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LIMBIC ENCEPHALITIS ASSOCIATED WITH ANTIBODIES TO THE NMDA RECEPTOR IN HODGKIN LYMPHOMA

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Convulsions, fever, and memory loss after chemotherapy are usually due to opportunistic infection, and often attributed to infection even if CSF viral PCR examination is negative. We describe a case of limbic encephalitis in a patient with relapsed Hodgkin lymphoma, in whom antibodies to the NMDA receptor were identified in serum and CSF, and whose anterograde memory improved with aggressive immunotherapy. Paraneoplastic limbic encephalitis in Hodgkin lymphoma has been reported before,[1,2] but no target antigen identified. The case adds to the clinical associations of NMDA receptor antibodies.

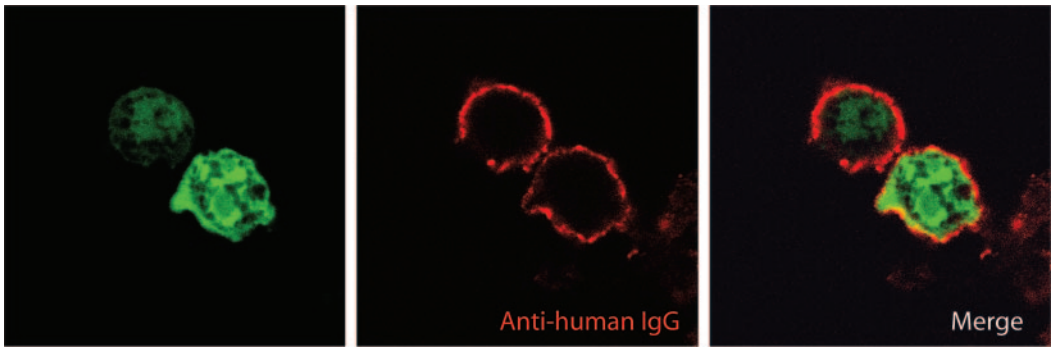
Case report. A 49-year-old man developed an amnesic syndrome temporally related to a second relapse of nodular sclerosing Hodgkin lymphoma. Eight years previously he had developed a large cervical lymph node and was successfully treated with mantle radiotherapy. He received chemotherapy to treat an abdominal relapse 2 years later, and maintained remission for 5 years. Last year he relapsed with a large abdominal para-aortic mass, and 3 weeks after his first cycle of treatment, with gemcitabine and cisplatin, he developed confusion and disorientation over 2 days, culminating in a generalized seizure while driving. Initial confusion and memory loss was assumed to be postictal, but his anterograde memory deficit persisted and worsened: at worst he could encode 4 of 7 parts of an address but could not recall or recognize any components at 5 minutes. He had no evidence of a movement disorder. There was no neutropenia. Erythrocyte sedimentation rate was 75 mm/hour (1–7), C-reactive protein 187 mg/L (0–6). MRI revealed abnormal signal bilaterally in the temporal lobes on T2 and fluid attenuation inversion recovery imaging (figure e-1 on the *Neurology*® Web site at www.neurology.org). CSF examination revealed 4×10^6/L white cells. He was treated with IV acyclovir and sodium valproate for possible herpes encephalitis. Initial EEG was within normal limits. CSF examination a few days later demonstrated 10×10^6/L lymphocytes, normal protein and glucose, and was sterile on culture; viral PCR was subsequently negative for herpes simplex and varicella zoster virus DNA, and enterovirus RNA. No malignant cells were seen. There were oligoclonal bands in the CSF, unmatched in the serum. Serum sodium, thyroid stimulating hormone, immunoglobulins, protein electrophoresis, B12, and red cell folate were normal. Lactate dehydrogenase was 306 U/L (120–240). Blood cultures were negative. Serum antibodies to thyroid peroxidase, Hu, Yo, Ri, voltage gated potassium channels, amphiphysin, Ma, CV2/CRMP5, tissue transglutaminase, and antiphospholipid antibodies were negative. There was no immunohistochemical evidence of anti-Tr. Serum and CSF antibodies to the NMDA receptor were present on a direct immunofluorescence cell based assay, in which serum was tested against NR1 and NR2b subunits expressed on human embryonic kidney cells (figure).[3]

Supplemental data at www.neurology.org

He received immunosuppression with high dose oral steroids, followed by IV immunoglobulin. Symptoms and further EEG and MRI were unchanged. He underwent 10 days of plasma exchange after which his neurologic symptoms started to improve: he could encode all 7 parts of an address, and recall 3 parts at 5 minutes, with a contemporaneous MRI showing marked resolution of the temporal lobe high signal. He received radical chemotherapy and then in December 2008 preparation for autologous stem cell transplantation, but unfortunately had radiologic evidence of significant abdominal disease and entered palliation. His anterograde memory has continued to improve functionally to date (at least 6 months after initial presentation).

Discussion. Limbic encephalitis in Hodgkin lymphoma was first described, and termed the Ophelia

Figure Immunofluorescence cell-based assay



Human embryonic kidney (HEK) cells cotransfected with NR1/2B and EGFP cDNA (green). The patient's antibodies bound strongly to the surface of the cells, as detected with Alexa Fluor–568 conjugated antihuman immunoglobulin G (red).

syndrome, by the pathologist Ian Carr in an account of his daughter's illness.[1] Paraneoplastic limbic encephalitis is most commonly due to small cell lung cancer, and rarely due to other cancers which express proteins that share epitopes with neurons and glia, including Hodgkin lymphoma.[2,4] Here, we describe limbic encephalitis associated with relapsed Hodgkin lymphoma, with antibodies to the NMDA receptor and response to plasmapheresis. This case adds to the clinical associations of anti-NMDAR encephalitis,[5] and should prompt antibody testing with a cell-based assay[6] in cases of relatively pure limbic encephalitis. Anti-NMDAR encephalitis was first described in young women with ovarian teratomata who exhibited a rhythmic movement disorder, hypoventilation requiring ventilation, and autonomic instability, although both sexes and a wider age range has now been reported.[5] The case for pathogenicity of anti-NMDAR antibodies is based on the surface expression of the targeted antigens and the often impressive response of patients to immunosuppression, in comparison to paraneoplastic degenerations where the neuronal target is intracellular.[7] This case should raise a wider recognition of paraneoplastic and autoimmune processes in patients whose symptoms might otherwise be attributed to chemotherapy or infection.

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