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MR Imaging of Autopsy-Proved Paraneoplastic Limbic Encephalitis in Non-Hodgkin Lymphoma

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Summary: We report the case of a 26-year-old man with underlying precursor T-cell acute lymphoblastic leukemia who developed paraneoplastic limbic encephalitis that was diagnosed on the basis of MR imaging findings and was proved post mortem. In our MR imaging studies, fluid-attenuated inversion recovery images and diffusion-weighted echo-planar images clearly depicted bilateral involvement of the medial temporal lobes and multifocal involvement of the brain, whereas T2-weighted turbo spin-echo images failed to show the changes.

Paraneoplastic limbic encephalitis is frequently associated with bronchial carcinoma and is considered a particular manifestation of paraneoplastic encephalomyelitis, which includes involvement of other areas in the central (pyriform cortex, frontal orbital surface of the temporal lobe, insula, cerebellum, brain stem) and peripheral nervous system (1). Non-Hodgkin lymphoma has not been previously described as an underlying disease causing paraneoplastic limbic encephalitis.

Patients with paraneoplastic limbic encephalitis present with subacute cognitive dysfunction, severe memory impairment, seizures, and psychiatric features including depression, anxiety, and hallucinations. Other causes of encephalopathy, metastases, drug neurotoxicity, infectious diseases such as herpes encephalitis, and meningeal carcinomatosis must be excluded. Sometimes, antineuronal antibodies such as anti-Hu or anti-Ma2 are found in the CSF in patients with paraneoplastic limbic encephalitis (2).

We report the case of 26-year-old man with underlying precursor T-cell acute lymphoblastic leukemia who developed paraneoplastic limbic encephalitis that was proved post mortem. We describe the evolutionary changes in the findings of MR imaging of the brain within the first days after onset of clinical symptoms.

Case Report

A 26-year-old man with underlying precursor T-cell acute lymphoblastic leukemia developed generalized seizures, had short-term memory loss, and was disoriented to time and place 1 month after undergoing unsuccessful allogeneic bone marrow transplantation. Additional symptoms included numbness and tingling of the hands and feet. EEG showed paroxysmal epileptiform activity in both temporal lobes. The results of viral serologic tests were negative. The results of CSF polymerase chain reaction for herpes simplex virus 1 and 2 were negative. Cell count, cytology, bacterial and fungal studies, and panels of CSF including glucose, protein, and oligoclonal bands were unremarkable. CSF examination showed 29 lymphocytes/mm³. CSF cytologic examination identified no malignant cells, and no antibodies typical for paraneoplastic limbic encephalitis, such as anti-Hu, were found.

One day after the first generalized seizure occurred, bilateral signal intensity increase was seen throughout both medial temporal lobes on the T2-weighted fluid-attenuated inversion recovery images (Fig 1A). Coronal view T2-weighted turbo spin-echo images failed to show the elevated signal intensity (Fig 1B). Three days later, the second set of MR images of the brain revealed multifocal involvement (Fig 2).

The diagnosis of paraneoplastic limbic encephalitis was presumed on the basis of MR imaging findings and exclusion of other causes. The patient died 1 month after the second set of MR images was obtained, as a result of a relapse of the precursor T-cell acute lymphoblastic leukemia and multiorgan failure.

At autopsy, multifocal subacute polioencephalomyelitis in the brain regions that were shown as affected on MR images confirmed the diagnosis of paraneoplastic limbic encephalitis with neuronal loss. Reactive astrocytosis (Fig 3A), lymphocytic infiltration with T cells (Fig 3B), hyperplasia of activated microglia (Fig 4), and neuronophagia were found. Leukemic nodules could not be observed in the brain, although bone marrow, liver, spleen, and multiple lymph nodes were infiltrated with leukemic cells. No intranuclear viral inclusions could be detected. Immunohistochemistry revealed that immunoglobulin M antibodies were bound to hippocampal neurons (Fig 5). CSF and serum were not available for postmortem immunoblot studies for further characterization of the antibody. Examination of the peripheral nervous system revealed subperineurial lymphocytic infiltration of the myelin.

