Virchows Arch
DOI 10.1007/s00428-005-0060-x

CASE REPORT

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Fatal CNS vasculopathy in a patient with refractory celiac disease and lymph node cavitation

Received: 31 May 2005 / Accepted: 3 August 2005

Abstract Celiac disease is an enteropathy occurring in genetically predisposed individuals due to a dietary intolerance to gluten. Patients with celiac disease may develop a neurological disorder of unknown cause, although autoimmune mechanisms are suspected. We report on a 56-year-old man with celiac disease, who became refractory to a gluten-free diet and died of a rapidly progressive encephalopathy. Magnetic resonance imaging indicated focal lesions of the cerebellum and brainstem, and electrodiagnostic studies suggested an axonal neuropathy. Autopsy revealed a flattened small-bowel mucosa with intraepithelial lymphocytosis, a spectrum of degenerative changes of the intra-abdominal and mediastinal lymph nodes, including cavitary degeneration, and splenomegaly. Histologically, the lymph nodes showed pseudocyst formation and lymphocytic vasculitis with fibrinoid necrosis, and sections of the brain exhibited fibrinoid degeneration of small blood vessels, sparse perivascular lymphocytic infiltrates, and perivascular ischemic lesions. Identical T-cell clones were identified in the duodenum, stomach, lymph nodes, and spleen. This patient had an unusual neurological disorder related to a vasculopathy, probably mediated by a circulating neoplastic clone of activated T cells.

Keywords Celiac disease · Encephalopathy · Vasculopathy · Neuropathy

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Introduction

Celiac disease is an immune-mediated, small intestinal enteropathy triggered by ingestion of gluten, the storage protein of wheat and related grains [30]. The disease is occasionally associated with disorders of the nervous system, including cerebellar ataxia, seizures, migraine headaches, and peripheral neuropathy [5, 27]. Little is known about the pathogenesis of these neurological disorders as autopsies are rarely performed in such individuals [4, 11, 13, 17, 22, 26, 28]. We describe an unusual case of fatal subacute encephalopathy due to a small vessel angiopathy in a patient with refractory celiac disease complicated by mediastinal and mesenteric lymph node cavitation (MLNC).

Clinical history

A 56-year-old man presented with a history of diminished appetite, diarrhea, and profound weight loss (70 lbs). He had been diagnosed with celiac disease 2.5 years earlier based on positive endomysial antibodies, a duodenal biopsy that revealed total villous atrophy with intraepithelial lymphocytosis, and response to a gluten-free diet. A strict gluten-free diet led to a diminution of symptoms and weight gain (58 lbs), and he returned to his usual state of health. He did well for more than a year, but became symptomatic again despite strict adherence to a gluten-free diet. On admission to the hospital, he complained of decreased appetite, nausea, diarrhea, weight loss, and mental

confusion. Examination revealed a cachectic man with bitemporal wasting, hypotension, tachycardia, and a fever of 101.9°F (38.8°C). Routine blood tests, including serum iron, folate, vitamin B12, and vitamin E levels, were normal. He had a low serum sodium level (128 mM/l) and elevations of total bilirubin (3.1 mg/dl), alkaline phosphatase (550 U/l), and serum ferritin (854 ng/ml). Antigliadin, anti-endomysial, and antinuclear antibodies were negative as was a serologic test for HIV. Urine, blood, and stool cultures were negative. An upper gastrointestinal series revealed dilatation of the small intestine, while an abdominal ultrasound and computerized tomography (CT) scan were normal. A repeat duodenal biopsy exhibited total villous atrophy and persistent intraepithelial lymphocytosis without morphologic evidence of collagenous sprue, lymphoma, or infection; gastric biopsies demonstrated lymphocytic gastritis. The patient received total parenteral nutrition, intravenous steroids, and azathioprine. Neurological examination showed diffuse muscle wasting and weakness (3/5 in the legs and 4/5 in the arms). He had diminished pain sensation in a glove–stocking distribution and areflexia with evidence of an axonal neuropathy on electrodiagnostic studies. Dysmetria and ataxia were detected. A CT scan of the brain was normal except for an ill-defined lucency in the left medial occipital lobe, attributed to focal atrophy. Lumbar cerebrospinal fluid (CSF) had a glucose level of 59 mg/dl, protein 244 mg/dl and one white blood cell. A venereal disease research laboratory test was nonreactive, and cultures for viruses, fungi, and bacteria were negative as were the results of polymerase chain reaction (PCR) for mycobacteria and herpes simplex virus.

