Carcinoma, villous atrophy, and steatorrhoea


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EDITORIAL SYNOPSIS  There appears to be an increased incidence of carcinoma of the fore and mid gut in patients with villous atrophy of the small intestine.

Intestinal reticulosis may arise as a complication of idiopathic steatorrhoea (Gough, Read, and Naish, 1962). Creamer (1964) has suggested that malignancy anywhere in the body may be accompanied by villous atrophy of the small intestinal mucosa. In this paper, seven patients with steatorrhoea and accompanying carcinoma are presented and the possible reasons for this association are discussed.

CASE REPORTS

CASE 1 A man aged 50 years was in good health until April 1961, when he complained of pain in the right buttock and was treated with phenylbutazone. He afterwards developed watery diarrhoea, passing six to 10 motions daily, which lasted a fortnight. Subsequently his bowels opened four times a day and the stools were clay coloured and offensive. His appetite was good. Apart from pallor, physical examination was normal.

Investigations showed that haemoglobin was 47% with evidence of iron deficiency. A small intestinal barium meal showed the features of steatorrhoea. Faecal fat was 90 g. in three days. Xylose absorption was normal. A glucose tolerance test (50 g.) produced a rise of 40 mg./100 ml. The patient refused to have a jejunal biopsy.

He was followed up in the Out-patient Department and the iron-deficiency anaemia was treated with oral and parenteral iron. When a gluten-free diet was prescribed his weight increased by 8 lb. and a subsequent three-day faecal fat estimation was 26 g. As anaemia persisted in spite of treatment, he was admitted for transfusion during the summer of 1962. A 51Cr-labelled red cell study was carried out and showed an average daily blood loss of 39-4 ml. Faecal fat was 23-9 g. in three days.

In December 1962 he was admitted as an emergency because of upper abdominal pain, and after a blood transfusion a laparotomy was carried out, at which an ulcerated annular tumour was found 10 cm. below the duodeno-jejunal flexure. The tumour and 15 cm. of jejunum were resected. Histological examination showed the tumour to be an adenocarcinoma with no lymph node metastases. The jejunum showed partial villous atrophy.

He has been in good health since the operation with bowels opening once a day. Haemoglobin has risen to 97%.

CASE 2 A man, aged 70 years at the time of death, had had attacks of diarrhoea and lower abdominal pain since 1946. Idiopathic steatorrhoea and megaloblastic anaemia were diagnosed in 1954. He was treated with a gluten-free diet and improved. He was admitted again in 1960 because of diarrhoea and weight loss. On examination he was small, wasted, and pale. Clubbing was present as were abdominal distension and dorsal kyphosis.

Investigations revealed 36 g. of fat in a 24-hour stool collection and only 1·7 g. of 25 g. of d-xylene was excreted in the urine in five hours. A glucose tolerance test revealed a maximum rise of 10 mg./100 ml. A jejunal biopsy showed subtotal villous atrophy. Serum albumin was 2·2 g./100 ml. and serum y globulin 2·2 g./100 ml. Serum calcium, magnesium, and potassium levels were low. A macrocytic anaemia (Hb 85%) with megaloblastic marrow was present.

He was treated with a gluten-free diet, potassium and magnesium supplements, folic acid, and calciferol. He improved slightly but developed attacks of 'bronchospasm'. This was followed by haemophilus influenzae pneumonia. In spite of treatment with antibiotics and antispasmodics, he deteriorated and died.

Post-mortem examination revealed a carcinoma of the trachea with local lymph node involvement. Histological examination of the jejunum showed subtotal villous atrophy.

CASE 3 A 46-year-old woman had noticed attacks of diarrhoea with greasy stools from the age of 20 years, and from time to time she had been run down and tired. In 1961 she presented with tiredness and weakness, and was found to be pale, thin, and pigmented. The tongue was smooth and the tip of the spleen was palpable. Investigations showed a haemoglobin of 64% with low serum folate and iron levels. The bone marrow was megaloblastic. A 50 g. glucose tolerance test produced a maximum rise of 40 mg. and xylose absorption was low. The level of plasma phosphate was low and that of alkaline

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phosphatase was raised. Skeletal survey showed thin bones, and a bone biopsy wide osteoid seams. Faecal fat excretion was normal and a barium follow-through examination was consistent with steatorrhea. A jejunal biopsy showed subtotal villous atrophy.

A diagnosis of idiopathic steatorrhea was made and she was treated with a high-protein, low-fat diet, folic acid, calciferol, and calcium gluconate. She improved and her weight increased by 13 kg. in six months. She remained well until 1963 when she complained of dysphagia. An extensive carcinoma of the pharynx was found and treated by radiotherapy.

