The existence of inflammatory bowel lesions in gluten-sensitive enteropathy

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Summary

Three patients with coincident coeliac disease and inflammatory bowel disease are described. In 2 patients with known coeliac disease the recurrence of diarrhoea was not due to dietary deviation but to an additional large bowel pathology.

Introduction

When diarrhoea occurs in a patient who has been treated for coeliac disease it is usual to assume that the diarrhoea has developed because the patient has taken gluten in his diet. Three patients are presented, 2 of whom were referred because of apparently refractory coeliac disease but in whom an eventual additional diagnosis of inflammatory bowel disease (IBD) was made. In the third case the previous diagnosis of IBD delayed subsequent diagnosis of coeliac disease.

Case reports

No. 1

A 42-year-old white female presented with a 7-year history of diarrhoea and a weight loss of 12.7 kg in 1967. A diagnosis of coeliac disease was made on the basis of a serum folate of 1.1 ng/ml, an abnormal xylose (25 g) tolerance test (90-min serum level of 10 mg/100 ml and a 5-hr urine excretion of 0.7 g), a faecal fat of 9 g/day and subtotal villous atrophy of the jejunum. She was treated with a gluten-free diet with initial improvement but her diarrhoea returned after a visit to Spain one year later. At this stage the jejunal biopsy showed an improvement with histological partial villous atrophy, but the faecal fat excretion estimations and xylose tolerance tests remained abnormal. A Lundh meal test for pancreatic function and a Schilling test with intrinsic factor were normal. Sigmoidoscopy showed a normal mucosa but a rectal biopsy showed very mild non-specific inflammatory changes. In view of the dichotomy between her symptoms and the appearance of the jejunal biopsy it was felt that the diagnosis of coeliac disease should be confirmed and she was therefore given a gluten challenge on a normal diet for one month. This produced deterioration of her gastrointestinal function tests and histologically subtotal villous atrophy of her jejunum. She was therefore restarted on a gluten-free diet. In January 1969 she presented again with severe diarrhoea and gripping abdominal pain with urgency; the stools were watery but without blood or mucus. A jejunal biopsy showed some improvement with a convoluted pattern and histological partial villous atrophy but the barium meal follow-through now showed dilatation. A barium enema examination was normal. The diarrhoea continued to persist despite a normal looking mucosa on sigmoidoscopy and a rectal biopsy repeated 7 months later showed a vast increase in inflammatory cells (Fig. 1), the relevance of which was not appreciated at that time.

Two years later in 1971 she had a low serum potassium and was found to be losing this in her stools. Stool volumes were > one litre/day. In view of the watery diarrhoea the possibility of a pancreatic adenoma was raised but both a pancreatic scan and pancreatic duct cannulation (ERCP) were inconclusive. An exploratory laparotomy was suggested but on reviewing her case it was felt that in view of the grossly abnormal, although non-specific rectal biopsy the patient probably had an inflammatory bowel condition in addition to coeliac disease. She was treated with high dose steroids and salazopyrine which produced a dramatic response in relieving her symptoms. She is currently (1978)
well, 4 years later, on salazopyrine and a gluten-free diet.

No. 2
A 40-year-old white male presented in 1970 with a one-year history of diarrhoea after a visit to the Middle East. In the past he had had unexplained episodes of diarrhoea in 1954 and 1966 but had not had any symptoms in childhood. A diagnosis of coeliac disease was made on the basis of a serum folate of one ng/ml; and subtotal villous atrophy on a jejunal biopsy. At that time a barium enema was normal (Fig. 2a). He was started on a gluten-free diet in 1970. In 1973 when he was seen again he had no diarrhoea and was feeling very well. He had gained weight and his jejunal biopsy was greatly improved, now showing partial villous atrophy. In January 1975, however, he developed severe diarrhoea with urgency and was on occasions incontinent; the stools were loose but without blood or mucus.

Investigations at this time showed a haemoglobin of 12-5 g/dl, MCV of 81, ESR of 6 mm/hr, and a low serum folate of 1-2 ng/ml. A jejunal biopsy showed a vast improvement on his initial biopsy with slightly shortened and broader villi but with no increase in inflammatory cells. Serum protein and immunoglobulin levels were normal, and fluorescent screening for tissue antibodies was negative. Sigmoidoscopy showed an excoriated anus with a granular and friable rectal mucosa. A rectal biopsy showed an intense inflammatory cell infiltrate, suggestive of ulcerative colitis and a barium enema now showed a tubular colon with no haustral pattern (Fig. 2b). A diagnosis of ulcerative colitis was made and the patient was treated with salazopyrine, folic acid and the continuation of his gluten-free diet. His symptoms rapidly improved and he now (1978) passes one normal stool/day.

No. 3
This 72-year-old white female first developed diarrhoea accompanied by blood and mucus 20 years ago following a left radical mastectomy for carcinoma of the breast. Sigmoidoscopy showed an inflamed friable mucosa and a rectal biopsy displayed the features of acute ulcerative colitis. Barium enema examination was normal. She was treated with salazopyrine and made a good recovery.

