Lessons Learned From Fatal Progressive Multifocal Leukoencephalopathy in a Patient With Multiple Sclerosis Treated With Natalizumab

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Objective: To describe the clinical, radiological, and histopathological features of a fatal case of progressive multifocal leukoencephalopathy (PML) in a patient with multiple sclerosis treated with natalizumab. We will use this case to review PML risk stratification and diagnosis.

Design: Case report.

Setting: Tertiary referral center hospitalized care.


Main Outcome Measures: Brain magnetic resonance imaging and cerebrospinal fluid JCV DNA polymerase chain reaction results.

Results: The patient developed subacute onset of bilateral blindness following his 44th dose of natalizumab. Ophthalmologic examination was normal, the brain magnetic resonance imaging was not suggestive of PML, and cerebrospinal fluid analysis did not reveal the presence of JCV DNA. The patient was subsequently treated for a presumed multiple sclerosis relapse with high-dose corticosteroids. Two weeks after his 45th dose of natalizumab, he developed hemiplegia that evolved into quadriplegia. Repeated magnetic resonance imaging and cerebrospinal fluid studies were diagnostic for PML. Postmortem histopathological analysis demonstrated PML-associated white matter and cortical demyelination.

Conclusions: The risks and benefits of natalizumab must be reassessed with continued therapy duration. When there is high clinical suspicion for PML in the setting of negative test results, close clinical vigilance is indicated, natalizumab treatment should be suspended, and JCV polymerase chain reaction testing and brain magnetic resonance imaging scans should be repeated.


PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) is a demyelinating infection of the central nervous system caused by JC virus (JCV) and a feared adverse event associated with natalizumab treatment in patients with multiple sclerosis (MS). The availability of the JCV antibody assay and an understanding of PML susceptibility allow more accurate risk assessment for individual patients. Herein, we describe the clinical, radiological, and histopathological features of a fatal case of PML in a patient with MS treated with natalizumab. We will use this case to review PML risk stratification and diagnosis.

REPORT OF A CASE

CLINICAL PRESENTATION

A 49-year-old white man was diagnosed with relapsing-remitting MS following symptoms of right-leg monoparesis and a brain magnetic resonance image (MRI) suggestive of white matter (WM) demyelination. Initially, he was treated with subcutaneous high-dose interferon beta-1a, 3 times weekly, for 2 years. He was unable to tolerate self-injections and he switched disease-modifying therapy to natalizumab. While taking interferon beta-1a and later natalizumab, he remained relapse free with low disability (Expanded Disability Status Scale score, 2). He was found to be JCV antibody positive during natalizumab therapy but opted to continue treatment.

In October 2011, after his 44th infusion, he developed blurry vision. He was found to have 20/400 visual acuity bilaterally. Concern for PML was raised. A brain MRI (Figure 1, scan 2) was initially read as unchanged from 1 year earlier by a neuroradiologist. Results of JCV polymerase chain reaction (PCR) testing in the patient's cerebrospinal fluid (CSF) were nega-
The patient was evaluated by an ophthalmologist and “no organic cause” for his blurry vision was identified. Presumed to be having an MS attack, he was treated with 5 doses of high-dose intravenous corticosteroids, followed by his 45th dose of natalizumab in November 2011. His vision did not improve and he developed new right hemiparesis 3 weeks after his last infusion. He was referred for admission to our hospital’s neurology service from the community for a presumed steroid-refractory MS relapse. Total plasma exchange was initiated. Following his first exchange, he developed encephalopathy and quadriplegia and was transferred to the medical intensive care unit. The MS service was consulted and repeated testing for PML was recommended. Repeated MRI scans were consistent with PML (Figure 1, scan 3) and CSF JCV DNA PCR results were positive. The patient died 5 days into his hospital stay.

Retrospective review of his MRI at symptom onset (Figure 1, scan 2) revealed extension of T2 signal abnormality into the right occipital and right parietal lobes consistent with PML.

His brain was obtained at autopsy 3 hours post mortem. Macroscopic and microscopic features of the brain were diagnostic for PML (Figure 2). Several well-demarcated, smooth lesions were observed, consistent with MS plaques.

**NEURORADIOLOGICAL DATA**

The brain MRI from September 2010 (Figure 1, scan 1) after onset of bilateral vision changes demonstrated abnormal increased T2 and fluid-attenuated inversion recovery signal involving the corpus callosum (Figure 1, scan 1 [arrow]) and radiating away from the ventricles.

