Gut, 1983, **24**, 565–574

Case reports

Small intestinal ulceration: diagnostic difficulties in relation to coeliac disease

D A F ROBERTSON, M F DIXON, B B SCOTT, F G SIMPSON, AND M S LOSOWSKY

From the Department of Medicine, St James's University Hospital, Leeds, Leeds General Infirmary, Leeds, and Lincoln County Hospital, Lincoln

SUMMARY Seven cases of ulceration of the small intestine are described and the relationship to coeliac disease is discussed. Evidence for coeliac disease is found in all cases but is less strong in some than in others, and coeliac disease was proved in only two cases. The ulcers were examined histologically in each case and in three cases were associated with malignant histiocytosis but the others showed only non-specific chronic inflammation. This suggests a spectrum of disorders with an inconsistent relationship to gluten sensitivity and small intestinal lymphoma.

Although becoming increasingly recognised, small intestinal ulceration associated with malabsorption is a confused subject which invariably presents problems in diagnosis and treatment. After excluding acknowledged causes of ulceration such as infection, Crohn's disease, ischaemia, and lymphoma, most cases are given a label such as 'idiopathic chronic ulcerative enteritis' as if they formed a distinct disease entity.[1 2] Other authors claim, however, that they are all examples of lymphoma and in particular that they represent bowel involvement by malignant histiocytosis.[3]

A second area of controversy surrounds the nature of malabsorption in these cases. While villous atrophy in the jejunum is a frequent finding, there is dispute as to whether this represents pre-existing coeliac disease (frequently covert), or is unrelated to gluten and either secondary to lymphoma or present for some unknown reason.

This paper describes seven cases of small intestinal ulceration, all with features suggestive of coeliac disease, but in whom precise classification presented difficulties. All seven patients have been studied by repeated multiple biopsies of the small intestine using a peroral hydraulic instrument,[4] together with laparotomy or post mortem specimens of the ulceration, to document the relationship between intestinal ulceration and both coeliac disease and small intestinal lymphoma.

Address for correspondence: D A F Robertson, Selly Oak Hospital, Raddlebarn Road, Birmingham B29 6JD.

Received for publication 27 August 1982

Case histories

CASE 1

A farmer's daughter, aged 19, was referred for investigation of small stature, mental backwardness, and failure of sexual development. After a severe respiratory infection at the age of 10 years, she had loose bowel motions for a year and seemed to stop developing mentally and physically. She was otherwise apparently healthy. There was no history of abdominal pain and no recent diarrhoea.

Examination showed the appearance and mentality of a 10 year old. Height 1·41 m. There was absence of body hair and of other signs of sexual development. She had finger clubbing but no lymphadenopathy, abdominal masses, or tenderness.

Two jejunal biopsies were taken from the first 15 cm of the jejunum, and showed severe partial villous atrophy with a marked increase in intraepithelial lymphocytes.

Small bowel enema showed a normal first 150 cm of small bowel followed abruptly by a dilated loop and a stricture 2 cm long followed by two other dilated loops and strictures. She was treated with a gluten free diet, oral ferrous sulphate, and intramuscular hydroxocobalamin. There having been no change in height or weight in the preceding nine years, during the next 12 months she gained 9·97 kg in weight and 5 cm in height and the results of all tests of nutrition became normal. Six months later, pubic hair had appeared, breast development was obvious, and menstruation had commenced.

Six weeks after commencing the diet, six biopsies taken from the first 25 cm of the jejunum were markedly improved showing varying degrees of partial villous atrophy with the proximal biopsies being more severely abnormal. Ten weeks later, seven biopsies from the duodenum and first 30 cm of jejunum were taken, three were normal and four showed mild partial villous atrophy. Seven months later multiple biopsies taken from the duodenum and proximal jejunum were normal, and two years after starting a gluten free diet six of seven biopsies were normal, one showed moderate partial villous atrophy with lymphoid hyperplasia and focal pyloric metaplasia.

Four and a half years after starting the gluten free diet she remained very well, but because of doubt about the nature and effects of the intestinal strictures a laparotomy was performed. The first 225 cm of small intestine was entirely normal, but there were then multiple strictures in a 120 cm length of ileum. The diseased bowel was resected leaving 15 cm of terminal ileum. She made an uneventful recovery. Histology of resected bowel showed a fissuring type of ulceration surrounded by a dense lymphocytic and plasma cell infiltrate containing small numbers of eosinophils. The intervening mucosa showed mild to moderate villous atrophy and there were increased lymphocytes in the lamina propria. There was extensive pyloric metaplasia and no evidence of lymphoma. The lymph node showed reactive changes only. Nine years after diagnosis the patient was symptom free and jejunal biopsy normal.