CASE 4 A woman aged 45 years at the time of death had had intermittent diarrhoea for 10 years, and macrocytic anaemia and recurrent attacks of tetany necessitated several admissions to hospital during these years. Idiopathic steatorrhea was diagnosed in 1944. On examination then she was thin and pale. The tongue was smooth and the neck pigmented. Trouseau's and Chvostek's signs were positive. Investigations revealed 'increased' faecal fat and a macrocytaemia (Hb 57%). Radiographs of the bones showed thinning. She was treated with a gluten-free diet and improved.

In 1948 she presented with a six months' history of dysphagia associated with retrosternal pain, and a barium meal examination showed a carcinoma of the oesophagus. This was confirmed by oesophagoscopy and shown to be a squamous cell carcinoma by biopsy. The neoplasm was removed surgically. Afterwards haemorrhage occurred from the site of the resection. She was transfused, but her condition deteriorated and she died.

Post-mortem examination showed that the carcinoma of the oesophagus had metastasized to local lymph nodes. Autolysis of the intestinal mucosa prevented adequate histological examination.

CASE 5 A 54-year-old man had diarrhoea, with pale, greasy stools for two years. He also complained of fatigue, malaise, weight loss, and sore tongue for one year. On examination he was thin, pale, and pigmented, his tongue was smooth, and finger clubbing was present. Investigations revealed a haemoglobin of 86% with macrocytic red cells. A fat balance showed steatorrhea and the glucose tolerance curve was flat. Following oral doses of vitamin A, the five-hour blood level was unchanged. The albumin was 3.5 g./100 ml and total globulin 4.2 g./100 ml. Radiographs of the skeleton showed thin bones and a barium follow-through examination was consistent with steatorrhea. He was treated with folic acid, vitamin B₁₂, and cortisone; marked clinical improvement followed, with an increase in weight of 8 kg. over two years. In 1959 he was well but noted that eating too much bread caused a return of diarrhoea. Haemoglobin was now 16.8 g./100 ml., albumin 4.3 g./100 ml., and total globulin 2.6 g./100 ml. Intestinal biopsy showed subtotal villous atrophy and a glucose tolerance test now produced a rise of 50 mg./100 ml.

He remained well until January 1964, when difficulty in swallowing associated with retrosternal pain developed, together with a dry, hacking cough and attacks of hiccoughs after meals. His weight fell by 7-5 kg. On examination he looked ill, pale, and wasted. Haemoglobin was 14.4 g./100 ml. A barium swallow revealed a neoplasm of the middle third of the oesophagus, which was resected and the oesophagus re-anastomosed. Histological examination showed a poorly differentiated adenocarcinoma, with invasion of veins and nerves. Towards the end of the year the patient deteriorated with breathlessness on slight exertion, cough, and anorexia. On examination he was emaciated, and a large left pleural effusion was present. He grew worse and died. Necropsy showed widespread metastases.

CASE 6 A man aged 65 years had suffered from attacks of vomiting and diarrhoea for eight years. During these attacks the stools were difficult to flush away. The diarrhoea subsided during the last four years. He said that as a child he was often unwell with diarrhoea and vomiting, and was much smaller than his school mates but at 13 or 14 years of age, he improved and grew to a normal height. He had had eczema for several years. During the last five months he had suffered from dull epigastric pain.

On examination he had obviously lost weight. The rest of the examination contributed nothing. Investigations revealed a faecal fat level of 9.5 g./day, and glucose tolerance test showed a maximal rise of only 20 mg./100 ml. Barium follow-through examination showed a pattern of malabsorption, a neoplasm of the jejunum, and a few diverticula. The haemoglobin was 11.1 g./%, and the E.S.R. 43 mm. in the first hour. The blood film showed evidence of iron deficiency and the serum iron level was low. Occult blood was present in the stool. The level of serum vitamin B₁₂, serum folate, and the bone marrow were normal. Electrophoresis of proteins gave: albumin 2.9 g./100 ml. and γ globulin 2.0 g./100 ml. A jejunal biopsy showed partial villous atrophy (Fig. 1).

At laparotomy an inoperable neoplasm was found 3 ft. from the duodeno-jejunal flexure and a side-to-side anastomosis was carried out. Histological examination of the tumour showed it to be an adenocarcinoma. Biopsy of the jejunum 2 ft. distal to the tumour showed partial villous atrophy and biopsy of the ileum was normal (Figs. 2 and 3).

After the operation the abdominal pain became worse and did not respond to analgesics. In an attempt to relieve pain, Geiger probes were inserted into the tumour and radiotherapy was given relating the tumour activity (³²P) to the time of radiation therapy (Hale, 1961). The patient's general condition deteriorated and he died.

