable interest, but in the absence of this information we still regard our patients as having coeliac disease as defined by Cooke and Asquith (1974).[18]

The onset of malignancy may be the event which precipitates the diagnosis of coeliac disease as in our case D. These individuals may show some initial response to gluten withdrawal, but this is short lived and such patients need urgent reappraisal. Coeliac patients who relapse for no apparent reason while on a gluten free diet also need careful assessment. The usual explanation is dietary indiscretion either by accident, or design. A more sinister reason is the development of malignancy, which may be difficult to diagnose early, while potentially treatable, as many of the initial features such as anorexia, weight loss, diarrhoea, and vomiting are non-specific and are commonly found in those who have broken diet. Another problem is that by the time many patients present, malignancy is widespread, making the outlook poor. It is noteworthy that, in this series of 18 patients, 14 (78%) were men, whereas coeliac disease is slightly more common among females. The significance of this finding is unclear.

Some helpful pointers to the diagnosis have emerged from this study. Anaemia is often marked and in some patients gastrointestinal blood loss appears to be the major contributing factor. Bleeding presumably occurs from the tumour itself. It is clearly useful to test for blood in the stools of all patients suspected

of the diagnosis. The presence of an abdominal mass suggests carcinoma rather than lymphoma, as in one group of coeliac patients who had developed lymphoma, none had a palpable abdominal mass.[25] The profound muscle weakness which commonly accompanies the lymphoma complication[25] was not prominent among the present series.

Barium studies were most valuable in detecting a lesion in this study, which is in contrast with lymphomatous involvement of the gut where radiology is often unreliable.[15]

While the outlook for coeliac patients who develop small intestinal lymphoma is very poor, if a carcinoma is diagnosed early and the tumour has not metastasised, survival may be prolonged, as in one of our patients who is well eight years after resection.

**References**


[1]Holmes GKT, Stokes PL, Sorahan TM, Prior P, Waterhouse JAH, Cooke WT. Coeliac disease, gluten free diet and malignancy. *Gut* 1976; **17:** 612–9.

[2]Harris OD, Cooke WT, Thompson H, Waterhouse JAH. Malignancy in adult coeliac disease and idiopathic steatorrhoea. *Am J Med* 1967; **42:** 899–912.

[3]Joske RA. Primary carcinoma of the jejunum with atrophic jejunitis and intestinal malabsorption. *Gastroenterology* 1960; **38:** 810–6.

[4]Kenwright S. Coeliac disease and small bowel carcinoma. *Postgrad Med J* 1972; **48:** 673–7.

[5]Fric P, Bednar B, Niederie B, Lepsik J. Jejunal adenocarcinoma in a woman with non-tropical sprue *Gastroenterology* 1963; **44:** 330–4.

[6]Case records of the Massachusetts General Hospital. *N Engl J Med* 1958; **259:** 491–5.

[7]Blackwell JB. Two cases of carcinoma of the small bowel with malabsorption. *Gut* 1961; **2:** 377.

[8]Girdwood RH, Delamore IW, Williams AW. Jejunal biopsy in malabsorption disorder of the adult. *Br Med J* 1961; **1:** 319–23.

[9]Moertel CG, Hargraves MM. Coexistence of adenocarcinoma of the jejunum and non-tropical sprue. *JAMA* 1961; **176:** 612–4.

[10]Brzechwa-Ajdukiewicz A, McCarthy CF, Austad W, Cornes J, Harrison WJ, Read A. Carcinoma, villous atrophy and steatorrhoea. *Gut* 1966; **7:** 572–7.

[11]Lee FD. Nature of the mucosal changes associated with malignant neoplasms in the small intestine. *Gut* 1966; **7:** 361–7.

[12]Asch T, Seaman WB. Idiopathic steatorrhoea and small bowel cancer. *Radiology* 1971; **100:** 217–5.

[13]Petreshock EP, Pessah M. Adenocarcinoma of the jejunum associated with tropical sprue. *Dig Diseases* 1975; **20:** 796–802.

[14]Collins SM, Hamilton JD, Lewis TD, Laufer I. Small bowel malabsorption and gastrointestinal malignancy. *Radiology* 1978; **126:** 603–9.

[15]Cooper BT, Holmes GKT, Ferguson R, Cooke WT. Malignancy in coeliac disease. *Med Balt* 1980; In press.

[16]Lowenfels AB. Why are small bowel tumours so rare? *Lancet* 1973; **1:** 24–6.

[17]Calman KC. Why are small bowel tumours rare? An experimental model. *Gut* 1974; **15:** 552–4.

[18]Cooke WT, Asquith P. *Clin gastroenterol* 1974; **3:** 1–10.

[19]Ogilvie TA, Shaw HM. Primary tumours of the small bowel. *Br Med J* 1955; **1:** 142–5.

[20]Stokes PL, Ferguson R, Holmes GKT, Cooke WT. Familial aspects of coeliac disease. *Quart J Med* 1976; **45:** 567–82.

[21]Girdwood RH. Malignancy and the small intestinal mucosa. *Br Med J* 1964; **2:** 1592.

[22]Fu YS, Perzin KH. Lymphosarcoma of the small intestine: a clinicopathologic study. *Cancer* 1972 **29:** 645–59.

[23]Gilat T, Fishel B, Danon J, Loewenthal M. Morphology of the small bowel mucosa in malignancy. *Digestion* 1973; **7:** 147–55.

[24]Cooke WT, Thompson H, Williams JA. Malignancy and adult coeliac disease. *Gut* 1969; **10:** 108–11.

[25]Holmes GKT, Cooper BT, Cooke WT. Malignant lymphoma in coeliac disease. In: McNicholl B, McCarthy CF, Fottrell PF, eds. *Perspectives in coeliac disease.* (1978); 301–8.