The patient deteriorated neurologically with onset of brainstem dysfunction, progression of the peripheral neuropathy, and seizures. He received intravenous immunoglobulin (30 g daily for 3 days) with minimal improvement. On the 14th hospital day, magnetic resonance (MR) imaging demonstrated an area of T2 hyperintensity involving the right cerebellar hemisphere, pons, midbrain, and thalamus (Fig. 1a). Contrast enhancement was observed along the periphery of the lesions (Fig. 1b). Repeat CSF examination showed 15 cells (lymphocytes and monocytes). Despite aggressive treatment, including intravenous antibiotics, intravenous steroids, and infusions of gamma globulin, the disorder progressed, and the patient died 6 weeks after the onset of his neurological disorder.

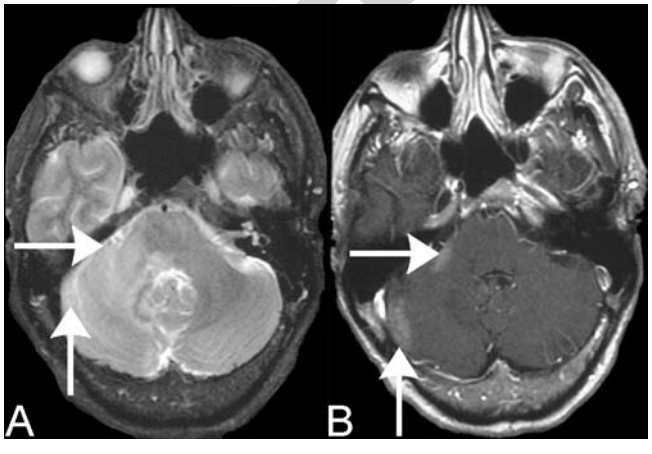

Fig. 1 Axial brain MR images. **a** T2-weighted image shows increased signal in the right pons, brachium pontis, and cerebellum (*arrows*). **b** Postcontrast T1-weighted image demonstrates enhancement along the lateral aspect of the signal abnormality (*arrows*)

Materials and methods

Morphologic assessment was performed using hematoxylin and eosin stained, formalin-fixed, paraffin-embedded tissue sections (3 μ). Sections of the brain were also stained with Bielschowsky, Gomori methenamine silver, periodic acid Schiff with and without diastase digestion, Ziehl–Neelsen (acid test bacteria), Gram, Giemsa, and Warthin–Starry stains. The following primary antibodies were used for immunohistochemical staining: CD2 (dilution 1:100; Novocastra, Burlingame, CA, USA), CD3 (dilution 1:800; Dako, Carpinteria, CA, USA), CD4 (dilution 1:50; Novocastra), CD5 (dilution 1:50; Novocastra), CD7 (dilution 1:200; Novocastra), CD8 (dilution 1:40; Dako), TIA-1 (dilution 1:1000; Dako), granzyme B (dilution 1:20; Chemicon, Temecula, CA, USA), perforin (dilution 1:50; Novocastra), CD30 (dilution 1:50; Dako), and C4d (dilution 1:100; ALPCO, Windham, NH, USA). The Envision plus system (Dako) was used for detection. Immunofluorescent (IF) staining was performed after pronase (*Streptomyces griseus*, 50,000 units; Calbiochem, La Jolla, CA, USA) pretreatment (0.03 g/ml for 10 min in TRIS buffer at 37°C) of paraffin-embedded tissue sections using the following fluorescein isothiocyanate–labeled antibodies: IgM, IgG, IgA, C3, C1q, fibrinogen, and albumin (Dako). PCR for T-cell receptor-γ (TCR-γ) gene rearrangement followed by polyacrylamide gel electrophoresis and heteroduplex analysis was performed according to the method of Bottaro et al. [3].

Results

A premortem right cerebellar hemisphere biopsy (performed on hospital day 15) demonstrated small vessel angiopathy, rare occlusive fibrin thrombi, and confluent areas of perivascular ischemic injury. Fibrinoid material was present in the vessel walls and perivascular areas accompanied by edema and an infiltrate of macrophages. Only sparse perivascular lymphocytes were noted in the neural tissue and leptomeninges. Histochemical stains and electron microscopy did not reveal any microorganisms.