Post-mortem examination was not carried out.

CASE 7 A 72-year-old woman presented in 1957 with a history of intermittent diarrhoea for 30 years. During the previous 10 months this had been worse and the stools were like putty. She also noticed stiffness and cramps in her arms and legs. At about this time unspecified haematinics were prescribed for a 'macrocytic anaemia'. Physical examination was normal. Investigations showed 57 g. of fat in 100 g. dried faeces. The level of serum calcium was low and that of alkaline phosphatase was raised. A barium follow-through examination showed dilatation, a coarse mucosal pattern, and flocculation of barium. A diagnosis of idiopathic steatorrhea was made.
FIG. 1. Jejunal mucosa showing partial villous atrophy.

FIG. 2. Dissecting microscope photograph of the jejunum showing cobblestone appearance.

FIG. 3. Dissecting microscope photograph of normal ileum.
and she was treated with a gluten-free diet, folic acid, calcium gluconate, and A.T.10. There was marked improvement.

During 1958 the patient relapsed with loss of weight, anorexia, and oedema. Serum albumin was 1·9 g.%. She improved following intravenous infusion of albumin, but another relapse occurred in 1964 with weight loss, colicky lower abdominal pain, and nausea and vomiting after meals. A barium follow-through examination showed a persistent stricture in the upper jejunum, which at laparotomy was resected and proved to be an adenocarcinoma 10 cm. distal to the duodeno-jejunal flexure. The jejunum, above and below the tumour, showed subtotal villous atrophy. Following the operation the patient made a satisfactory recovery and has remained well.

DISCUSSION

In reviewing the literature on the association of carcinoma and steatorrhoea, it is difficult to separate patients with well-documented idiopathic steatorrhoea who later develop a carcinoma from those who have steatorrhoea and villous atrophy, which may be attributed to the presence of the carcinoma. An attempt to do this has been made based mainly on the duration of steatorrhoea in the two groups (Tables I and II).

Joske (1960) first drew attention to the association of carcinoma of the small intestine and partial villous atrophy. He described a man of 72 years who had an adenocarcinoma of the jejunum, atrophic jejunitis, and malabsorption, which persisted after removal of the tumour. This man was also described by Blackwell (1961) who added the report of a man of 57 years who had an anaplastic carcinoma of the jejunum, subtotal villous atrophy, and malabsorption. In his report he mentions 12 other cases of carcinoma of the small intestine, but only two of these had 'mild changes of atrophic jejunitis', and none had steatorrhoea. Girdwood, Delamore, and Williams (1961), in their article on jejunal biopsy in malabsorptive disorder, describe a man of 48 years who had a five-month history of diarrhoea. Malabsorption of fat, carbohydrate, and folic acid was demonstrated. At laparotomy for intestinal obstruction two years later, an adenocarcinoma of the ileum was resected, and jejunal biopsy several months later showed partial villous atrophy. Lee (1966) reports a man of 53 years without a history of malabsorption, who had an adenocarcinoma of the jejunum and subtotal villous atrophy.

Villous atrophy is not now considered to be diagnostic of idiopathic steatorrhoea, as it has been observed in other conditions. Creamer (1964) suggested that malignancy anywhere in the body may be accompanied by villous atrophy. Townley, Cass, and Anderson (1964) presented evidence suggesting that villous atrophy is a non-specific response of the small intestine to injury.

The cause of the steatorrhoea associated with neoplasms of the small intestine is not known. Obviously an important factor may be the villous atrophy which could disrupt the normal mechanisms of absorption with the production of steatorrhoea. Villous atrophy is not necessarily localized to that part of the small intestine bearing the carcinoma, and in some cases the severity of the villous atrophy is greatest in the jejunum although the ileum may be normal.

Turner and Williams (1962) describe a man with a carcinoma of the bronchus, steatorrhoea, and

<table>
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Small intestine

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1Refers to the number of male patients reported by these authors.

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hyponatraemia. At laparotomy, following an 18-hour fast pre-operatively, the mesenteric lacteals were engorged. A jejunal biopsy showed submucosal oedema only and at necropsy there was considerable oedema of the jejunal villi. The thoracic duct was not dilated but was obstructed by lymph nodes containing neoplastic masses.

Wangel and Deller (1965) report a man with a carcinoma of the bronchus, steatorrhoea, and subtotal villous atrophy. At necropsy patchy subtotal villous atrophy of the duodenum and the jejunum was found.