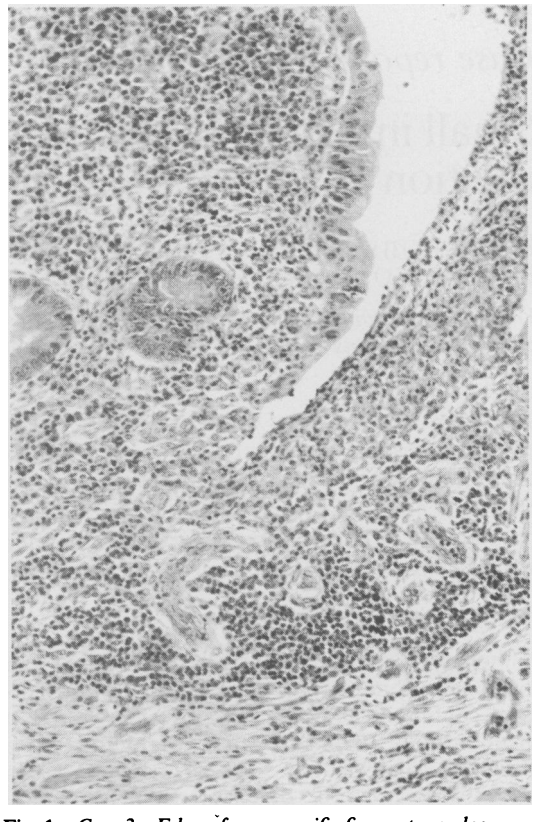

Fig. 1 *Case 3 – Edge of non-specific fissure type ulcer remote from adenocarcinoma. There is chronic inflammatory cell infiltrate comprising mature lymphocytes, plasma cells, and macrophages. H & E ×160 (original magnification).*

CASE 2

A 37 year old housewife, mother of three children, was admitted to hospital as an emergency complaining of continuous central abdominal pain and nausea for four days and vomiting for one day. During the preceding six years she had experienced several similar but less severe attacks. In between, her bowel motions had been normal. During the previous six months she had lost about 13 kg in weight. On examination she was thin and anxious. There was no finger clubbing or lymphadenopathy. There was ill-defined central abdominal tenderness. Stool cultures, sigmoidoscopy, barium meal, and enema showed no abnormality.

During the next two weeks there was further diarrhoea and vomiting, requiring intravenous fluids. Laparotomy was performed and showed thickening and inflammation of 200 cm of small bowel beginning 200 cm from the duodenojejunal junction and terminating 120 cm from the ileocaecal valve. The appearance was thought not to resemble that of Crohn's disease.

A biopsy taken at a distance of 300 cm from the duodenojejunal junction with the Crosby capsule showed severe partial villous atrophy.

Recurrent attacks of small bowel obstruction occurred requiring two operations for division of adhesions six weeks and 12 weeks after the initial laparotomy. Progressive improvement of the serosal appearance of the abnormal small bowel was noted on each occasion. Despite this, the patient remained very ill, losing weight and developing pressure sores.

Four biopsies of the proximal small bowel were taken with the peroral hydraulic instrument five months after admission. One biopsy from the second part of the duodenum showed severe partial villous atrophy. Two of three biopies from the duodenojejunal junction showed severe partial villous atrophy, the other one showing moderate partial villous atrophy. A gluten free diet, prednisolone, and tetracosactrin were then started

simultaneously, and continued until death.

There was initial gain in weight and improvement in general conditions, although abdominal pain recurred frequently. Four further biopsies of the proximal small bowel just beyond the duodenojejunal junction were taken after two months on the gluten free diet. One was normal, three showed mild partial villous atrophy.

During the next month, the patient's condition deteriorated, with terminal herpes zoster and staphylococcal septicaemia. The patient died eight months after her admission.

At necropsy there was free pus in the peritoneal cavity with no obvious site of perforation. Starting at 20 cm from the duodenojejunal junction, and terminating two-thirds way along the small intestine, the bowel wall was thin and translucent with occasional tiny mucosal haemorrhages. In the outwardly normal ileum there were two small ulcers. The spleen was very small. Sections of small intestine revealed marked post-mortem autolysis but ghost villi could be recognised. Sections from an ileal ulcer revealed adjacent mild chronic inflammation and a peritoneal reaction. There was no evidence of lymphoma in the small intestine, spleen, or mesenteric lymph nodes.

CASE 3

A 28 year old leather-dresser was referred for investigation. At the age of 19 years he gave a five year history of loose, pale stools, failure to gain weight and poor appetite, with recent ankle oedema. On examination he was small for his age, weight 43·9 kg, he had finger clubbing and mouth ulcers. Abdominal examination was negative. He had no pubic hair and his genitalia were prepubertal. The results of investigations at that time are shown in section 3A of Table 1. A barium meal and follow-through showed multiple dilated segments of jejunum with narrowed segments between.

No small bowel biopsy was taken, a diagnosis of coeliac disease was made and he was treated with a gluten free diet. No antibiotics were given. There was symptomatic improvement and he gained 9·5 kg in weight in two months, and 1·3 cm in height in four months. Improvement was maintained over the next few years, although he had several recurrences of diarrhoea and weight loss when he strayed from the gluten free diet.

At the age of 24 year he was reinvestigated because of flatulence and occasional epigastric pain. The results are shown in section 3B of Table 1. At 25 years he started shaving and achieved puberty. His external genitalia were noted to be normal. At 26 years he stopped taking the gluten free diet and after some months diarrhoea returned and he then began to lose weight. He resumed the diet one year later with a dramatic improvement in symptoms, and gain in weight. The results of investigations after referral to this hospital are shown in section 3C of Table 1.

