Case reports

Lymphadenopathy in coeliac disease

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SUMMARY We present two cases of adult coeliac disease whose major clinical feature was marked lymphadenopathy. One patient also displayed a peripheral lymphocytosis which varied with treatment of the underlying disease.

The development of lymphadenopathy in coeliac disease is generally thought to be an ominous sign because of the increased incidence of malignancy in this condition.¹ We present two such patients in whom the lymphadenopathy regressed with treatment of the underlying disorder and, in addition, one demonstrated a marked lymphocytosis which seemed to reflect the degree of control of his coeliac disease.

Case reports

CASE 1

A 55 year old man presented with a three month history of weight loss and progressive ill-health. For the previous five days he had noticed a swelling in the left side of his neck, causing slight dysphagia. Examination revealed him to be anaemic, emaciated, dehydrated with signs of a chest infection, and there was marked lymphadenopathy in the left cervical region.

Nine years previously, after complaining of dyspnoea, he had been diagnosed as having sarcoidosis on the basis of a radiograph of the chest showing diffuse fibrotic changes, and a positive Kveim test. He was treated with prednisolone 10 mg daily for five years with gradual resolution of the radiographic abnormalities. A mild megaloblastic anaemia due to folate deficiency was also noted and a 24 hour faecal fat estimation was slightly raised. However, no other deficiencies were found and apart from a barium meal, which was normal, no other investigations were performed.

Investigations on current admission: haemoglobin was 8.0 g/dl, folate 0.2 µg/l (normal >1.9 µg/l), B12 normal, bone marrow showed megaloblastic

anaemia together with toxic changes in granulopoiesis. Total protein was 58 g/l, albumin 21 g/l, calcium 1.6 mmol/l. Radiograph of the chest was normal; liver scan was normal with absent splenic activity. The enlarged cervical lymph nodes were biopsied and histology showed a mass of necrotic tissue infiltrated with polymorphs and lymphocytes, all demonstrating degenerative changes. There was no evidence of malignancy, sarcoid, or tuberculosis and culture of the tissue was negative. During the first week of his admission, he also developed enlarged lymph nodes in the right cervical region and these were also biopsied with identical histological findings. Using a Crosby capsule, a jejunal biopsy was obtained and this showed subtotal villous atrophy with a diffuse chronic inflammatory infiltrate (HLA typing: A1, Aw30, B8, B13, Cw6).

He was initially treated with intravenous rehydration and antibiotics and, once the diagnosis of coeliac disease was made, a gluten free diet was started. His general condition improved and the lymphadenopathy gradually resolved over the next two months. Shortly before starting his diet, a peripheral lymphocytosis was noted and this became more marked over the next two months before gradually returning to normal six months later (Fig. 1). When this was at its maximum—that is, the peripheral white cell count was $13.6 \times 10^9/l$ —it was further investigated by assessing the proportion of T and B lymphocytes. The T lymphocyte count was $8.3 \times 10^9/l$ —that is, 61% of the total white cell count (normal range 50–70% total)—and the B lymphocyte count was $2.7 \times 10^9/l$ —20% of the total (normal range 10–20%). In addition, there was a normal distribution of light and heavy chains on the B lymphocytes, and a normal κ to λ light chain ratio in the marrow. There was thus no evidence of monoclonality or lymphoid malignancy. A second bone marrow and a

Figure Case 1. Serial leucocyte counts. White column: total white cell count. Hatched column: Lymphocyte count.

liver biopsy at that time both showed a non-specific increase in lymphocytes but no evidence of malignancy. A jejunal biopsy was repeated after five months on his diet and showed early villous formation. However, two months after his peripheral white cell count had returned to normal, the lymphocytosis recurred and persisted for the next six months. Towards the end of this period he admitted that he had not been keeping to his diet and another jejunal biopsy showed an identical degree of villous atrophy to his first biopsy. Since resuming his diet, the lymphocytosis has again returned to normal. He has remained well for 18 months since these investigations with an increase in his weight from 40 kg to 68 kg and, apart from the temporary recurrence of his lymphocytosis at the time of his dietary lapse, there have been no abnormal clinical or haematological signs.

CASE 2

In 1970, a 25 year old female presented with bilateral ankle oedema. She was found to have an iron-deficiency anaemia and hypoproteinaemia. A radiograph of the chest showed multiple bilateral nodular opacities and a Kveim test was positive, so a provisional diagnosis of sarcoidosis was made. Six months later, she developed a hard, irregular, and deeply-fixed mass in the periumbilical region and complained of anorexia and weight loss. Barium studies were unhelpful so a laparotomy was performed—this revealed large numbers of enlarged lymph nodes in the small bowel mesentery but no other abnormality. Biopsies of these nodes were

difficult to interpret and showed patchy necrosis and chronic inflammation, but no evidence of malignancy or sarcoid. Cultures for tuberculosis were negative.