Postmortem examination was significant for cachexia, hepatomegaly (2,750 g), and mild splenomegaly (210 g); no distinct mass lesions were identified in any organ. Sections of the duodenum and jejunum showed total villous atrophy (Fig. 2a) and a moderate intraepithelial lymphocytosis (Fig. 2a, insert). Although the intraepithelial lymphocytes lacked morphological atypia, they had an abnormal phenotype: CD2+, CD3+, CD5−, CD7+, CD4−, CD8−, CD30−, TIA-1+, granzyme B+, and perforin+.

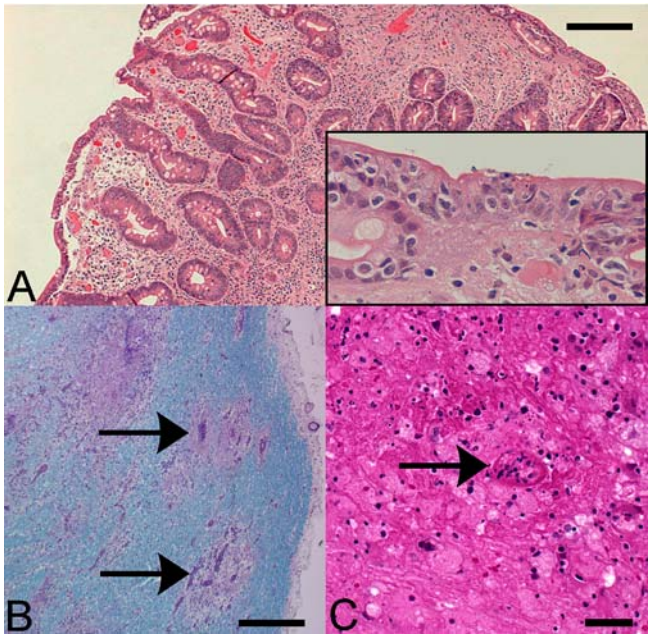

Fig. 2 Duodenum (**a**) and transverse sections of the pons (**b** and **c**). **a** Total villous atrophy and crypt hyperplasia. Hematoxylin & eosin, *bar*=500 μm. *Inset*: intraepithelial lymphocytosis. Hematoxylin & eosin. **b** The basis pontis exhibits small perivascular areas of ischemic injury (*arrows*) as reflected by loss of myelin. Luxol fast blue–periodic acid Schiff, *bar*=500 μm. **c** Fibrinoid material is present in the vessel wall (*arrow*) and the surrounding neural tissue accompanied by macrophages. Hematoxylin & eosin, *bar*=50 μm

