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Case report

Malignant histiocytosis and encephalomyeloradiculopathy complicating coeliac disease

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SUMMARY A 62 year old Irish woman with an eight year history of probable coeliac disease developed brain stem signs, unilateral facial numbness and weakness, wasting and anaesthesia in both lower limbs. Over the next two years, a progressive deterioration in neurological function and in intestinal absorption, and the development of anaemia led to a suspicion of malignancy. Bone marrow biopsy revealed malignant histiocytosis. Treatment with cytotoxic drugs led to a transient, marked improvement in intestinal structure and function, and in power of the lower limbs. Relapse was associated with bone marrow failure, resulting in overwhelming infection. Post mortem examination confirmed the presence of an unusual demyelinating encephalomyelopathy affecting the brain stem and the posterior columns of the spinal cord.

Various neurological complications have been described in patients with coeliac disease. These include: peripheral neuropathy, myopathy, myelopathy, cerebellar syndrome, and encephalomyeloradiculopathy.[1 2] On occasion, neurological symptoms may be related to a deficiency of water soluble vitamins or to metabolic complication of malabsorption, such as osteomalacia. In most instances, however, such causative factors cannot be implicated.

Malignant complications are also well recognised in coeliac disease with increased prevalence of both gastrointestinal adenocarcinomas and of lymphomas with and without gut involvement.[3] It has recently been shown[4 5] that these 'lymphomas' consist of cells with morphological and immunohistochemical characteristics of histiocytes, and the condition could therefore be classified as malignant histiocytosis.

This paper describes a patient with coeliac disease who developed a neurological syndrome resembling the encephalomyeloradiculopathy described in patients with coeliac disease by Cooke and Smith.[6] She later developed malignant histiocytosis with evidence of involvement of bone marrow.

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Case report

A 54 year old Irish woman first presented to her local hospital in 1970 with a two year history of abdominal pain; pale, watery stools; ankle swelling and weight loss. Blood tests revealed iron, folic acid and vitamin K deficiency, and low levels of serum albumin and calcium. A peroral suction biopsy of the third part of the duodenum showed partial villous atrophy, flattening of surface enterocytes, increased epithelial lymphocytes, and increased mononuclear cell infiltration in the lamina propria suggesting adult coeliac disease. A gluten free diet was instituted and the diet supplemented with iron, folic acid, calcium, and vitamin B_{12}. Within weeks, her pain and diarrhoea had disappeared, and her weight, haematological and biochemical abnormalities had returned to normal. The jejunal morphology was not, however, reassessed. She continued to enjoy good health until seven years later when, after a three month period of anorexia

and weight loss, she developed deafness in the right ear, numbness on the right side of the face, an absent right corneal reflex, and some unsteadiness of gait. The clinical features suggested a lesion in the region of the right cerebellopontine angle or affecting the right side of the brain stem. Full radiological studies of the skull (including CT scan and vertebral and carotid angiograms) were non-contributory.

Over the next six months, the lower limbs became progressively weaker. Examination revealed that the cranial nerve signs had receded somewhat but there was now weakness of both lower limbs. Tendon reflexes and perception of pinprick were absent below the knees. The plantar responses were equivocal, possibly extensor. The visual evoked responses were normal, as was the spinal fluid. The haemoglobin was 14·2 g/dl, albumin 40 g/l, calcium 2·45 mmol/l, red cell folate 64 ng/ml (normal 160–640), and urine D-xylose excretion after five hours was 16 mmol (N: 33). The clinical diagnoses at this time were coeliac disease with peripheral neuropathy, although the possibility of multiple sclerosis had been considered at one stage. She was treated with a course of ACTH and prednisolone and improved markedly. Within six months she was fully ambulant.

This remission was not sustained, however, and six months later (January 1980) there was rapid deterioration with weakness in both legs (R>L) and numbness and burning pain in the right leg and foot. For the first time, she also had saddle anaesthesia and loss of anal, urethral, and vaginal sensation. She was referred to the National Hospital for Nervous Diseases, London, where detailed examination and extensive investigations suggested multiple discrete neurological lesions involving the postchiasmatic optic tracts; the brain stem at the level of the left cochlear nucleus; the posterior (and possibly lateral) columns of the spinal cord; and the lumbo-sacral nerve roots (widely and asymmetrically). The sural nerve action potentials were retained, and histamine flares were brisk over the feet. Computerised tomographic scan and metrizamide myelography did not reveal any space occupying lesion in the brain, cerebellopontine angle, or spinal cord. The cerebrospinal fluid contained 38 mg protein per 100 ml with an oligoclonal pattern on electrophoresis. Eighteen leucocytes were also detected per mm^3 of CSF (56% lymphocytes, 33% polymorphs, and 11% histiocytes).

