

CASE REPORT

Enteropathy associated T cell lymphoma presenting as an isolated CNS lymphoma three years after diagnosis of coeliac disease: T cell receptor polymerase chain reaction studies failed to show the original enteropathy to be a clonal disorder

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Abstract

A case of enteropathy associated T cell lymphoma is reported in a 45 year old woman, presenting with isolated disease in the CNS, three years after diagnosis of coeliac disease. Initial staging showed no evidence of gastrointestinal tract lymphoma. A presumptive diagnosis of T cell primary cerebral lymphoma was made and the patient was treated with combination chemotherapy and craniospinal radiotherapy. The patient relapsed, seven months after treatment, with small bowel lymphoma. The immunophenotype and T cell receptor polymerase chain reaction analysis confirmed the same tumour as in the CNS. Retrospective polymerase chain reaction analysis of intraepithelial lymphocytes in the duodenal biopsy sample, taken at the time of diagnosis of coeliac disease, failed to show evidence of a clonal T cell proliferation.

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Keywords: enteropathy associated T cell lymphoma, primary cerebral lymphoma, coeliac disease, T cell receptor, polyclonal.

Coeliac disease is known to be associated with an increased risk of malignancy.¹⁻³ The relative risk for development of non-Hodgkin's lymphoma is 42.7 (95% confidence interval (95% CI) 19.6-81.4),⁴ for adenocarcinoma of the small intestine 82.7 (95% CI not available),⁵ squamous cell carcinoma of the oesophagus 12.3 (95% CI 2.5-36.5),⁴ and squamous cell carcinoma of the oral cavity and pharynx 9.7 (95% CI 2.0-28.3).⁴

The lymphoma, originally described as malignant histiocytosis of the intestine, is characterised by a pleomorphic infiltrate, multinucleate giant cells, histiocyte-like cells in the base of ulcers, and a dense infiltrate of plasma cells or eosinophils. The typical immunohistochemical features are CD3+, CD4-, CD8-, CD7+, CD103+, CD45RO+, and CD30+ with a clonal rearrangement of the T cell receptor β chain. The pathological entity has now been renamed enteropathy associated T cell lymphoma.

Enteropathy associated T cell lymphoma usually presents as extranodal intestinal disease. Nodal involvement with associated lesions in the lung, thyroid, skin, and Waldeyer's ring have been described. Isolated lymphoma has also been reported in the lung, thyroid, skin, and Waldeyer's ring alone.^{5 6}

We report a case of coeliac associated T cell lymphoma, presenting as isolated CNS disease mimicking primary CNS lymphoma, and the presumed course of the lymphoma based on gene rearrangement studies.

Case report

A 45 year old woman presented in 1992 with intermittent diarrhoea, abdominal discomfort, skin rash, and a haematological picture consistent with malabsorption. A distal duodenal biopsy specimen showed subvillous atrophy and intraepithelial lymphocytosis consistent with coeliac disease. A gluten free diet was started with rapid resolution of the symptoms. Duodenal biopsy was not repeated. She remained on a gluten free diet.