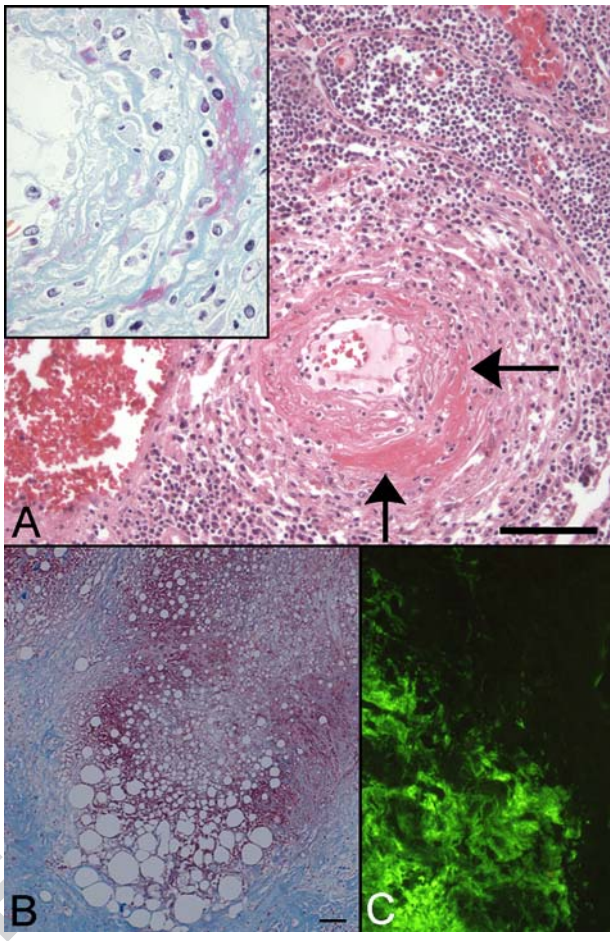

Fig. 3 Lymph node paracortex (**a**) and lymph node pseudocyst (**a** and **b**). **a** Small caliber blood vessel with an "onion-skin" appearance, infiltrating lymphocytes, and fibrin extravasate in the vessel wall (*arrows*). Hematoxylin & eosin, *bar*=100 μm. *Inset*: Lendrum stain highlights fibrin deposits. **b** Lymph node pseudocyst containing amorphous, granular, and flocculent material (chyle). Trichrome stain, *bar*=100 μm. **c** IF stain for fibrinogen

Mesenteric, para-aortic, and hilar lymph nodes showed a spectrum of histologic alterations from multifocal paracortical histiocytic aggregates to lymphocyte depletion and chylous pseudocyst formation to fibrosis and atrophy. In addition, numerous lymph nodes showed lymphocytic vasculitis of small-sized vessels with fibrinoid necrosis (Fig. 3a). The lymphocytes surrounding and infiltrating the vessel walls had the same immunophenotype as the intraepithelial lymphocytes, and there was no evidence of immune-complex deposition on staining for the different immunoglobulin heavy chains and complement components C1q, C3, and C4d. The amorphous fluid in the cavitary lymph nodes showed scattered clumps of fibrinogen by IF staining (Fig. 3c) that stained bright red with a trichrome stain (Fig. 3b). Apoptotic paracortical lymphocytes were also seen in the areas infiltrated by the atypical lymphocytes. Sections of the spleen showed marked white pulp depletion and a sparse red pulp infiltrate of small lymphocytes. PCR analysis for TCR-γ gene rearrangement demonstrated clonal T-cell products of similar molecular weight with the V10/11 family primers in the small intestine, stomach, lymph nodes, and spleen (Fig. 4).

Sections of the cerebellum revealed widespread loss of Purkinje cells and neurons of the dentate nucleus and astrocytosis, in addition to the histologic changes observed in the premortem biopsy. Microscopic lesions similar to the premortem cerebellar biopsy were also detected in the right pons (Fig. 2b,c), midbrain, thalamus, and basal ganglia. The spinal cord exhibited mild degeneration of the pyramidal tracts and the posterior columns with loss of myelinated nerve fibers in the nerve roots. No peripheral nerves were examined. Nearly all the perivascular lymphocytes were T cells, but no inflammatory cell infiltrates were noted within the blood vessel walls. Due to the paucity of the lymphocytic infiltrate, the immunophenotype of these cells

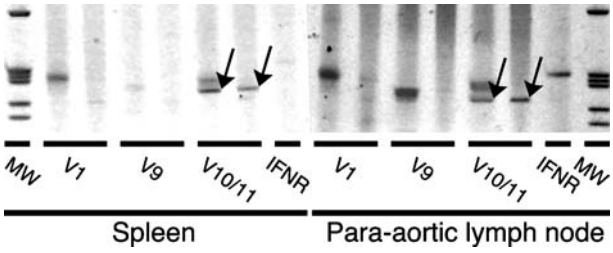

Fig. 4 Results of PCR heteroduplex analysis for TCR-γ gene rearrangement from patient's spleen and para-aortic lymph node (*arrows* indicate monoclonal products of similar molecular weight with the V10/11 primers). The first lane of every primer type was loaded with half of the PCR product run directly and the second lane with the remaining PCR product after heat denaturation and reannealing (heteroduplex analysis). *MW* Molecular weight, *IFNR* interferon receptor (control for DNA quality)

could not be determined reliably, and PCR for TCR-γ gene rearrangement of the brain tissue yielded unamplifiable DNA, possibly due to prolonged formalin fixation (1 week).

