CME

Enteropathy-associated T-cell lymphoma with initial manifestation in the CNS

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We report a patient with asymptomatic celiac disease who developed an enteropathy-associated T-cell lymphoma (EATCL) with primary manifestation in the CNS. A previously healthy 56-year-old woman was admitted after a 6-week history of depression, headache, and progressive cognitive decline. Her medical history was unremarkable, except for celiac disease diagnosed in 1992, which, upon gluten-free diet, resolved rapidly and remained asymptomatic. Clinically, she was disoriented and somnolent and had sensorimotor aphasia, apraxia, and acalculia. The remaining neurologic state was unremarkable. Full blood count and chemistry were within the normal range. The anti-gliadin IgA (IgA 21 kU/L) and IgG (IgG 127 kU/L) titers were elevated (normal IgA $<$ 20 kU/L, IgG $<$ 20 kU/L), and anti-endomysium IgA was negative. Cranial MRI showed multiple subcortical and periventricular, partially gadolinium-enhancing lesions, without leptomeningeal involvement (figure, A and B). CSF contained 39 cells (normal $<$4.7; 98% lymphocytes) and elevated protein with 0.8 g/L (normal $<$0.48 g/L). Cytologic analysis failed to detect malignant cells. A stereotactic brain biopsy on the right prefrontal region revealed white matter diffusely infiltrated by pleomorphic atypical lymphoid cells, which were immunoreactive for CD2, CD3, CD7, CD8, CD30, CD56, and T cell internal antigen-1 (TIA-1) and negative for CD4, CD5, and CD20 (see the figure, C through E). A diagnosis of peripheral T-cell lymphoma of the brain with cytotoxic phenotype was made. Upon whole-body CT scan, no evidence of an extracranial manifestation of the lymphoma was found. Under chemotherapy (dexamethasone and six cycles of methotrexate 4,000 mg/m^2, followed by leucovorin rescue), her deficits resolved completely. Ten weeks later, she became again symptomatic with nausea and confusion. Cranial MRI was not conclusive, but CSF contained CD30$^+$ atypical lymphoid cells, thus confirming disease recurrence. After initiation of dexamethasone therapy, an acute abdomen prompted surgical exploration, which revealed a perforated gastric ulcer. Histologic and immunohistochemical examination (see the figure, F and G) showed a lymphoma with an identical morphology in the gastric wall as in the CNS. Duodenal biopsies taken at the same time demonstrated the features of chronic enteropathy (see the figure, H). Multicolor multiplex PCR analysis[1] revealed three T-cell receptor γ rearrangements, pointing to three different V-gene subtypes in all analyzed probes. Equal sizes of the PCR products indicated the presence of the same T-cell clones in brain, stomach, and duodenum (see the figure, I). Sequence analysis of the PCR products confirmed the clonal identity of the infiltrates (see the figure, K). In conclusion, the patient had a cryptogenic EATCL of the duodenum, which clinically first manifested as primary lymphoma of the CNS and later on recurred as a gastric lymphoma. Despite chemotherapy and whole-brain irradiation, the disease was progressive and the patient died 9 months after diagnosis.

Neurologic complications occur in approximately 6% of adults with celiac disease.[2] Cerebellar ataxia is the most frequent symptom reported, but chronic headache and white matter abnormalities have also been described.[3] In our patient, the white matter lesions consisted of an infiltration by a T-cell non-Hodgkin's lymphoma. Malignancies occur in 11% of patients with celiac disease and represent the most severe complication of the disease. EATCL is a tumor originating from intraepithelial T lymphocytes. Approximately 20% of the cases are CD56$^+$, suggesting an origin from activated cytotoxic CD56$^+$ and CD8$^+$ intraepithelial lymphocytes.[4] There are only scarce reports of EATCL presenting with CNS involvement.[5,6] There is one report[5] of a 70-year-old man presenting with grand mal seizures resulting from CNS involvement in recurrent disseminated EATCL. A second patient has been reported[6] presenting with cognitive decline and personality changes caused by EATCL, which was manifesting as primary CNS lymphoma according to stereotactic brain biopsy. In contrast to that report, we confirm the intestinal involvement by molecular methods and already establish intra vitam the diagnosis of cryptogenic T-cell lymphoma of the duodenum. Whereas there is a clear association between celiac disease and EATCL, the evolution of the disease remains unpredictable. In some patients, a period of refractory celiac disease with clonal proliferation of intraepithelial lymphocytes precedes EATCL. Such a course of disease was demonstrated at the molecular level in at least one patient.[7] It is tempting to speculate that chronic stimulation of gluten-sensitive T cells, even without clinical symptoms of sprue, may lead to clonal selection and finally to malignant transformation.