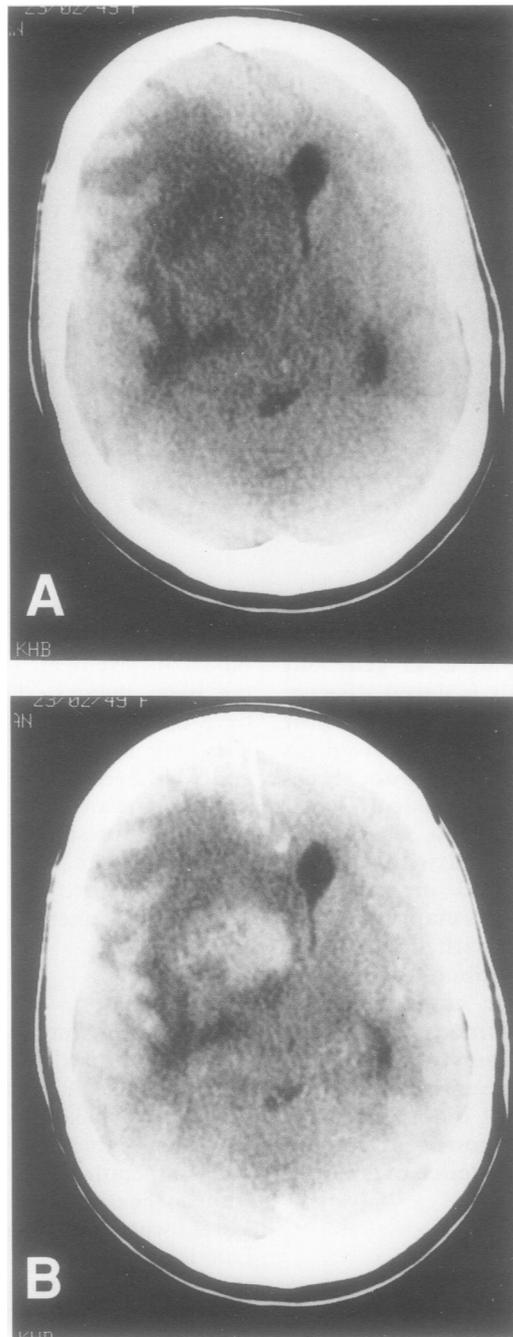
In 1995 she developed lethargy, confusion, short term memory impairment, and bitemporal headache. Brain computed tomography (CT) scan showed a low attenuation mass adjacent to and compressing the anterior horn of the right lateral ventricle, with considerable surrounding oedema and enhancement with intravenous contrast (Figure). The appearances were suggestive of primary cerebral lymphoma. A stereotactic biopsy specimen showed a necrotic tumour composed of pleomorphic lymphoid cells with immunophenotype CD45+ CD45RO+ CD3+ CD30+ CD20- EMA-. Polymerase chain reaction analysis for T cell receptor and immunoglobulin heavy chains was performed using three primer pairs.⁷ This demonstrated a clonal rearrangement of T cell receptor β and γ chain genes of 80 bp and 70 bp respectively. The histological diagnosis was of a T cell variant of large cell anaplastic lymphoma.

Staging investigations, which included full blood count, erythrocyte sedimentation rate, lactate dehydrogenase, bone marrow aspirate, and

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Pretreatment brain CT scan. (A) Unenhanced; (B) contrast enhanced.

trephine biopsy, small bowel barium studies, and a whole body CT scan, were normal with no evidence of lymphoma outside the CNS.

Histological review of the distal duodenal biopsy specimen in 1992 showed a pattern typical of coeliac enteropathy with no evidence of lymphoma and no clonal rearrangements of the T cell receptor on polymerase chain reaction. The final diagnosis was of a T cell lymphoma, localised to the brain in a patient with a history of coeliac disease.

She was treated with a six week course of weekly chemotherapy alternating 50 mg/m² adriamycin and 350 mg/m² cyclophosphamide on weeks 1, 3, and 5 with 2 g/m² methotrexate and 1.4 mg/m² vincristine on weeks 2, 4, and 6 together with 60 mg oral prednisolone daily for six weeks. This was followed four weeks

later by radiotherapy. She received cranio-spinal axis irradiation to a dose of 40 Gy in 24 fractions to the whole brain and 30 Gy in 20 fractions to the spine. The original mass, with a 2 cm margin, received a boost to a total tumour dose of 55 Gy in 33 fractions.

During chemotherapy our patient's cognitive function deteriorated despite complete radiological resolution of the enhancing mass. After completion of radiotherapy cognitive function remained unchanged. A low density lesion, consistent with an infarction, was noted in the basal ganglia. There was no evidence of residual primary cerebral lymphoma.

Four months after completion of treatment she developed a left 3rd nerve palsy. Brain magnetic resonance imaging did not show any enhancing masses and was unchanged. Cytology of cerebrospinal fluid was negative. Seven months after treatment she developed abdominal pain with watery diarrhoea and signs consistent with an acute abdomen. An abdominal ultrasound scan and plain radiograph showed ascites and thickened bowel loops, but no evidence of hepatic or splenic abnormality. There were bilateral pulmonary infiltrates on chest radiography. Despite supportive therapy her condition deteriorated and she died 11 months after the diagnosis of primary cerebral lymphoma and three years after the diagnosis of coeliac disease.

A postmortem examination confirmed the presence of small bowel high grade T cell lymphoma with involved adjacent lymph nodes and histological features consistent with enteropathy associated T cell lymphoma. The histological appearance, immunophenotype, and the T cell receptor β and γ chain gene rearrangements were identical with those of the cerebral lesion. There was no evidence of residual lymphoma in the brain. A perivascular lymphomatous infiltrate and fungal hyphae were noted in the lungs. No associated enteropathy of the small bowel was noted.