Her neurological status continued to deteriorate, so that by May 1980, when she was referred to Hammersmith Hospital, she was severely incapacitated with deafness in the right ear, weakness of both lower limbs, impaired sensation (all modalities) in L_5-S_5 dermatomes, and reduced bowel and bladder sensation. She had no complaints referable to the gastrointestinal tract.

The clinical diagnosis was revised to encephalomyeloradiculopathy complicating coeliac disease.[6] A detailed dietary assessment revealed that gluten had been ingested consistently during the past 10 years. Haemoglobin was 13 g/dl, serum albumin 45 g/l, B_{12} level 300 ng/l, and serum and red cell folates (while on supplements) were 94 and 4656 μg/l, respectively. Jejunal biopsy performed while on a gluten restricted (though not completely gluten free) diet showed partial villous atrophy, infiltration of epithelium by lymphocytes, increased cellularity of the lamina propria, and crypt hyperplasia (Fig. 1). Intestinal function tests revealed reduced urinary

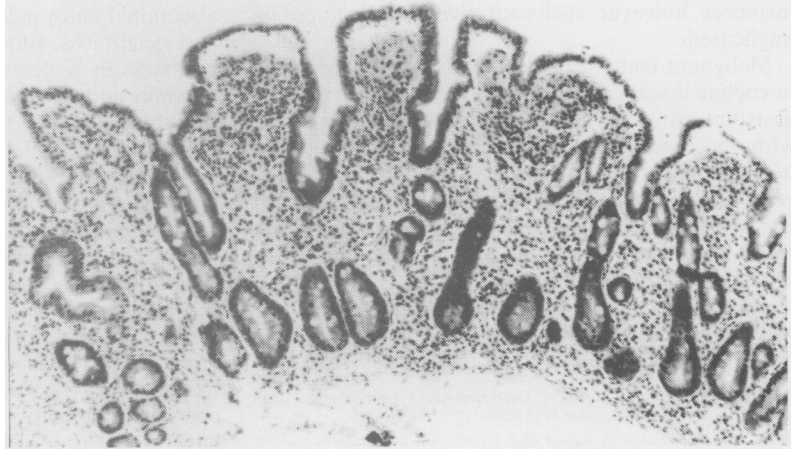

Fig. 1 *Photomicrograph of jejunal biopsy showing partial villous atrophy and increased chronic inflammatory infiltrate in lamina propria (H and E, ×80, original magnification).*

excretion of a 25 g D-xylose load (16 mmol or 2·4 g in five hours), increased faecal fat excretion (36 mmol (10 g/day), and marginally low vitamin B_{12} absorption (8% on a Schilling test performed with intrinsic factor). These findings were still consistent with poorly-treated coeliac disease. Although there were no ocular or mucocutaneous signs of nutritional deficiencies, assays were performed for B vitamins (thiamine, biotin, pyridoxine, B_{12}) and trace elements (copper, zinc, magnesium). The serum levels were all within the normal range. Clinical management was based on the assumption that the neurological disorder was a nutritional complication of active coeliac disease and accordingly a therapeutic trial of high dose vitamin and mineral therapy together with a strict gluten free diet and intensive physiotherapy was instituted. After two weeks without obvious improvement, prednisolone 30 mg/day was added to this regime, but there was no improvement in neurological symptoms and signs, or in gut morphology or function.

Between June and October 1980 there was weight loss of 6 kg, a progressive fall in haemoglobin, serum cholesterol, and albumin levels (Table) and for the first time, there was evidence of hyposplenism on the blood film (Howell-Jolly bodies). Splenic hypofunction was confirmed by showing reduced clearance of ^{51}Cr labelled heat-damaged erythrocytes. Furthermore, the serum iron level, D-xylose, and vitamin B_{12} absorption continued to fall (Table). Over the same four month period, serial neurological examinations by an individual observer (CAP) and myometric analyses (Fig. 2) confirmed progressive deterioration. In view of the suspicion of a malignancy complicating coeliac disease, bone marrow examination and a barium series were performed, but revealed no abnormalities. She was therefore subjected to elective laparotomy at which no evidence of malignancy was found macroscopically or on biopsies of the intestine and liver.