Two of six biopsies showed patchy mild partial villous atrophy, the other four were normal. Small bowel enema showed numerous strictures and intervening dilated segments with grossly increased motility. The jejunum was more severely involved than the ileum and ulceration was seen at the strictures. Because of uncertainty in the diagnosis of coeliac disease he was allowed a normal diet. Biopsies were taken at three and six months. There was no unequivocal deterioration and he was then given a high gluten diet.[5] Biopsies taken after three months showed mild but definite deterioration with two of eight biopsies being normal, the rest showing changes ranging from an increase in intraepithelial lymphocytes to moderate villous atrophy. Biopsies

Table 1 *Results of investigations for malabsorption*

				Case 3						
	Normal	*Case 1*	*Case 2*	*A*	*B*	*C*	*Case 4*	*Case 5*	*Case 6*	*Case 7*
Haemoglobin (g/dl)		7·9	12·3	6·5	12·0	14·1	13·4	12·5	10·8	5·6
Serum iron (μmol/l)	>11	4·1	11·6	2·3	11·1	6·3	16·1	10·6	4·0	—
Serum folate (μg/l)	>3·0	5·7	1·4	—	—	7·9	5·4	2·4	2·0	2·6
Serum B_{12} (ng/l)	>110	90	260	800	720	95	564	320	270	1511
Serum albumin (g/l)	>35	29	21	23	42	39	23	25	28	33
Serum calcium (mmol/l)	>2·25	2·02	1·90	1·97	2·00	2·27	1·75	1·90	2·00	1·75
Serum alkaline phosphatase (KA units)	<13	19·5	8·8	23	32	15·2	6	13	19·7	25·0
Serum carotene (μmol/l)	>0·74	0·58	0·22	—	—	0·33	0·78	0·91	0·1	—
Xylose test*	>22	6	27	—	—	7	41	4	—	—
Urinary indican (mmol/24 h)	<0·47	0·20	0·40	—	—	0·86	1·17	0·74	—	—
Faecal fat (mmol/24 h)	<21	10	43	99	56	67	183	1·41	—	—

* Percentage of 5 g oral xylose appearing in urine in 5 h.

after seven months on a high gluten diet showed mild partial villous atrophy in three, and three were normal.

He then had two episodes of melaena. Upper gastrointestinal endoscopy, colonoscopy, and barium enema were negative. Coeliac, superior mesenteric and inferior mesenteric arteriography showed non-opacification of the main superior and inferior mesenteric veins with wide collateral veins, suggesting thrombosis of both mesenteric veins. He resumed a gluten free diet and remained well and at work. He had further melaena 10 months later and laparotomy was advised. He was unwilling to have this immediately and it was postponed for five months. Laparotomy then showed that 120 cm of small intestine was dilated and strictured intermittently. Lymph nodes were grossly enlarged and there were multiple small metastatic deposits in the liver. The affected bowel was resected and histology showed an ulcerated adenocarcinoma. There were, however, other areas of ulceration and suppuration not attributable to carcinoma (Fig. 1), the intervening mucosa consisting of expanded villi composed of highly vascular connective tissue. The crypts were hyperplastic and in one area dyplastic, merging with an area of well differentiated carcinoma, and there was extensive pyloric metaplasia. Three months postoperatively he had further melaena and abdominal distension and died five days later. Necropsy showed massive recurrent carcinoma causing partial strictures of duodenum and terminal ileum. Multiple metastatic deposits were found in the liver and parietal peritoneum. Histology confirmed extensive serosal spread of poorly differentiated adenocarcinoma.

CASE 4

An Irish club owner was well until the age of 49 years when he developed anorexia, diarrhoea, central abdominal pain, and weight loss of 12·7 kg in

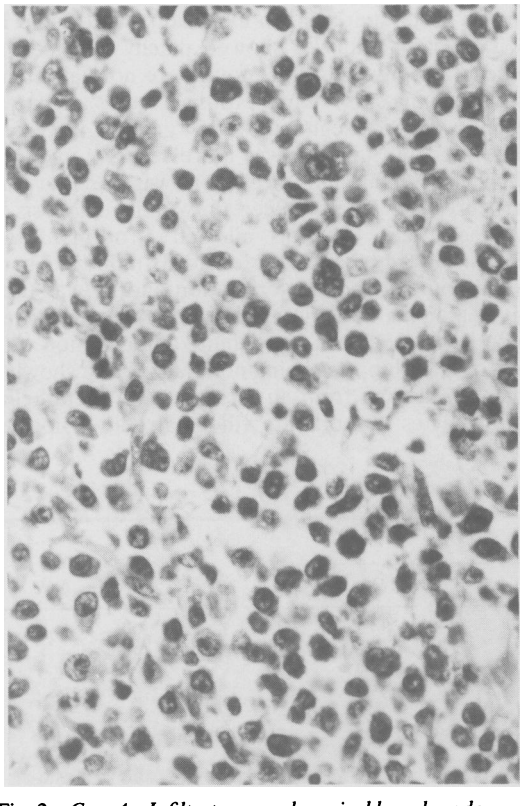

Fig. 2 *Case 4 – Infiltrate around cervical lymph node consisting of pleomorphic cells including multinucleate forms. Cells revealed histiocytic markers on immunoperoxidase staining. H & E ×640 (original magnification).*

