Case report

Cronkhite Canada syndrome: a new hypothesis

K FREEMAN, P P ANTHONY, D S MILLER, AND A P WARIN

From the Departments of Dermatology, Geriatric Medicine and Histopathology, Royal Devon & Exeter Hospital, Exeter, Devon

SUMMARY The occurrence of Cronkhite Canada syndrome in a 78 year old man is described. The presence of total gastrointestinal mucosal atrophy with nail loss is reported for the first time. It is suggested that the polyps represent residues of aged cells with no absorptive function and that the condition results from the loss of normal proliferative stimuli or acquired resistance to them. The primary biochemical abnormality may be in the affected epithelia but the changes here could alternatively be secondary to failure of synthesis or release of growth factors.

Case report

A 78 year old white man was admitted to hospital in October 1982 for investigation of flatulence, abdominal discomfort, diarrhoea, faecal incontinence, and weight loss. His symptoms had developed insidiously over the year preceding his admission. He was one of four siblings, with no family history of bowel or skin disease and had previously been in good health. Until retirement he had been a bank manager. He was passing three or four pale, offensive smelling, semiformal stools daily which were difficult to flush away; there was no noticeable blood or mucus. At times he was aware of the need to pass a stool but unable to control this need, on other occasions he appeared to have no awareness of rectal contents. He had lost 4 kg in weight despite eating a normal diet. Three months earlier his finger and toe nails had whitened and then been shed.

Physical examination revealed a wasted elderly male with non-scarring loss of all nails (Fig. 1). No other abnormalities were detected. External anal sphincter tone was normal. Investigations showed that he was not anaemic but macrocytosis was shown. His serum folate level was low, 1.5 µg/l, and he had a malabsorptive pattern Schilling test. A butter fat absorption test showed no evidence of absorption. Faecal fatty acids averaged 46 mmol/

day (normal range 11-18 mmol/day). These results suggested malabsorption because of gastrointestinal disease and a jejunal biopsy was taken. The biopsy was interpreted as total villous atrophy (Fig. 2). It was considered that he had late onset gluten sensitive enteropathy and he was treated with a gluten free diet, codeine phosphate, folic acid, and vitamin supplementation. Despite adherence to the gluten free diet the diarrhoea became worse, he lost a further 5 kg in weight and he became confused and weak.

In April 1983 he was noted to have developed brown, macular hyperpigmentation of the palms of both hands (Fig. 3). His skin was very soft to touch and his nails had not regrown. Tetany of facial muscles developed. His total serum calcium was 1.6 mmol/l, ionised calcium 0.86 mmol/l, serum magnesium 0.46 mmol/l and serum albumin 30 g/l. The tetany responded to intravenous calcium and magnesium. Dihydroxycholesterol together with oral supplements of calcium and magnesium subsequently maintained normal electrolyte levels. The differential diagnosis was gluten sensitive enteropathy resistant to diet or soya flour sensitivity. A soya and gluten free diet resulted in no improvement. In view of the possibility of a small intestinal lymphoma a second jejunal biopsy was taken, which showed the same histological abnormalities as the initial specimen and, on this occasion, the comment was made that it did not resemble jejunal mucosa at all. A barium meal and follow through revealed multiple rounded filling defects throughout the stomach and duodenum (Fig. 4). As a

Address for correspondence: Dr K Freeman, Royal Devon and Exeter Hospital (Wonford), Banack Road, Exeter EX2 5DW.

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Fig. 1 Non-scarring loss of finger nails.

Fig. 2 Biopsy of jejunal mucosa shows a flat, non-villous surface with few crypts. The glands are tortuous, some dilated and are lined by mucus secreting cells. Most of the bulk of the tissue is accounted for by loose connective stroma. (Haematoxylin and eosin $\times 80$ original magnification).

Fig. 3 Macular hyperpigmentation of palms and fingers.

result of profuse diarrhoea several attempts at sigmoidoscopy failed to give any useful information and a barium enema examination could not be carried out. The diagnosis of Cronkhite Canada syndrome was made.

He was given a high protein, low fat diet supplemented by vitamins and folic acid. Over the next six months his condition deteriorated further. By November 1983 he was weak, confused, and bedridden. He died of bronchopneumonia approximately two years after the onset of his symptoms.

NECROPSY FINDINGS

The presence of widespread gastrointestinal polyposis was confirmed. The body and antrum of the stomach showed innumerable small, pink, faintly translucent polyps up to 1 centimetre in size. These were most numerous near the pylorus (Fig. 5). Similar polyps were present in the duodenum and throughout the small intestine, being particularly numerous in the ileum. A large number of polyps were present in the colon.

Blocks for histology were taken at 22 levels from

the stomach to rectum, from polyps as well as from intervening mucosa as this did not appear normal at any level. The mucosa of the whole of the gastrointestinal tract was abnormal being replaced by distorted and often cystic glands separated by loose, oedematous stroma. Specialised cells – that is, gastric oxyntic or chief cells, Paneth cells or endocrine cells, were few or absent and the glands were lined by simple mucus secreting cells only. Villous atrophy in the small intestine was total. The appearances were the same as those seen in the jejunal biopsies taken during life (Fig. 2). At any level there was no difference between polyps and intervening mucosa except in volume.