Table *Serial measurements of body weight, haemoglobin, albumen, calcium, cholesterol and iron levels and D-xylose and vitamin B_{12} (Schilling plus intrinsic factor) absorption tests between June and November 1980*

	J	*J*	*A*	*S*	*O*	*N*
Mean weight (kg)	55	54·2	53·6	51·2	50·3	48·8
Hb (g/dl)	13	12·2	10·5	11	9·2	8·1
Ca (mmol/l, uncorrected)	2·45	2·24	2·27	2·25	2·13	1·75
Albumin (g/l)	45	45	34	37	33	24
Cholesterol (mmol/l)	6·8	6	2·8	2·3	1·8	1·6
Fe (μmol/l)	15·9		22·5		11·5	
D-xylose (g/5 h)	2·4	1·6		1·7		0·8
Schilling (%)	8	1·4	2·1	2·1		

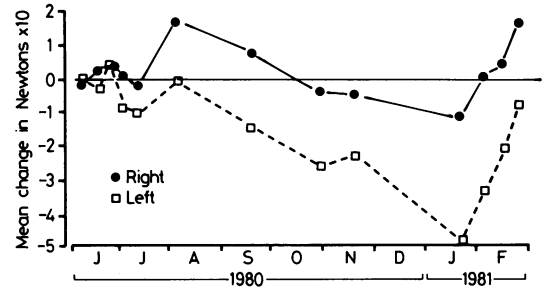

Fig. 2 *Graph of the change in muscle power in two lower limbs. Each point is mean of the power recorded in all muscle groups tested in each limb, compared with the muscle power on presentation. Letters on horizontal axis indicate month starting with June 1980.*

Four weeks postoperatively, she developed ankle swelling, deterioration of the weakness and wasting in the lower limbs, and general lethargy. The haemoglobin level had fallen to 9·4 g/dl and the albumin to 24 g/l, and both the total leucocyte and platelet counts were falling rapidly. A repeat bone marrow biopsy revealed hypercellular fragments consisting predominantly of malignant histiocytes (Fig. 3). The histiocytic nature of the cells was supported by positive immunocytochemical staining for muramidase and α_1-antitrypsin.

Treatment was begun with cyclophosphamide, vinblastine, adriamycin, and prednisolone in conventional dosage and, within two weeks of the first course of treatment, there was an improvement in her general condition and nutritional status (Hb 14 g/dl, cholesterol 5·8 mmol/l, albumin 42 g/l). D-xylose (33 mmol (5 g) excreted in five hours, after 25 g load) and B_{12} absorption (Schilling test with intrinsic factor 17% excretion in 24 hours) returned to normal and the jejunal mucosa (Fig. 4) showed taller villi, less crypt hyperplasia, and reduced mononuclear cell infiltration. A trephine marrow biopsy was hypocellular and no malignant histiocytes were detected.

At this stage, further examination of the cerebrospinal fluid revealed histiocytes, the malignant nature of which was uncertain. In view of the possibility of malignant infiltration of the meninges, however, she was treated with intrathecal methotrexate. As shown by myometric testing, there was a marked improvement in the power in both lower limbs after the first cycle of systemic and intrathecal chemotherapy.