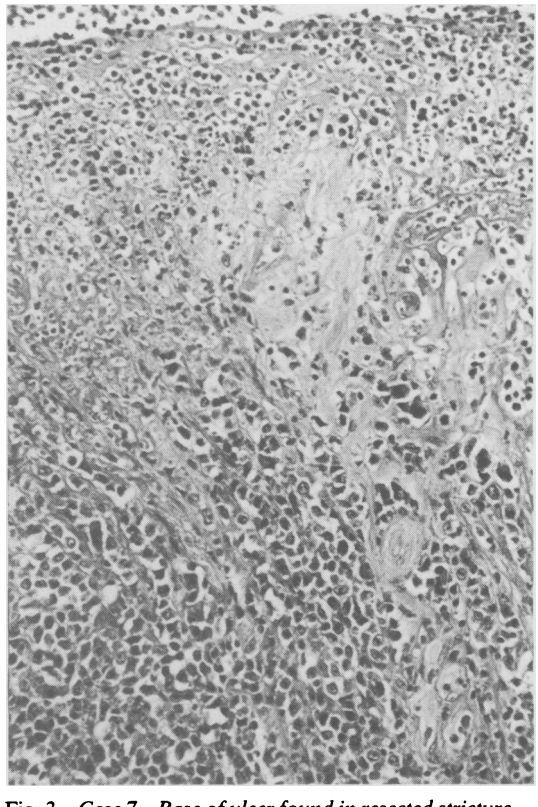

Fig. 3 *Case 7 – Base of ulcer found in resected stricture. Fibrin and necrotic cells overlie a dense infiltrate of pleomorphic cells which had characteristics of malignant histiocytosis on immunoperoxidase staining. H & E ×256 (original magnification).*

six months. On examination he was cachetic with slight right sided abdominal tenderness. He was not anaemic (Hb 12·8 g/dl) but a blood film showed macrocytosis and the serum folate was low (1·8 μg/l). Barium meal and follow-through showed delayed filling and irregularity of the jejunum, the ileum was normal; barium enema was normal. Laparotomy showed the whole of the jejunum and all except 100 cm of ileum to be thickened and mildly inflamed. The jejunum was opened and the mucosa noted to be oedematous, with numerous transverse ulcers. Full thickness biopsies of the jejunum showed a combination of subtotal and severe partial villous atrophy with ulceration at 20 cm past the duodenojejunal junction and partial villous atrophy with ulceration in the inflamed distal jejunum. An excised mesenteric lymph node showed inflammatory reactive changes only. The histology was quite unlike that of Crohn's disease or tuberculosis and there was no evidence of lymphoma. Postoperative investigations showed steatorrhoea (102 mmol fat/24 h).

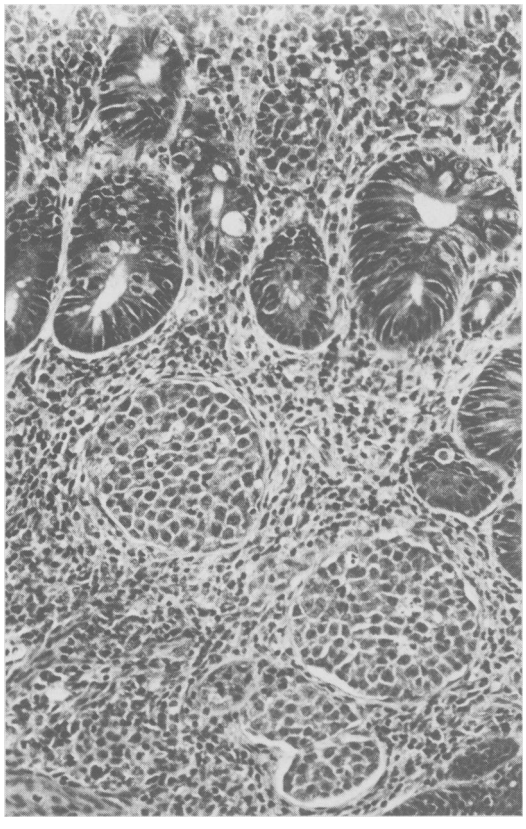

Fig. 4 *Case 7 – Mucosa adjacent to ulcer showing clusters of pleomorphic cells, apparently within lymphatics in the deep lamina. H & E ×256 (original magnification).*

He was discharged on folic acid but diarrhoea, pain, and vomiting continued until he was given prednisolone and sulphasalazine. He then gained weight, his appetite returned and his bowels were normal except for occasional brief diarrhoea.

Two years later he had epigastric pain, anorexia, vomiting, and weight loss but no diarrhoea. He was noted to have finger clubbing, upper abdominal distension, and a succussion splash. Barium meal showed a grossly distended duodenum and proximal jejunum with atonia. Laparotomy showed the duodenum was very dilated and the jejunal wall thickened, but there was no obstruction. The gross appearance resembled those of Crohn's disease but no biopsy was taken. He was discharged taking prednisolone 30 mg per day and for the next 18 months he was extremely well with gradual weight gain and no diarrhoea. He then developed diarrhoea, abdominal distension, and discomfort which continued despite oral lincomycin and he was reinvestigated.

Seven biopsies were taken from the duodenum and first 20 cm of the jejunum, all of which were abnormal, ranging from mild to severe partial villous atrophy.