Discussion

We report the occurrence of an isolated T cell CNS lymphoma with an immunophenotype of enteropathy associated T cell lymphoma in a patient with coeliac disease maintained on a gluten free diet.

Primary cerebral lymphoma is a rare tumour representing 1–2% of primary brain tumours. It is usually of B cell type, and it occurs sporadically or in association with immune deficiency after organ transplantation or HIV infection. A T cell variant has been reported in 15% of patients with primary cerebral lymphoma, which is in keeping with our experience of three cases of T cell variant out of 30 cases of primary cerebral lymphoma. However, the histological and immunophenotypic appearance of T cell primary cerebral lymphoma and enteropathy associated T cell lymphoma are distinct and enteropathy associated T cell lymphoma presenting as isolated disease in the CNS has not been reported.

It is not clear whether true coeliac disease precedes the development of lymphoma, or

Evidence for relation of enteropathy associated T cell lymphoma (EATL) and coeliac disease

Coeliac disease causally linked to EATL

- (1) Immunohistochemical evidence shows that patients with enteropathy and EATL have the same intraepithelial T cell immunophenotype as patients with coeliac disease¹⁸
- (2) HLA type is very similar in patients with coeliac disease and EATL¹⁹⁻²¹
- (3) The enteropathy in EATL, although sometimes initially unresponsive to gluten withdrawal, becomes responsive after the lymphoma is treated²³
- (4) Coeliac disease has an increased incidence in first degree relatives of patients with coeliac disease. EATL also has an increased incidence in first degree relatives of patients with coeliac disease²⁵
- (5) Gluten free diet protects against the development of lymphoma in patients with coeliac disease⁴
- (6) Theoretical models exist for the development of clonal lymphoid proliferation in chronically inflamed mucosal lymphocytic tissue

Enteropathy caused by EATL and not gluten sensitivity

- (1) Clonal rearrangement of the T cell receptor on intraepithelial lymphocytes has been reported within the apparently non-neoplastic coeliac enteropathy in patients with EATL¹⁵⁻¹⁷
- (2) The indolent nature of EATL may lead to enteropathy presenting before the occult underlying lymphoma²²
- (3) Patients with EATL without coeliac disease rarely have a positive antigliadin antibody. It is usually detected in coeliac disease²⁴

whether an indolent, occult, T cell lymphoma coexists with a coeliac-like subvillous atrophy mediated by neoplastic intraepithelial lymphocytes. The Table gives the arguments linking the relation between coeliac disease and lymphoma.

T cell receptor gene polymerase chain reaction analysis of the duodenal biopsy sample, on which the original diagnosis of coeliac disease was made, failed to show clonal lymphocytes. We accept that this may be a sampling phenomenon, but it argues against the enteropathy being a consequence of infiltration by epitheliotropic clonal lymphocytes from a clinically occult T cell lymphoma. It is more in keeping with the hypothesis of lymphoma developing due to polygenic stimulation of T lymphocytes by gliadin injury.

It is suggested that a group of patients with coeliac disease, at increased risk of lymphoma, may be identified using specific histological criteria. These are the presence of hypoplastic jejunal crypts,¹² low lamina propria plasma cell counts,¹³ and histiocytic aggregates.¹⁴ There has been no prospective study of patients with these features.

A gluten free diet for over five years reduces the risk of subsequent lymphoma, and other associated malignancy to the same as that of non-coeliac populations.⁴

Conclusion

We have documented an isolated CNS presentation of enteropathy associated T cell lymphoma in a patient with coeliac disease maintaining a gluten free diet. The relapse with small bowel enteropathy associated T cell lymphoma suggests that the disease may have been microscopically disseminated at presentation, with the initial site of bulk disease in the CNS. Although enteropathy associated T cell lymphoma has appeared at isolated sites outside the small bowel⁵⁻⁶ it has not previously been reported presenting in the CNS.

The immunophenotyping and genotyping of the tumour and initial duodenal biopsy specimen suggest that enteropathy associated T cell lymphoma developed after a non-neoplastic, coeliac, enteropathy and that the original malabsorption was unlikely to have been due to a clonal neoplastic enteropathy as has been suggested in other cases.¹⁵⁻¹⁷

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