Despite this promising initial response to the first

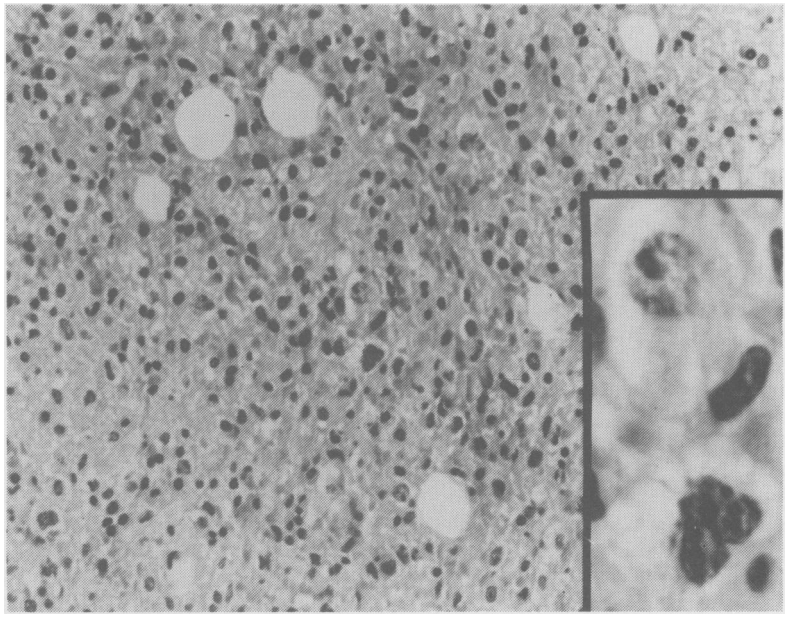

Fig. 3 *Photomicrograph of bone marrow biopsy showing hypercellularity due to infiltration by histiocytes (H and E, ×275, original magnification). Inset – histiocytes with atypical cytological features (H and E, ×800, original magnification).*

cycle of cytotoxic therapy, within 28 days there was rapid deterioration and evidence of bone marrow failure shown to be because of recurrent malignant infiltration of the bone marrow. This first recurrence responded partially to further chemotherapy; however, a devastating recurrence occurred soon after the second cycle of chemotherapy and in spite of intensive supportive therapy she died in April 1981 with uncontrolled haemorrhage and infection secondary to bone marrow failure with evidence of malignant histiocytic infiltration.

Necropsy revealed malignant histiocytosis in the bone marrow (confirmed immunohistochemically using antimuramidase and stains for α_1-antitrypsin). Although occasional histiocytes with somewhat atypical morphology were present in other organs (lymph nodes, liver), no definite evidence of involvement of these organs by malignant histiocytosis was found.

The intestinal epithelium was autolysed; however, well-formed villi were recognisable, suggesting recovery from the villous atrophy existing before

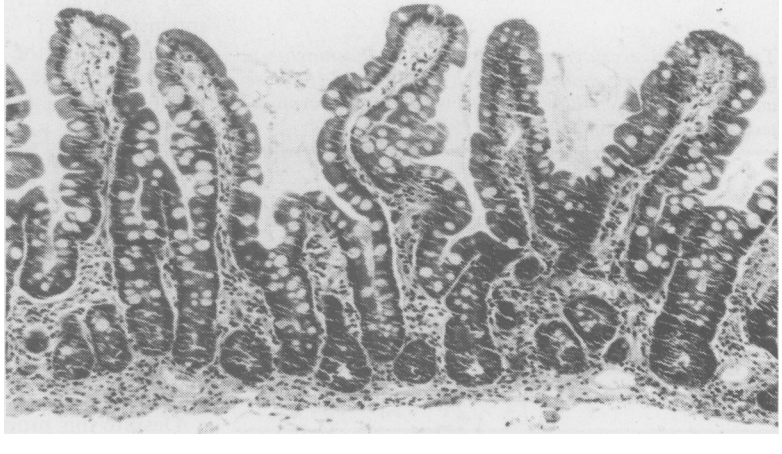

Fig. 4 *Photomicrographs of jejunal biopsy (taken after first course of cytotoxic chemotherapy) showing tall villi, and reduced mononuclear cell infiltrate in lamina propria (H and E, ×80, original magnification).*

treatment with cytotoxic chemotherapy. There was no evidence of malignant histiocytosis in a large number of sections taken from various levels of the intestine. Failure to identify infiltration by malignant histiocytes in the viscera usually affected (small intestine, liver, and lymph nodes) may have been because of the cytotoxic agents administered.

The central and peripheral nervous system also showed no evidence of histiocytosis at postmortem examination. There was, however, a small area of myelin loss in the brain stem in the pattern seen with central pontine myelinolysis (Fig. 5). The spinal cord showed dorsal column pallor (demyelination with some axonal degeneration) which was most marked in the lumbar segments (Fig. 6).

Discussion

The initial diagnosis of coeliac disease in this patient was based on the clinical picture, histological assessment consistent with this diagnosis and a prompt clinical, haematological, and biochemical response to a gluten free diet. As follow-up biopsies were not performed, however, no clear histological response to gluten restriction was shown and compliance with a gluten free diet was not rigorous over the 10 year period between the initial presentation and first development of neurological symptoms.