He was discharged taking tetracycline and prednisolone with improvement. Several months later he was started on a gluten free diet and within two weeks he reported definite further improvement in his general state of health. Eight biopsies taken after two months on the gluten free diet showed definite improvement. Four were normal, two showed pyloric glandular metaplasia, and two showed mild partial villous atrophy. Subsequently (six years after initial presentation) he developed tender enlargement of the cervical lymph nodes which revealed lymphoma on biopsy (Fig. 2). Immunoperoxidase staining was performed on trypsinised paraffin sections for all heavy chain classes of immunoglobulin, kappa and lambda light chains, and for α1-antitrypsin, and lysozyme. These revealed a high content of α1-antitrypsin, a weak reaction for lysozyme, and a polyclonal immunoglobulin content, consistent with the diagnosis of malignant histiocytosis.[6] Despite treatment with radiotherapy and chemotherapy he died after three months.

Necropsy revealed malignant histiocytosis infiltrating the submucosa and sub-serosa of the ulcerated small bowel with involvement of lymph nodes, lungs, heart, bladder, and peritoneum.

CASE 5

A 61 year old housewife had been found to be

severely anaemic (Hb 7 g/dl) at the age of 43, responding only temporarily to iron therapy, until haemorrhoidectomy after which her haemoglobin remained normal. At 45 years she was found to have a low serum calcium (1·9 mmol/l), a raised serum alkaline phosphatase (45 KA units) and radiological osteomalacia.

At 55 years she was investigated for severe diarrhoea and ankle oedema. She was found to have a low serum albumin (18 g/dl), steatorrhoea (120 mmol fat/24 h), impaired xylose absorption and a flat glucose tolerance test. Barium meal and follow-through showed rapid passage of barium through a dilated jejunum but no other abnormality was noted. A small bowel biopsy was not taken but treatment was started with a gluten free diet. The diarrhoea improved and she gained 3·6 kg in weight in the next three months. She did not find this diet agreeable and admitted to frequent lapses followed by worsening of diarrhoea.

Four years later she was readmitted with anorexia, nausea, and bruising. The prothrombin time was markedly raised at 75 seconds (control 13 sec). She was transfused and given parenteral vitamin K with rapid restoration of the prothrombin time to normal. On examination she was thin and wasted with finger clubbing. There was no lymphadenopathy. A biopsy taken with a Crosby capsule showed severe partial villous atrophy. Small bowel enema showed a 4 cm long, sharply shouldered stricture of the second part of the duodenum, and also a central, firmly fixed point of adhesion between several loops of jejunum and ileum; skeletal survey showed osteomalacia of the spine and pelvis.

Laparotomy showed seven loops of bowel and two loops of colon all emptying by small fistulae into a central granulating cavity. The loops were separated and the holes oversewn. There were two calcified fibrous nodules constricting the second part of the duodenum. Examination of 15 cm of resected bowel showed two ulcers surrounded by non-specific chronic inflammatory changes, the intervening mucosa showing moderate partial villous atrophy and pyloric metaplasia. There was no evidence of lymphoma.

Postoperatively four small bowel biopsies taken from the first 30 cm of the jejunum were all flat and featureless on steromicroscopy, and histology showed total villous atrophy.

A gluten free diet was restarted in hospital and four weeks later seven biopsies taken from the duodenum, and first 30 cm of jejunum, showed a flat mosaic pattern on steromicroscopy and total villous atrophy in four, and severe partial villous atrophy in three.

She was recommended to continue the gluten free diet but did not abide by this advice and 10 months later was readmitted very severely ill and died three days later. Necropsy showed that the jejunum was dilated and thin-walled and histology showed total or severe partial villous atrophy in different sites. The cause of death was bronchopneumonia. There was no evidence of lymphoma in sections of jejunum, bone marrow, or liver.

CASE 6

A 62 year old company director underwent screening at a private health centre because of vague ill health, diarrhoea, and weight loss. The diarrhoea he thought was because of taking antacids which had been prescribed for oesophagitis diagnosed one year previously. Examination was negative, but investigations revealed erythrocyte sedimentation rate 65 mm/h and serum albumin 29 g/l.

One month later he presented as an emergency with peritonitis and at laparotomy several litres of turbid fluid were found in the peritoneal cavity. There was gross dilatation and hypertrophy of the proximal small intestine, as far as a perforated ulcer, 100 cm from the terminal ileum. There was no other intra-abdominal pathology. Fifty centimetres of ileum were resected with end to end anastomosis and the patient made a satisfactory postoperative recovery.

The resected small bowel showed four mucosal ulcers 2·5 cm, 2 cm, 1·3 cm, and 0·7 cm in diameter, the largest of which was perforated. The ulcers were lined with dense collections of pleomorphic cells having the appearance of malignant histiocytosis. On immunoperoxidase staining the cells were strongly positive for α1-antitrypsin and lysozyme and contained polyclonal immunoglobulins. There was no significant villous atrophy in the adjacent mucosa, but a slight increase in lymphocytes and plasma cells.

Subsequently he developed severe diarrhoea accompanied by gaseous distension and borborygmi, although there was no evidence for obstruction on small bowel enema. Five jejunal biopsies showed total villous atrophy in two and severe partial villous atrophy in three.

A gluten free diet was then instituted but despite this and general nutritional support his condition continued to deteriorate. Six weeks later jejunal biopsy showed no significant improvement and he died one week later.