Discussion

Cancer of the lung, particularly small cell lung cancer, and testicular germ cell tumors are the most frequently found neoplasms associated with paraneoplastic limbic encephalitis (2). It may be rarely associated with thymoma, adenocarcinoma of the colon, renal cell cancer, esophageal cancer, bladder cancer, breast cancer, small cell carcinoma of the prostate, ovarian carcinoma, neuroblastoma, testicular semi-
FIG 1. Initial MR images obtained 1 day after the first generalized seizure occurred.

A, Axial fluid-attenuated inversion recovery image (9000/110 [TR/TE]; inversion time, 2261 ms) shows a slightly elevated signal intensity of both hippocampal formations (black arrows) and amygdala (white arrows).

B, Coronal conventional T2-weighted turbo spin-echo image (4462/120/3 [TR/TE/NEX]) shows no signal intensity abnormality.

FIG 2. Follow-up MR images obtained 4 days after the first seizure occurred.

A, Fluid-attenuated inversion recovery image shows high signal intensity in both medial temporal lobes and hyperintensities of the right frontobasal cortex (arrowhead).

B, Fluid-attenuated inversion recovery image shows high signal intensity in both medial temporal lobes and hyperintensities of the right insular cortex (arrowhead). No mass effect was seen.

C, Diffusion-weighted echo-planar image (5400/103/1; b value of 1000 s/mm²) shows the corresponding alterations of the limbic (arrows) and the right frontobasal cortex (arrowhead).

D, T1-weighted image (548/12/2) shows low signal intensity of the right medial temporal lobe (arrow).

E, Contrast-enhanced T1-weighted image (525/17/2) shows no contrast enhancement.
noma, or Hodgkin disease (2). Generally, the association of T-cell lymphoma with paraneoplastic disorders of the nervous system is rare. Ducrocq et al (3) reported the case of a patient with pleomorphic T-cell lymphoma in which paraneoplastic opsoclonus-myoclonus syndrome preceded the diagnosis of lymphoma. Ang et al (4) presented the case of a male patient with aggressive T-cell lymphoma and severe cerebellar degeneration. A paraneoplastic choreic syndrome was reported to occur in a patient with T-cell lymphoma (5).

The diagnosis of paraneoplastic limbic encephalitis was supposed on the basis of imaging findings and exclusion of other causes, such as herpes encephalitis, lupus erythematosus (6), and neurosyphilis (7). No evidence indicated that graft versus host disease or drug toxicity was responsible for the symptoms, which occurred 1 month after bone marrow transplantation, although they are possible causes for neurologic and psychiatric complications (8). Cyclosporine-associated changes consist of bilateral abnormalities, primarily in the posterior temporal, occipital, and parietal lobes (9) but not in the medial aspects of the temporal lobes.

FIG 3. Reactive astrocytosis and lymphocytic infiltration with T cells were found. A, Glial fibrillary acidic protein immunostaining. Neuronal loss in the hippocampus and replacement by astrocytes (arrows). Granular layer of CA1 of the hippocampus (arrowhead). Scale bar = 250 μm.

B, Immunostaining with anti-CD3 antibody shows interstitial inflammatory infiltrates of T cells in the mesial temporal lobe (arrows). Section counterstained with hemalaun. Scale bar = 50 μm.

FIG 4. CD68 immunostaining reveals activated microglial cells, which cluster around damaged neurons (arrows). Scale bar = 70 μm.