Her symptoms recurred in 1972 and a further rectal biopsy showed changes of an acute flare-up in a chronic stage ulcerative colitis (Fig. 3). At this time she was noted to be anaemic with a haemoglobin of 10-3 g/dl. A blood film showed hypochromia with occasional macrocytes. Bone marrow aspiration showed megaloblastic changes; serum folate was 3-75 ng/ml and a serum vitamin B_{12} level was at the lower range of normal (165 pg/ml). Intrinsic factor (IF) antibodies were present in the serum. A vitamin B_{12} absorption test without IF was 4-5% improving to 13-4% with IF. Pernicious anaemia was diagnosed and she was started on intramuscular hydroxy-cyanocobalamin 1000 µg every 2 months.

Despite some improvement in her anaemia her folate levels remained low, and in January 1976 when diarrhoea recurred she was admitted for further assessment. Her haemoglobin had again fallen to 9-1 g/dl, red cell folate 65 ng/ml. serum
Case reports

**Fig. 2.** (a) Barium enema examination (Case 2) before the onset of ulcerative colitis and (b) five years later showing a tubular colon.

**Fig. 3.** Rectal biopsy (Case 3) showing an intense inflammatory infiltrate with disorientation of glands in chronic ulcerative colitis.
calcium 1.83 mmol/l, serum phosphate 0.83 mmol/l, alkaline phosphatase 175 u/l. Faecal fat excretion was elevated at 56 mmol/24 hr. A jejunal biopsy showed severe partial villous atrophy and a moderate increase in plasma cells. This, plus her folate deficiency, steatorrhoea and hypocalcaemia was very suggestive of adult coeliac disease. There was no evidence of exacerbation of her ulcerative colitis.

She was started on a gluten-free diet 10 months ago, has gained 11 kg and remains (1978) symptom-free. Her haemoglobin has risen to 12.3 g/dl.

Discussion
The occurrence of inflammatory bowel disease in patients with coeliac disease is not a common problem. A case of ulcerative colitis and gluten sensitive enteropathy was described in a patient who also had a selective IgA deficiency (Falchuk and Falchuk, 1973) The authors report 3 patients with coeliac disease who have in addition an inflammatory bowel lesion; 2 of these have ulcerative colitis and the third has a non-specific but well defined inflammatory bowel condition. These 3 patients had their immunoglobulins estimated and in 2 of them these were found to be within the normal ranges and are thus unlike the patient of Falchuk and Falchuk.

Jejunal mucosal abnormalities have previously been described in patients with ulcerative colitis and Crohn’s disease (Binder, Soltoft and Gudmand-Hoyer, 1974; Ferguson, Allan and Cooke, 1975; Jankey and Price, 1969; Salem and Truelove, 1965). In the 10 patients with ulcerative colitis described by Jankey and Price (1969), 4 patients had a convoluted macroscopic picture with histological partial villous atrophy whilst the remaining 6 were normal. None had subtotal villous atrophy. Salem and Truelove (1963) reported the jejunal appearances in 60 patients with ulcerative colitis and found that 12 had partial villous atrophy and 2 had subtotal villous atrophy. They were able to correlate the clinical activity of the colitis with the appearances of the jejunal mucosa; the 2 patients with flat jejunal biopsies had severe symptoms of colitis. Further, with improvement of the colitis the jejunal morphological changes improved towards normal. However, Binder et al. (1974) were unable to correlate the jejunal villous changes in patients with ulcerative colitis to the degree of diarrhoea, weight loss, anaemia or fever, although 11 of their 21 patients with active colitis had minor changes in villous pattern as compared to slight changes in 4 of 14 with inactive colitis. It is interesting that when the inflammatory bowel disease of 2 of the present patients was in exacerbation (cases 1 and 2), the jejunal morphological appearances had improved on a gluten-free diet and so were unlikely to be due to the colonic lesion.

In case 1 the diagnosis of coeliac disease was confirmed with a gluten challenge by showing deterioration of her jejunal morphology on taking a normal diet for a period of one month. The other 2 patients did not have a gluten challenge but there seemed little doubt about the diagnosis of coeliac disease with the villous atrophy, low folates, and response to a gluten-free diet and, in patient 3, the low serum calcium. (In a child under the age of 2 years, a flat biopsy is not necessarily due to coeliac disease, but in an adult it is almost always so.) In 2 of the 3 patients described here the diagnosis of coeliac disease was made before the development of inflammatory bowel disease. Although in case 2, the delay in the second diagnosis was only 3 months, in case 1 it proved to be extremely difficult and took 3 years before the diagnosis was finally confirmed. In this case the possibility of a laparotomy was seriously considered in view of the severity of the symptoms and suspicions of pancreatic disease on the pancreatic scan and ERCP. Unfortunately, the significance of the findings on her first abnormal rectal biopsy was not appreciated. A further point to note was the abnormality of the rectal biopsy despite a normal-looking rectal mucosa on sigmoidoscopic examination.

The third case differed from the other 2 in that the inflammatory bowel disease was diagnosed before her jejunal atrophy.

In conclusion, 3 patients with coeliac disease are described in whom an inflammatory bowel condition was also found. The authors suggest that in patients with treated coeliac disease the recurrence of severe diarrhoea does not always imply a dietary deviation.

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