At necropsy there was a non-perforated ulcer 2 cm in diameter at 25 cm beyond the duodenojejunal junction with three smaller ulcers 100 cm from the duodenojejunal junction, and at 100 cm and 10 cm from the ileocaecal valve. Malignant histiocytosis

was found in numerous lymph nodes and in the spleen, which was small (60 g).

CASE 7

A 57 year old woman secretary presented with a six month history of diarrhoea and weight loss of 12·7 kg. She had had intermittent diarrhoea for many years and when aged 27 years she had been treated successfully with folic acid for severe macrocytic anaemia. On examination she was cachetic, pigmented, and had finger clubbing. Her abdomen was distended and there were loud borborygmi. She was anaemic (Hb 5·6 g/dl) and the film showed moderate microcytosis, slight macrocytosis, target cells, and Howell-Jolly bodies. Results of investigations for malabsorption are shown in Table 1. Three biopsies from the second part of the duodenum and three from the duodenojejunal junction showed a flat mucosa and some a mosaic pattern on steromicroscopy, and severe partial villous atrophy on histology. A gluten free diet was started and she was also given oral folic acid and iron. After two weeks she complained of paraesthesiae of hands and proximal weakness of legs such that she could not rise from a chair without using her arms. These symptoms were thought to be because of vitamin D deficiency and she was given calciferol intramuscularly at one to two weekly intervals for two months. Over the next few months she gradually improved. Her weight rose 2·7 kg, the diarrhoea lessened considerably and the paraesthesia and muscle weakness disappeared. Six months after starting the gluten free diet six biopsies were taken from the second part of the duodenum and they all showed leaf shaped villi on steromicroscopy, and on histology there was partial villous atrophy but with normal epithelial cells. She complained, however, of abdominal distension and embarrassing borborygmi. A small bowel enema taken five months after starting a gluten free diet showed grossly dilated loops of small bowel. At laparotomy six months after starting the gluten free diet a pin-point symmetrical stricture was found at the junction of the jejunum and ileum. The stricture was resected and the patient made a satisfactory postoperative recovery, and is asymptomatic two years later.

The specimen was cut into seven blocks, and one, from the region of the stricture, was occupied by a small, transmural collection of lymphoma cells showing moderate pleomorphism, bizarre mitotic figures and occasional bi- or multinucleate forms (Figs 3, 4). Immunoperoxidase methods revealed strongly positive staining for α1-antitrypsin and lysozyme and a polyclonal immunoglobulin content. The appearances were those of malignant histiocytosis. Adjacent mucosa showed normal or mildly atrophic villi, with an increase in lymphocytes and plasma cells.

The findings with regard to small bowel ulceration and the response to a gluten free diet are summarised in Table 2.

Discussion

EVIDENCE FOR COELIAC DISEASE

Although all seven patients had evidence of malabsorption and villous atrophy, only two (cases 1 and 7) had definite coeliac disease. The others had features very suggestive of coeliac disease but did not fulfil the strict criterion of an unequivocal morphological response of the small bowel mucosa to treatment with a gluten free diet. These patients serve to illustrate difficulties in diagnosing coeliac disease in patients with small-intestinal ulceration, when (a) there is patchy villous atrophy, (b) there is no pretreatment biopsy, (c) steroids are given either before or together with a gluten free diet, (d) there is complicating lymphoma or carcinoma, or (e) the patient refuses to adhere to a strict gluten free diet.

Patients 2 and 4 showed both a histological and clinical response to a gluten free diet but steroids were given at the same time and might, therefore,

Table 2 *Clinical data and nature of ulceration*

Case	*Age/Sex*	*Response to GFD**	*Nature of ulceration*	*Outcome*
1	19 F	+	Non-specific chronic inflammation	Alive/well, 9 years
2	37 F	+ With steroids	Non-specific chronic inflammation	Died 8 months after admission
3	28 M	+ (No pre-treatment biopsy)	Non-specific chronic inflammation and adenocarcinoma	Died 3 months after operation
4	55 M	+ With steroids	(a) Non-specific chronic inflammation (b) Malignant histiocytes	Died 3 months after diagnosis of malignant histiocytosis
5	61 F	−	Non-specific chronic inflammation	Died 10 months after operation
6	62 M	−	Malignant histiocytosis	Died 7 weeks after operation
7	57 F	+	Malignant histiocytosis	Alive/well, 2 years

* Gluten free diet.

have been responsible for the improvement as described in coeliac disease by Wall *et al*[7] although these authors described only minor morphological and brush border enzyme improvements, and it is not known whether villous atrophy which is not due to coeliac disease responds in this manner. Occasionally the response to a gluten free diet in coeliac disease appears to depend upon concomitant steroid administration.[8]

Patient 3 probably had coeliac disease, and had unequivocal clinical responses to a gluten free diet and relapses on a normal diet, but he had not been biopsied before treatment. Multiple biopsies taken while he was on a gluten free diet showed both normal mucosa and villous atrophy and it was therefore difficult to assess the response to gluten challenge. There was a mild but definite deterioration, however, in biopsy appearances on a high gluten diet and such a delayed response to gluten challenge is compatible with coeliac disease,[9] although recent evidence suggests that even normal individuals may develop small intestinal abnormalities after a very high gluten intake.[10] It seems most unlikely that the small intestinal carcinoma could account for the patient's clinical course over 12 years. This patient probably had underlying coeliac disease, which predisposed to ulcers and strictures and also the the small intestinal carcinoma as previously reported in a number of coeliac patients[11] as carcinoma at this site is otherwise very rare.[12] It has been suggested that malignancy at sites remote from the small intestine may cause villous atrophy,[13–15] but there is no firm evidence for this view which is no longer widely held.