Over the next two months, she developed ascites and the hypoproteinaemia persisted. Faecal fat estimation was raised at 14.6 g/24 h and a barium meal and follow-through showed changes suggestive of malabsorption. However, a jejunal biopsy was unsuccessful and she refused further investigation for the next 1½ years. After this time, she again presented with further weight loss and diarrhoea. She was found to be anaemic once more and the abdominal mass was still present. Faecal fat was still raised at 16.5 g/24 h and a jejunal biopsy showed total villous atrophy with infiltration by plasma cells and lymphocytes. A gluten free diet was started and, as she followed this, her weight increased, the abdominal mass resolved, and for the past seven years her health has remained satisfactory (HLA typing: A1, A2; B8, B27; Cw1).

Discussion

These patients with coeliac disease demonstrated the clinical feature of pronounced lymphadenopathy and malignancy was strongly suspected as the cause. However, extensive investigations failed to confirm this and subsequently the lymphadenopathy regressed spontaneously with treatment of the coeliac disease. These cases illustrate that, although there is an increased incidence of malignancy, particularly lymphoma,¹⁻³ in coeliac disease and peripheral lymphadenopathy may sometimes be a manifestation of this, lymph node enlargement can also occur as part of the disease itself and resolves with treatment.

Lymphadenopathy is a rare presenting sign in coeliac disease, its incidence being 12% in one series⁵ but nil in several others,⁶⁻⁸ and, indeed, the opposite findings of lymphoid hypoplasia⁹ and splenic atrophy¹⁰ are well-recognised features of this condition. However, it is interesting that in one of the earlier reports on coeliac disease and mucosal abnormalities,¹¹ three out of four patients subjected to laparotomy were found to have markedly enlarged mesenteric nodes and the remaining patient was noted to have small abnormal glands in the jejunal mesentery. These findings are very similar to those in our second case and the histology of these abnormal nodes was also similar to that of both cases, showing fibrosis and infiltration with chronic inflammatory cells. It is, therefore, possible that this mesenteric lymphadenopathy is present in many cases of coeliac disease, but is no longer recognised now that laparotomy is not required to obtain jejunal histology and our second patient may repre-

sent an extreme example with clinically detectable nodes.

Reports of peripheral lymphocyte counts in coeliac disease vary. In two series,^{12, 13} values were normal and Bullen and Losowsky¹⁴ also found no significant difference in total lymphocyte counts in controls, patients with untreated coeliac disease, and those with treated coeliac disease and no evidence of hyposplenism. Treated patients with hyposplenism had significantly higher counts but these were well below the values obtained in our patient. In isolated cases, raised counts have been found,¹⁵ but these reached a maximum of only $6.0 \times 10^9/l$, well below the levels reached in our case, both at presentation and later when he lapsed from his gluten free diet. Holmes¹⁵ showed that the peripheral lymphocyte count in patients on diet was significantly lower than in patients not on a diet (although both counts were within the normal range) and this agrees with our patient's reduction in lymphocytosis when on diet.

T lymphocyte numbers are usually reduced in untreated coeliac disease compared with treated patients and healthy controls,^{13, 14} and this contrasts with the findings in this case. Treated patients with hyposplenism have a reduced percentage of T lymphocytes when compared with treated patients without hyposplenism,¹⁴ but absolute numbers are similar because of the relative lymphocytosis in those patients with splenic atrophy.

Splenic hypofunction is a well-recognised cause of both relative and absolute lymphocytosis in many disorders¹⁶ and it is possible that this partly accounts for the abnormal finding in our patient. However, as mentioned before, the values obtained in this case were much higher than those found in other coeliac patients with hyposplenism, so this is unlikely to be the sole explanation. In addition, hyposplenism alone could not account for the recurrence of lymphocytosis on cessation of the gluten free diet. Severe non-specific illness in the presence of splenic atrophy may also cause a marked lymphocytosis, but again this would not explain the recurrent rise at a time when our patient was symptom-free. The cause of the lymphocytosis is, therefore, uncertain and, although malignancy was initially suspected, especially in the presence of lymphadenopathy, no evidence of monoclonality suggestive of lymphoma was found and the patient has remained well under follow-up for 18 months. One possible explanation is that coeliac disease patients on a normal diet produce more lymphocytes because of extra antigenic stimulation to their lymphoid tissues and the

recurrence of lymphocytosis in our patient on stopping his gluten free diet would support this.

A wide range of immunological abnormalities has been described in coeliac disease but the basic cause of the condition is still unclear and these cases provide additional evidence of the complexity of the immune system dysfunction that underlies the disease.

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