FIG 5. Immunoglobulin M immunostaining. Antineuronal antibodies of immunoglobulin M type are bound to the cytoplasm of hippocampal neuron (arrow). Scale bar = 50 μm.
Our findings of multifocal involvement of brain (Fig 2) were consistent with the diagnosis of paraneoplastic limbic encephalitis. Pathologic changes of the brain are found not only in limbic structures but also in the pyriform cortex, frontal orbital surface of the temporal lobe, and insula (1). The peripheral nervous system is often damaged. Pathologic changes of the brain are found not only in limbic structures but also in the pyriform cortex, frontal orbital surface of the temporal lobe, and insula (1). The peripheral nervous system is often damaged because of sensorimotor neuropathy (1), which could be histologically proved in our patient with precursor T-cell acute lymphoblastic leukemia.

MR imaging–based diagnosis of paraneoplastic limbic encephalitis requires depiction of signal intensity changes of the temporobasal region. It is important to observe the initial subtle finding of increased signal intensity of both medial temporal lobes on T2-weighted images, and this was visible only on the fluid-attenuated inversion recovery images in our study (Fig 1A). Conventional T2-weighted turbo spin-echo images failed to reveal the abnormalities (Fig 1B). The advantage of fluid-attenuated inversion recovery imaging in diagnosing hippocampal disease was shown by Jack et al (10), who reported significantly higher accuracy of fluid-attenuated inversion recovery imaging in identification of increased signal intensity of the hippocampus in cases of mesial temporal sclerosis as compared with conventional spin-echo imaging. The fluid-attenuated inversion recovery sequence might be more appropriate for identification of increased signal intensity of the hippocampus because of complete suppression of the high signal intensity of the CSF while yielding T2-weighted contrast properties. The use of conventional T2-weighted turbo spin-echo sequences might be a reason for the fairly high rate of negative MR imaging findings in cases of paraneoplastic limbic encephalitis reported by Gultekin et al (2). They noted that 19 (43.2%) of 44 patients had no signal intensity abnormalities shown on T2-weighted images of the limbic system. Reports of diffusion-weighted and fluid-attenuated inversion recovery imaging in cases of paraneoplastic limbic encephalitis have been lacking. We observed hypointensity of the right mesial temporal lobe without contrast enhancement on T1-weighted images. In accordance with our case, contrast enhancement is very rare and only single cases are published. Contrast enhancement of the mesial temporal lobes was observed for a patient with testicular seminoma (11), a patient with testicular carcinoma (12), and a patient with Hodgkin disease (13).

In line with our anti-Hu-negative case, Alamowitch et al (14) noted that increased signal intensity on T2-weighted images is more frequently combined with decreased signal intensity on T1-weighted images of patients without anti-Hu antibody than on T1-weighted images of patients with anti-Hu antibody. Dirr et al (15) and Alamowitch et al (14) described atrophy shown on T1-weighted images in cases with longer clinical courses. The atrophy was seen in the medial aspect of one or both temporal lobes after several months.

We found an immunoglobulin M antibody bound to cytoplasm (Fig 5), suggesting an active immuno-

logic mechanism. This concept is supported by the absence of antibodies in other degenerative or inflammatory disorders of the nervous system. Furthermore, infiltrates of T cells (Fig 3B) might play a major pathogenic role. The mechanism by which T cells recognize antigens expressed in neurons (which in normal circumstances lack expression of the antigen presenting molecules of major histocompatibility complex classes I and II) is unknown. It is possible that these inflammatory infiltrates are not the primary cause of the neuronal damage but a consequence of the antineuronal antibody that causes neuronal dysfunction. Because neuronal dysfunction can result in expression of major histocompatibility complex molecules, the T-cell infiltrates would be a “second hit” resulting in neuronal loss. To date, however, an animal model is lacking. Immunization of animals with purified recombinant HuD fusion protein has not reproduced the disease (16).

Conclusion

MR imaging can aid in establishing the diagnosis of paraneoplastic limbic encephalitis, especially in those cases in which no characterized antineuronal antibody can be detected in serum or CSF. Diffusion-weighted imaging and fluid-attenuated inversion recovery imaging are useful in revealing the encephalomyelitis of the mesial temporal lobes and other areas of the brain. These imaging techniques should be used whenever hippocampal pathologic abnormality is likely.

References