Patients 5 and 6 showed no histological improvement on a gluten free diet but this was only of four and six weeks duration, such a delay in response being consistent with coeliac disease. Patient 5 illustrates the ever present difficulty of making a correct diagnosis when the patient refuses to adhere to a gluten free diet. Furthermore, in patient 6, villous atrophy may have been because of involvement with lymphoma, as evidence of lymphoma was seen on biopsy.

There was no evidence that villous atrophy occurred particularly in the vicinity of ulcers. Jejunal biopsies were taken from the proximal small bowel in every case, and ulceration occurred in each case distal to the site of biopsy. In cases 5 and 6, there were normal villi adjacent to ulcerated areas. Evidence of patchiness of villous atrophy, a well recognised feature of coeliac disease,[16] was seen in six patients.

All six of the patients tested possessed the histocompatibility antigen HLA-B8, which has a strong association with coeliac disease.[17 18] Three patients had splenic atrophy, which has a strong association with coeliac disease.[19]

EVIDENCE OF ULCERATION

Ulceration was shown in all of the patients. In one (case 4) numerous transverse ulcers were seen in the jejunum at laparotomy; in three others (cases 5, 6, and 7) ulcers were present in resected bowel; in another (case 2) an ulcer was seen in the ileum at necropsy and in another (case 3) unequivocal ulceration was shown radiologically at the site of a stricture, and was confirmed later at laparotomy. In the other patient (case 1) previous ulceration was initially presumed on the basis of multiple strictures and pyloric glandular metaplasia of small-intestinal mucosa, and ulceration was subsequently confirmed at laparotomy.

Four patients had pyloric glandular metaplasia (cases 1, 3, 4, and 5). This feature has been previously described[20–24] and all these authors consider that it occurs only in the vicinity of ulcers.

AETIOLOGY OF ULCERATION

A definite cause for ulceration was found in cases 4, 6, and 7 where it was the result of infiltration of the small bowel by malignant histiocytosis, and in cases 1, 2, 3, and 5 it was of the non-specific chronic inflammatory type, which in case 3 was associated with adenocarcinoma elsewhere. There as no evidence to indicate that these four cases were due to malignant histiocytosis, which has been proposed as a unifying hypothesis to explain all cases of intestinal ulceration, although multiple serial sections were not available for analysis; these are recommended by some authors[3] but thought unnecessary by others.[2] The long survival in good health of case 1 argues strongly against this hypothesis in that treatment consisted only of surgical resection and a gluten free diet.

Furthermore, in case 4, although the terminal ulceration was attributable to malignant histiocytosis, the patient had been operated on six years before his presentation with lymphoma, when the findings were those of non-specific ulceration. It has been suggested that intestinal ulceration occurs in coeliac disease as a result of regenerative failure,[24] that is, the rate of cell loss exceeds the rate of cell birth. This suggestion is not supported by our cases in that ulcers were found distally in the less severely affected bowel, and in case 1, ulcers persisted despite restoration of villous architecture to normal.

Ulceration is unlikely to be a late stage of villous atrophy or the end result of whatever mechanism causes such atrophy, as one of our cases was only 19 years old at diagnosis, and conversely, there are

many cases of coeliac disease diagnosed in the sixth and seventh decade of life who do not have ulceration.

We conclude that intestinal ulceration associated with malabsorption is due to, or associated with, a heterogenous group of conditions. A causal relationship may be discernible in some cases but generalisations about aetiology or treatment cannot usefully be made. In some, but not all cases, ulceration is due to involvement of the small bowel by malignant histiocytosis.

Also, in some cases ulceration appears to be a complication of untreated coeliac disease and it does not appear to resolve on a gluten free diet. The prognosis in this group of conditions depends upon the associated diseases and their response to treatment, and the poor overall prognosis justifies an aggressive approach to investigation in these patients.

We thank our pathologist colleagues for referring material, in particular Drs E M Allibone, S I Jacobs, G J Hardy, G A Dossett, and D Jenkins, and Ms L Walton and Mr G Robinson for technical assistance.

Addendum (Since writing this paper the authors wish to add a further case to those already presented)

A woman, aged 60 years. She and her brother had been thought to have intestinal tuberculosis during childhood because of diarrhoea and abdominal distension. Her brother had subsequently been shown to have coeliac disease and responded to a gluten free diet. Five year history of upper abdominal pain, nausea, and vomiting. Endoscopy at age 56 years showed duodenal ulceration and scarring at the pylorus. Medical therapy was unsuccessful in relieving her pain, and vagotomy and pyloroplasty was performed. At operation no ulceration was found but the duodenum was scarred. Nineteen short strictures were found extending from 10 cm beyond the duodenojejunal flexure to within 1·2 m of the ileocaecal junction. Resection of one stricture and adjacent Meckel's diverticulum showed chronic inflammation of lamina propria and submucosa. Postoperatively, intestinal obstruction developed and two months later a posterior gastroenterostomy was performed, bypassing 1·2 m of bowel containing many of the most severe strictures. Thereafter she complained of increasing malaise, loss of weight, abdominal pain, nausea, and diarrhoea. Latterly she had also developed symptoms suggesting peripheral neuropathy.