In summary, any extraintestinal manifestation—particularly in the brain—of a T-cell non-Hodgkin's lymphoma in a patient with established celiac disease should be considered as a possible manifestation of a cryptogenic EATCL, even if the enteropathy is clinically asymptomatic. This results in important implications for the clinical management of such patients as the prognosis of overt EATCL is generally very poor.

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See also pages 1566, 1581, 1672, and 1674

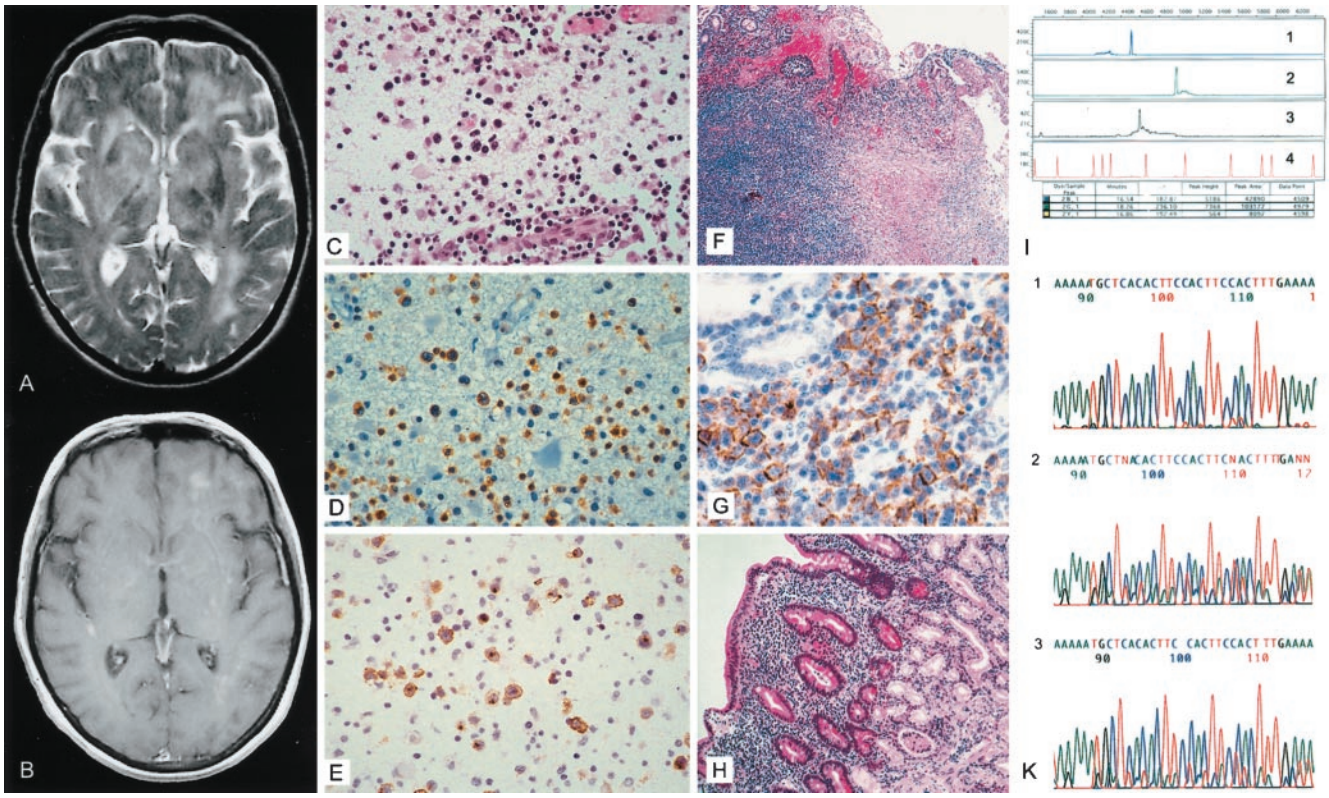

Figure. (A) T2-weighted cranial MRI with CNS T-cell lymphoma involvement of the left temporoparietal and right prefrontal region and bilateral involvement of the basal ganglia. (B) T1-weighted image with gadolinium-enhancing lesions, without leptomeningeal involvement. MRI images by courtesy of the Division of Neuroradiology, Department of Radiology, Basel, Switzerland. (C) Brain biopsy shows pleomorphic atypical large- to medium-sized lymphoid cells infiltrating cerebral white matter. Hematoxylin–eosin. (D, E) The malignant cells are strongly CD3 (D) and CD30 (E) immunoreactive. (F) The gastric biopsy shows an ulcerated tumor consisting of a dense infiltrate of lymphoid cells. Hematoxylin–eosin. (G) By immunohistochemistry, the large-cell component is positive for CD30. (H) Hematoxylin–eosin section of the intestinal mucosa of the corresponding duodenal biopsy shows villous atrophy and increased number of intraepithelial lymphocytes. A tumor infiltrate could not be identified morphologically. (I) Determination of the V-gene subtype involved in T-cell rearrangements in the patient's stomach using a multicolor multiplex PCR assay.[1] Clonal T-cell rearrangements are visible as peaks in panel 1 (V1 and V5P genes) at 183 bp, panel 2 (V3P, V4P, and V6P genes) at 236 bp, and panel 3 (V2 genes) at 192 bp; panel 4 = molecular weight marker. (K) Sequencing of the clonal PCR products confirms identical sequences of the rearranged V4P gene of the T-cell receptor γ-chain present in lymphomas from stomach (1), duodenum (2), and brain (3).

A family with *Campylobacter* enteritis: Anti-GD1a antibody with/without Guillain–Barré syndrome