The cause of death was bilateral bronchopneumonia. The only additional finding was the presence of a slightly nodular liver which, on histology, showed mild parenchymal regenerative hyperplasia without fibrosis.

Discussion

Cronkhite and Canada¹ first described two cases of

Fig. 4 Barium meal shows multiple rounded filling defects. Innumerable smaller polyps were also seen at necropsy.

Fig. 5 Multiple tiny polyps near the pylorus. On close inspection, the whole mucosal surface is abnormal, with a fine cobblestone-like appearance.

non-familial gastrointestinal polyposis associated with cutaneous hyperpigmentation, alopecia and nail dystrophy; since then, a further 54 cases of this syndrome have been reported. The literature has recently been the subject of an extensive review.² The mean age at onset of symptoms was 60 years (Fig. 6). Sixty per cent of the 56 reported cases were men. No evidence of a genetic predisposition has been found.

The clinical presentation of general lassitude, diarrhoea and weight loss are typical. Loss of taste, dry mouth, vomiting and peripheral paraesthesiae have been reported less frequently. Anaemia is commonly caused by malabsorption of folate and iron, oedema developing after gastrointestinal loss of albumin and tetany is due to hypocalcaemia and hypomagnesaemia associated with malabsorption. Hypokalaemia is common. A low serum vitamin B12 level has been reported in only one patient but the malabsorption type of Schilling test, observed in our patient has been found in 8 out of 10 patients studied.

Brown macular hyperpigmentation was noted in 45 patients. This most frequently occurred on the upper limbs followed by the lower limbs and face; mucosal hyperpigmentation was seen in only two cases. The loss of nails in our patient was striking. This has been reported in only 10 patients. In other cases, the nails were dystrophic, fragile and discoloured to a varying degree with thinning, ridging, and splitting. The appearance of multiple, rounded filling defects on the barium meal is characteristic; in some cases, giant rugal folds in the stomach has led to an initial diagnosis of Menetrier's disease. The stomach and the colon are involved in almost all cases, the duodenum in 75% and the jejunum and ileum in 50%. Biopsy

findings in life have been variable. Cotterill *et al*³ and Nonamura *et al*⁴ reported only minor abnormalities in jejunal biopsies; the finding of jejunal diverticulosis in one case by Cunliffe and Anderson⁵ remains unique. Small intestinal, and in particular, jejunal changes have been little documented. Nineteen of the 21 cases autopsied showed mild polypoid changes in the small bowel. Histology of interpolyoid areas is not recorded. In the remaining 34 cases jejunal histology was not reported. The mechanism of diarrhoea is also unexplained. It may cease spontaneously or as a result of symptomatic treatment or remit when only part of the polyp bearing intestine is removed.⁶⁻⁸ Conversely, in one case⁹ polyps were known to be present for 16 years without diarrhoea, but this is exceptional.

The structural changes throughout the gastrointestinal tract in our case were striking and unlike those seen in coeliac disease. Though the appearances in coeliac disease are called atrophy this is a misnomer. The lack of villi is because of increased cell turnover and failure to differentiate: the condition is one of extreme epithelial hyperplasia with accelerated loss of cells from the surface.¹⁰ Moreover, neither stomach nor colon are affected. Though the cell kinetics of the gastrointestinal tract or skin have not been studied in the Cronkhite Canada syndrome, it should be a fruitful subject for this approach and may well turn out to be the opposite to coeliac disease.

The morphological changes of glandular disorganisation, cystic dilatation, loss of specialised cells and the increase in connective tissue that accompanied them in our case suggest a low turnover state – that is, a true atrophy. Normally, control of cell proliferation in epithelia, particularly of the gastrointestinal tract and of skin, is subject to homeostatic control for which chalone, epidermal and other growth factors and enteroglucagon have been held responsible.¹¹ Overstimulation results in hyperplasia, as in coeliac disease, while loss of the stimulus for renewal or acquired resistance to it may lead to atrophy, the mucosa being transformed into a reservoir of aged cells with no absorptive role. The same would apply to skin, nails, and hair. The changes could thus be due to a primary abnormality in the affected epithelia, producing the loss of, or resistance to, stimuli for proliferative activity, or could be because of inhibition of proliferative stimuli at source as a result of a biochemical failure of their synthesis or an inhibition of their release. Skin 'atrophy' has never been measured but its softness is often commented upon. Hyperpigmentation has been ascribed to accumulation of

Fig. 6 Age at onset of symptoms in the 56 reported cases of Cronkhite Canada syndrome.

melanin, without any increase in the number of pigment producing melanocytes. Although 'panaplasia' of the gut was present in our patient, there had been no evidence of hypopituitarism; thyroid and adrenal function had been normal and at no stage had he developed hyponatraemia or hypoglycaemia.

The small number of reported cases makes assessment of treatment difficult. Replacement and supplementation therapy with blood, fluids, albumin, vitamins, amino acids and lipids is clearly beneficial. Corticosteroids have been used in 10 patients and anabolic steroids in five with inconclusive results. It is doubtful if antibiotics have any role. Surgical excision of involved stomach or bowel carry a high operative risk. The outlook remains dismal: of the 56 reported cases only six are known to have survived for more than 24 months after diagnosis. Cachexia, anaemia, bronchopneumonia, septicaemia and congestive cardiac failure were the causes of death. More effective therapy for Cronkhite Canada syndrome is likely once the pathogenesis is better understood.

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