There have been relatively few reports of the cause of death in idiopathic steatorrhoea, so it is not possible to determine the incidence of malignancy. The main causes have been 'exhaustion', infection, and haemorrhage (Snell, 1939; Himes and Adlersberg, 1957; French, Hawkins, and Smith, 1957), although the association of idiopathic steatorrhoea and carcinoma has been recorded. Bossak, Wang, and Adlersberg (1957) reviewed their clinical observations of 94 patients with idiopathic steatorrhoea. There were five patients with neoplasms: one of the oesophagus, three of the stomach, and one of the ascending colon. The duration of the idiopathic steatorrhoea until the diagnosis of the associated neoplasm had been respectively 12, nine, 13, 17, and three years. Three patients were in remission at the time the carcinoma developed. Green and Wollaeer (1960) discussed the clinical behaviour of sprue in the United States, basing their observations on 230 patients seen at the Mayo Clinic. Eleven deaths are reported, including one due to a carcinoma of the tonsil. This was followed by two further reports from the same centre. Huizenga, Wollaeer, Green, and McKenzie (1961) reviewed serum globulin deficiencies in non-tropical sprue and reported two cases with acquired hypogammaglobulinaemia. One of these was a woman of 56 years who developed an adenocarcinoma of the stomach. The other report was by Moertel and Hargraves (1961) who describe a man of 68 years who had non-tropical sprue for 11 years and developed an adenocarcinoma of the jejunum.

Ogilvie and Shaw (1955), in an article on 'primary tumours of the small bowel', included a man of 40 years, who had had 'steatorrhoea for years' and developed an adenocarcinoma of the duodeno-junal junction. A well-documented case was presented at a clinico-pathological conference at the Massachusetts General Hospital (1958). A man of 60 years had symptoms of idiopathic steatorrhoea for six and a half years before he developed an adenocarcinoma of the jejunum. Girdwood et al. (1961) presented a patient with idiopathic steatorrhoea since the age of 24 years. At the age of 50 years he developed intestinal obstruction due to an anaplastic carcinoma 70 cm. below the duodeno-jejunal flexure. The only woman with idiopathic steatorrhoea and carcinoma was described by Frič, Bednář, Niederle, and Lepšík (1963). She was aged 44 and had had idiopathic steatorrhoea for 29 years. An adenocarcinoma of the jejunum was responsible for clinical deterioration.

Kelley, Troup, Logan, and Terry (1961) describe a man of 55 years with a carcinoma of the caecum and probable idiopathic steatorrhoea. Three years later he developed rectal bleeding and a malignant polyp was resected from the rectum.

If the occurrence of carcinoma is merely coincidental with the presence of steatorrhoea it is surprising that such common non-gastrointestinal tumours as those of the breast and bronchus have been so infrequently reported. Harris, Cooke, Thompson, and Waterhouse (1966) found 31 patients with malignant disease in a group of 202 patients with adult coeliac disease or idiopathic steatorrhoea. Of the 31 tumours, only four were non-gastrointestinal carcinomas (lung, ovary, skin, unknown), whereas 13 were gastrointestinal carcinomas and 14 were lymphomas. The carcinomas that have been recorded occur predominantly but not entirely in structures derived from the foregut and the midgut.

If local factors are important in the aetiology of carcinoma then the site of maximal incidence might be expected to be the small intestine, where the pathological changes of this disease occur. This is not so, as from the figures available the oesophagus and the stomach are at least as commonly involved, but if reticulosis of the small intestine is considered then probably the small intestine shows malignant change more commonly than other organs.

The ratio of deaths due to malignant disease involving the stomach and oesophagus is 13, 681 to 2,439 (1963, General Register Office). This ratio is reversed when carcinoma of the stomach and the oesophagus in idiopathic steatorrhoea are considered. Why this is so, is not apparent.

If some widespread disturbance of the defence mechanisms against malignant disease is postulated to be responsible for the development of carcinoma in idiopathic steatorrhoea, it might be expected that the incidence of such common tumours as of the bronchus, breast, and rectum would be increased. From the figures available this does not seem to be so.

Although the characteristic changes of idiopathic steatorrhoea occur in the small intestine, it is possible to produce histological changes in the large bowel by instillation of wheat or gliadin enemas (Dobbins and Rubin, 1964). Whether these minor changes are significant in the pathogenesis of carcinoma, remains to be seen. As far as we are aware, the oesophagus
has not been studied in patients with idiopathic steatorrhoea, but changes due to iron deficiency, which is present in idiopathic steatorrhoea, might be expected to be present.

SUMMARY

Seven patients with steatorrhoea and carcinoma are presented. It is suggested that six of these had idiopathic steatorrhoea. The sites of the carcinoma suggest that lesions of the foregut and midgut are more likely to occur. Reasons for such an association are discussed.

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