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Guillain–Barré syndrome (GBS) is characterized by acute, motor-predominant neuropathy frequently preceded by infection. *Campylobacter jejuni* enteritis is involved in about one-third of patients.[1] Molecular mimicry between *C. jejuni* and gangliosides can lead to the production of serum anti-ganglioside antibodies, which may cause neuropathies.

A literature search revealed only one report describing a family with *C. jejuni* enteritis, in which GBS developed in one of three affected members. That report implicated anti-ganglioside antibody as the cause of GBS.[2] We now describe a second such family in which additional factors as well as anti-ganglioside antibodies may have contributed to the GBS onset.

Two brothers, 16 and 19 years old, had diarrhea of 3-days' duration. A week after the onset, the younger brother had severe tetraparesis. Neurologic and electrophysiologic findings were consistent with a diagnosis of axonal GBS. Blood specimens were obtained from the two brothers on the fourth day after the GBS onset. The brothers were sero-positive for anti–*C. jejuni* antibody. Anti-ganglioside antibodies were examined as described previously, using GM1, GM2, GM3, GD1a, GD1b, GalNAc-GD1a, GD3, GT1b, and GQ1b as antigens.[3] The brother with GBS had anti-GM1 IgM (1:320) and IgG (1:160) and anti-GD1a IgG (1:80) antibodies (normal <1:40 for both IgM and IgG). IV immunoglobulin therapy produced prompt marked improvement in the patient's condition. The elder brother had no signs or symptoms suggestive of GBS. The serum was strongly positive for anti-GD1a IgG antibody (1:320), confirmed to react with GD1a on thin-layer chromatography (figure). Anti-ganglioside antibody titers for both brothers decreased to <1:40 3 months after the disease onset.

Our study showed that GBS developed in only one of the two siblings with anti-ganglioside antibodies. One explanation is that anti-GM1 antibody was involved in the pathogenesis of the disease, whereas anti-GD1a antibody was not. The pathogenicity of anti-GM1 antibody is experimentally evidenced in GM1-immunized animals. However, anti-GD1a IgG antibody is more closely associated with acute motor axonal neuropathy than anti-GM1 IgG antibody.[4] Among 600 patients with definite or probable GBS, 4 were positive for only anti-GD1a IgG antibody, with titers ranging from 1:160 to 1:320 (S. Kusunoki, unpublished observation). The antibody titer in the patient without GBS was therefore comparable with that in patients with GBS. In addition, the