Discussion

Our patient had refractory celiac disease, based on an initial response to gluten-free diet with subsequent loss of responsiveness to the diet [29]. He subsequently developed a rapidly evolving fatal encephalopathy caused by an acute small-vessel angiopathy, superimposed on a subacute degeneration of the cerebellum and a peripheral neuropathy. The patient was receiving corticosteroids and antimicrobial treatment when he developed neurological symptoms, but cultures, PCR analysis, histologic exam, and electron microscopy ruled out an opportunistic infection. Autopsy revealed mild splenomegaly and a spectrum of destructive changes of the intra-abdominal and mediastinal lymph nodes, including chylous pseudocyst formation in numerous mesenteric lymph nodes, the latter consistent with MLNC [20, 25]. The small-bowel mucosa was flattened, and a clonal expansion of intraepithelial lymphocytes was observed. These lymphocytes lacked morphologic atypia but had an aberrant phenotype (CD4-CD8-). Generalized gastrointestinal mucosal and extraintestinal spread of clonal T cells to the blood and other organs, in the absence of a morphologically overt lymphoma, has been described in patients with refractory celiac disease [9, 10, 31], and many of these patients are believed to have a cryptic enteropathy-associated T-cell lymphoma (EATL) [8, 9].

The pathogenesis of MLNC is unclear; the two extant theories have proposed lymph node damage either due to chronic immune stimulation [18] or the consequence of complement-mediated endothelial damage due to vascular immune complex deposition [23]. Moreover, none of the reported cases of MLNC have documented extra-abdominal lymph node involvement or the presence of a clonal T-cell population within the lymph nodes. Our findings suggest that vascular damage and lymphocyte depletion of secondary lymphoid organs in our case could have been mediated by circulating activated T cells that originated from the small-bowel epithelial compartment. It remains unclear, however, whether cytokines or a contact-mediated mechanism (or both) were responsible for endothelial damage and bystander killing of lymphocytes.

Numerous neurological disorders have been associated with celiac disease [6, 11, 16], and patients with refractory sprue are at the greatest risk for developing these complications [26]. However, the prevalence of these disorders is not known, and an etiologic link with celiac disease remains controversial. Holmes [19] estimated that 6% of patients with celiac disease have neurological disorders. The most common neurological syndromes include cerebellar ataxia and peripheral neuropathy [17, 27]. Of all patients with ataxia, 50% or more have a coexisting neuropathy, usually caused by axonal degeneration [5, 17]. Both disorders often progress slowly [5, 7, 17], although, occasionally, the encephalopathy is rapid and fatal within a few weeks of onset as in our patient [24]. The cause of neurologic dysfunction remains unknown, but a link with HLA-DQ2 in a large percent of patients with gluten sensitivity and cerebellar ataxia suggests an underlying genetic predisposition [5, 7]. The presence of anti-ganglioside antibodies in a high proportion of patients who have peripheral neuropathies is also supportive of an autoimmune etiology [1].

A wide spectrum of histologic changes of the central nervous system (CNS) have been reported in patients with celiac-disease-associated neurological disorders [4, 11, 13, 17, 22, 26], but Purkinje cell loss and astrocytosis with or without a coexistent neuropathy are the most common finding. Less frequent pathologic features include perivascular lymphocytic infiltrates and reactive changes in endothelial cells of small vessels. Isolated CNS vasculitis has only been reported in one instance [28]. Our patient showed histologic signs of small blood vessel injury of the brain with marked perivascular edema, exudation of fibrin, and ischemic injury of the neural tissue. These findings are similar to those reported in a minority of patients who die due to a cerebral disorder associated with systemic lupus erythematosus [12, 21]. CNS vasculopathy mediated by a clonal circulating T-cell population has not been reported in any of the 21 published studies of celiac disease, where autopsy data was provided.

There are no standardized treatment regimens for celiac-disease-associated CNS complications or neuropathies, and gluten-free diet, the mainstay therapy, often fails to prevent or ameliorate neurological complications [26, 27]. A beneficial response to early dietary intervention, after the onset of neurological complications, has been reported in some patients with neuropathies [15]. Since the vast majority of patients with neurological symptoms do not have a detectable hypovitaminosis, treatment with vitamins (i.e. vitamin B12, folic acid, or vitamin D) is deemed to be of little value [26, 27]. An improvement in symptoms was reported for a patient with cerebral vasculitis, treated with prednisone and cyclophosphamide [28], and for a patient with a brainstem–cerebellar syndrome, who was treated with prednisone alone [14]. Similar immunosuppressive regimens, however, have failed to halt or revert the neurological manifestations of other patients [2, 24, 26].

In summary, we describe a patient with refractory celiac disease who had a CNS disorder due to a small vessel vasculitis in association with MLNC, both possibly linked to the presence of a circulating clone of activated T cells, conceivably representing a cryptic EATL.

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