Biopsy of the duodenum showed partial villous atrophy with severe inflammatory changes. Multiple biopsies from the efferent loop showed complete absence of villi and findings typical of coeliac disease. Presumably the duodenal changes were less severe because this region was not exposed to much gluten. She was placed on a gluten free diet and multiple biopsies from the efferent loop three weeks later showed a definite increase in enterocyte height ($24·9 \pm 2·52$ μm, rising to $33·2 \pm 1·98$ μm; $p<0·001$) and marked histological improvement with much less inflammation and definite short villi present.

References

1 Baer AN, Bayless TM, Yardley JH. Intestinal ulceration and malabsorption syndromes. *Gastroenterology* 1980; **79:** 754–65.
2 Mills PR, Brown IL, Watkinson G. Idiopathic chronic ulcerative enteritis. *Q J Med* 1980; **194:** 133–49.
3 Isaacson P, Wright DH. Malignant histiocytosis of the intestine. Its relationship to malabsorption and ulcerative jejunitis. *Hum Pathol* 1978; **9:** 661–77.
4 Flick AL, Quinton WE, Rubin CE. A peroral hydraulic biopsy tube for multiple sampling at any level of the gastrointestinal tract. *Gastroenterology* 1961; **40:** 120–6.
5 Lundh G, Borgstrom B. In: De Reuch AVS, Cameron MP, eds. *Ciba Foundation Symposium on the exocrine pancreas.* London: Churchill, 1962: 259.
6 Isaacson P, Wright DH. Malabsorption and intestinal lymphomas. In: Wright R, ed. *Recent advances in gastrointestinal pathology.* London: Saunders, 1980: 206.
7 Wall AJ, Douglas AP, Booth CC, Pearse AGE. Response of the jejunal mucosa in adult coeliac disease to oral prednisolone. *Gut* 1970; **11:** 7–14.
8 Hamilton JD, Chambers RA, Wynn Williams A. Role of gluten, prednisone, and azothiaprine in non-responsive coeliac disease. *Lancet* 1976; **1:** 1213–6.
9 McNicholl B, Egan-Mitchell B, Fottrell PF. In: Hekkens WTJM, Peña AS, eds. *Coeliac disease: proceedings of the second international coeliac symposium.* Leiden: Stenfert Kroese, 1974: 413.
10 Doherty M, Barry RE. Gluten-induced mucosal changes in subjects without overt small bowel disease. *Lancet* 1981; **1:** 517–20.
11 Brzechwa-Ajdukiewicz A, McCarthy CF, Austad W, Cornes J, Harrison WJ, Read AEA. Carcinoma, villous atrophy and steatorrhoea. *Gut* 1966; **7:** 572–7.
12 Lowenfels AB. Why are small-bowel tumours so rare? *Lancet* 1973; **1:** 24–5.
13 Creamer B. Malignancy and the small intestinal mucosa. *Br Med J* 1964; **2:** 1435–6.
14 Deller DJ, Murrell TGE, Blowes R. Jejunal biopsy in malignant disease. *Aust Ann Med* 1967; **16:** 236–41.

15 Dymock IW, Mackay N, Miller V *et al.* Small intestinal function in neoplastic disease. *Br J Cancer* 1967; **21:** 505–11.
16 MacDonald WC, Brandborg LL, Flick AL, Trier JS, Rubin CE. Studies of coeliac sprue. IV. The response of the whole length of the small bowel to a gluten free diet. *Gastroenterology* 1964; **47:** 573–89.
17 Stokes PL, Asquith P, Holmes GKT, Mackintosh P, Cooke WT. Histocompatibility antigens associated with adult coeliac disease. *Lancet* 1972; **2:** 162–4.
18 Falchuk ZM, Rogentine GN, Strober W. Predominance of histocompatibility antigen HLA-A8 in patients with gluten-sensitive enteropathy. *J Clin Invest* 1972; **51:** 1602–5.
19 Marsh GW, Stewart JS. Splenic function in adult coeliac disease. *Br J Haematol* 1970; **19:** 445–57.
20 Neale G. A case of malabsorption, intestinal mucosal atrophy and ulceration, cirrhosis and emphysema. *Br Med J* 1970; **3:** 207–12.
21 Whitehead R. In: *Major problems in pathology. Mucosal biopsy of the gastrointestinal tract.* Vol 3. London: Saunders, 1973: 97–103, and 123.
22 Yokoyama I, Kozuka S, Ito K, Kubota K, Yokoyama Y, Kondo T. Gastric gland metaplasia in the small and large intestine. *Gut* 1977; **18:** 214–8.
23 Lee FD. Pyloric metaplasia in the small intestine. *J Pathol Bact* 1964; **87:** 267–77.
24 Bayless TM, Kapelowitz RF, Shelley WM, Ballinger WF, Hendrix TR. Intestinal ulceration: a complication of coeliac disease. *N Engl J Med* 1967; **276:** 996–1002.