The neurological condition was characterised by evidence of discrete lesions dispersed in the central nervous system, with involvement of the post-chiasmatic optic tracks, brain stem at the level of the cochlear nucleus, the posterior columns in the spinal cord, and the lumbosacral roots. The presence of an oligoclonal pattern in the CSF, with prolonged visual evoked responses and multiple lesions suggested a diagnosis of multiple sclerosis. The size of the brain stem lesion and the evidence of radicular involvement, however, were more consistent with a diagnosis of encephalomyeloradiculopathy complicating coeliac disease.

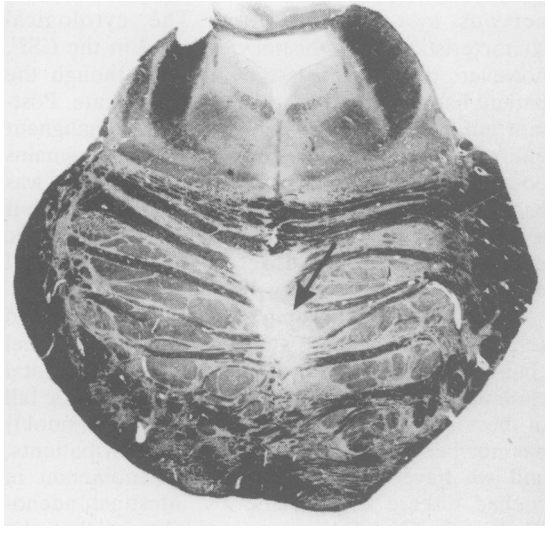

Fig. 5 *Photomicrograph of transverse section taken through the pons showing a small central pontine area of myelin loss (Luxol fast blue, ×3, original magnification).*

Cooke and Smith[6] reported 16 patients with biopsy-proven coeliac disease who developed a picture characterised by sensory ataxia with loss of all modalities of sensation, associated in some patients with cerebellar signs and unexplained episodes of unconsciousness. Fourteen patients developed the neurological complication while on a gluten free diet and 10 patients suffered progressive deterioration. Necropsy in nine patients showed tract degeneration (posterior and lateral columns of the spinal cord) in the majority and focal demyelination, cerebellar cortical degeneration, and vascular-type lesions in occasional cases. The aetiology of these complications was not determined; only one of Cooke and Smith's patients was deficient in vitamin B_{12}; no patients responded to B_{12} therapy; however, five recovered while receiving high dose parenteral supplementation of water soluble vitamins. This was the basis for the therapeutic trial attempted in our patient, albeit without success.

In our patient the main necropsy findings in the central nervous system were posterior column degeneration, and focal brain stem myelin loss resembling a small area of central pontine myelinolysis. The former is consistent with the experience of Cooke and Smith while the latter finding may be seen as a terminal event in desperately ill patients where maintaining adequate nutritional support is difficult.[7]

An increased incidence of lymphoma is well recognised in patients with coeliac disease.[8 9] In a recent report[3] 27 out of 385 patients with coeliac disease developed lymphoma: in 23 of these patients the histological type was described as reticulum cell sarcoma. In a series of 18 patients with malabsorption associated with small intestinal lymphoma reported by Isaacson and Wright,[5] the cell type was believed to be histiocytic in all and recently an MRC co-ordinated study of malignancy in coeliac disease[10] confirmed that the lymphoma should be preferably classified as a malignant histiocytosis.

Using strict morphological and immunohistochemical criteria, the lymphoma in the patient described here was classified as malignant histio-

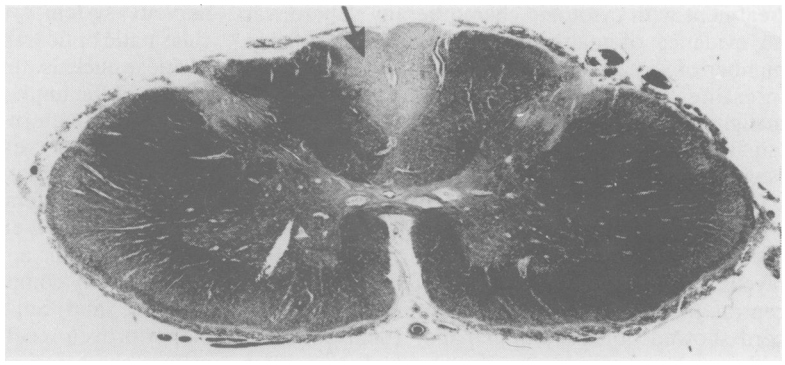

Fig. 6 *Photomicrograph of a transverse section through thoracic segment of spinal cord, stained for myelin, showing dorsal column pallor (Luxol fast blue, ×9, original magnification).*

cytosis. It is intriguing to note that one of the patients reported by Isaacson and Wright[5] had suffered from malabsorption, thought to be because of coeliac disease, for nine years before malignant histiocytosis was diagnosed. Although it is generally accepted that coeliac disease may be complicated by malignant histiocytosis, there are few reported cases of overtly life-long coeliac disease with this complication, most patients presenting with a malignancy or developing one within a few years of the diagnosis of coeliac disease in middle-age. It seems possible that this condition is distinct from childhood coeliac disease and represents a histiocytic disorder affecting the gut with a long latency before malignant proliferation is evident. In this case the role of gluten sensitivity may be secondary. Clarification of this problem requires the demonstration of a clear morphological response to a gluten free diet in individuals who subsequently and at a much later date, develop malignant histiocytosis. This case does not fulfill these criteria.

Although bone marrow infiltration in patients with malignant histiocytosis of the intestine is not uncommon (five out of 18 in Isaacson and Wright's series[5]), involvement of the central nervous system is unusual. A patient with histiocytic lymphoma of the small intestine complicating coeliac disease[11] later developed a histiocytic tumour in the right parietotemporal region.[12] Another patient reported from the Massachusetts General Hospital showed many similarities to the patient reported here.[13] This was a 50 year old man who had suffered from coeliac disease for 10 years when (while apparently in remission) he developed sensory ataxia with loss of posterior column sensation. Four years later, in a preterminal illness, he developed head and neck ache, cerebellar signs and haematemesis. Postmortem examination revealed reticulum cell sarcoma (a term probably synonymous with malignant histiocytosis) at various sites in small and large intestine, liver, spleen, lymph nodes, leptomeninges, and spinal roots. There was also old demyelination of the posterior columns of the spinal cord (which was considered responsible for the neurological picture that developed four years before his death). The small intestine showed many features consistent with a diagnosis of coeliac disease. Interestingly, one of the 16 patients with encephalomyeloradiculopathy originally described by Cooke and Smith[6] was found to have a multifocal histiocytic tumour (called reticulum cell sarcoma) of the small intestine. There was no evidence, however, of malignant infiltration of the nervous system.

It was conceivable that the progressive neurological deterioration in the final year of the patient's illness may have been because of central nervous system infiltration. The cytological characteristics of the histiocytes found in the CSF, however, did not suggest malignancy though the patient had received intrathecal methotrexate. Postmortem examination did not reveal malignant infiltration of neural tissue or nerve roots. It remains possible that the neurological deterioration was because of a paraneoplastic phenomenon, though it is doubtful if this occurs in patients with histiocytic malignancies.[14] An unrecognised nutritional deficiency (cf. ref 15) may also be postulated.

A study of the biochemical parameters measured serially in this patient's illness revealed parallel changes in the haemoglobin, albumin, and total cholesterol levels. The progressive and dramatic fall in the total serum cholesterol level (to 1·5 mmol/l) has not been reported previously in such patients, and we have not observed this phenomenon in coeliac disease complicated by intestinal adenocarcinoma. One intriguing possibility is that the cholesterol was being sequestered by the malignant histiocytes. Lampert, Catovsky, and Bergier[16] reported low plasma cholesterol levels in six of their

12 patients with histiocytic medullary reticulosis.

Although there was no improvement in gut morphology and function over several months of strict gluten exclusion, a striking improvement in jejunal morphology and intestinal function occurred with eight days of the first course of cytotoxic therapy. This kind of improvement in villous morphology may be seen in uncomplicated coeliac disease treated with a gluten free diet but in our experience usually takes a minimum of two or three months and often longer. There are no reports of the use of cytotoxic or immunosuppressant combination chemotherapy in uncomplicated coeliac disease for obvious reasons but it is interesting to speculate that the delayed morphological response characteristically seen after gluten withdrawal may be because of persisting immunological mechanisms directed against the gut. The alternative explanation is that the intestinal lesion in patients with malignant histiocytosis is a response to the malignancy *per se* and not to gluten hypersensitivity and responds accordingly to chemotherapy and tumour regression.

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