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**Figure 1.** Magnetic resonance imaging scans obtained 1 year prior to symptom onset (scan 1), 1 month prior to hospital admission (scan 2), and during hospital stay (scan 3). All magnetic resonance images were at 1.5 T. From left to right: sagittal fluid-attenuated inversion recovery (FLAIR); axial FLAIR at the level of the periaentric white matter of the lateral ventricles; corresponding postgadolinium T1; axial FLAIR at the level of the upper lateral ventricles and periventricular white matter; and corresponding T1 axial postgadolinium images. A, Scan 1, September 2010. The FLAIR images demonstrate abnormal foci of increased T2 signal radiating away from the ventricles in a perpendicular fashion with involvement of the corpus callosum (arrow). Corresponding T1 postgadolinium images show no evidence of gadolinium enhancement to suggest active inflammation. B, Scan 2, October 2011, after onset of visual symptoms. The FLAIR images demonstrate new increased T2 signal changes extending into the right occipital and right parietal lobes (arrows). Postcontrast images do not demonstrate corresponding contrast enhancement. C, Scan 3, November 2011, 1 month after onset of progressive multifocal leukoencephalopathy-related symptoms. The FLAIR images demonstrate progression of white matter increased T2 signal changes, most notable in the right occipital, left occipital, and left frontal lobes with involvement of both white and gray matter (arrows). Postcontrast images demonstrate the vasculature without enhancement in the corresponding white matter.
A, Example of a tissue section labeled with proteolipid protein (PLP) showed a subcortical white matter lesion (WML) (1) that expands into the lower layers of the adjacent cortex (CL) (2). There are additional patchy areas of cortical demyelination. Myelinated white matter and cortex are labeled as normal-appearing white matter (NAWM) (3) and normal-appearing gray matter (NAGM), respectively. B and C, Immunostaining with CD68, a marker for microglia and macrophages, shows swollen, myelin-laden macrophages in demyelinated white matter (B, arrows) and adjacent demyelinated cortex (C, arrows). D, Normal adjacent white matter and normal-appearing cortex contained ramified microglia (arrow). E and F, Immunolabeling with the astroglial marker glial fibrillary acidic protein (GFAP) demonstrates balloononed and highly reactive astrocytes within white matter and cortical lesions (arrows). G, In contrast, in NAWM, astrocytes were small and had thin, elongated processes (arrows). H, The JC virus capsid protein VP-1 was expressed in demyelinated white matter predominantly in the cytoplasm of reactive astrocytes (arrows). I, In contrast, in cortical lesions, VP-1 was present predominately within neuronal cytoplasm and oligodendrocytes (arrows). J, In normal adjacent white matter, VP-1 was expressed in occasional oligodendrocytes (arrow) (parts B-J counterstained with hematoxylin).

In 11 examined tissue blocks derived from the occipital and temporal lobes, demyelinating lesions were widespread in WM and adjacent cortex. Separate isolated patchy areas of demyelinated cortex unconnected to WM demyelination were also observed (Figure 2A). White matter lesions were dominated by infiltration with myelin-laden (foamy) CD68⁺ macrophages (Figure 2B). Myelin-laden macrophages were abundant in cortical lesions (Figure 2C). Immunolabeling with glial fibrillary acidic protein revealed reactive, bizarrely shaped astrocytes within WM and cortical lesions (Figure 2E and F). In contrast, myelin-phagocytosing macrophages and reactive astrocytes are usually absent in cortical MS plaques.1,2

The JCV capsid protein VP-1, indicative of productive, lytic infection, was present in WM lesions within astrocytes and less frequently in oligodendrocytes (Figure 2H). In cortical demyelinating lesions, VP-1 was observed in the cytoplasm of astrocytes and neurons (Figure 2I).3 In the perimeter of white and cortical gray matter lesions and less frequently in remote WM, VP-1 was detected in oligodendrocytes (Figure 2J). Thus, JCV-induced demyelination was widespread in WM and cortex and was characterized by intense microglia/macrophage-dominated infiltration and astrogliotic reaction. This strong inflammatory reaction in the cortex is usually not seen in demyelinating MS lesions.

This case highlights the importance of using clinical judgment to remain suspicious for PML in the setting of negative CSF test results in patients with MS taking natalizumab. Furthermore, MRI changes from PML can be subtle and may be missed even by an experienced neuroradiologist.

Progressive multifocal leukoencephalopathy is a demyelinating disease of the central nervous system caused by JCV. Its manifestations may be confused with an acute MS relapse. The most common presentations of PML include bilateral cortical blindness, hemiplegia, and encephalopathy. These are not common presentations of MS relapses. The subacute onset of bilateral blindness in this patient taking natalizumab with a normal ophthalmologic examination and unchanged brain MRI scan was highly concerning for cortical blindness secondary to PML. Presentation of simultaneous bilateral optic neuritis in MS is rare and has been reported in 1 cohort to occur in only 0.42% of cases.4 Similarly, acute-onset hemiparesis is an uncommon presentation of an MS relapse.5 This case provides an important clinical lesson. When the clinical presentation is suspicious for PML and atypical for an MS relapse, a negative initial CSF JCV PCR result does not exclude a PML diagnosis. Magnetic resonance imaging should be carefully reviewed to look for subtle changes.
concerning for PML. These lesions are most apparent on T2 and fluid-attenuated inversion recovery sequences as hyperintense and on T1 sequences as hypointense mainly within subcortical WM. In such cases, it appears most appropriate to hold natalizumab treatment and repeat testing. Holding natalizumab treatment for less than 3 months generally does not place the patient with MS at risk of increased disease activity.⁶

Additionally, the appropriate use of this therapy and the continued evaluation of the risk vs benefit ratio throughout duration of therapy are essential to caring for this patient population. Because of the risk of PML, natalizumab is often used as second-line therapy. In the present case, disease-modifying therapy was switched to natalizumab because of poor tolerability of interferon beta-1a rather than lack of efficacy, given the absence of relapses. Even though the patient was JCV antibody positive, the risk of developing PML was presumed to be low during the first year. The incidence of PML during the first 12 doses of natalizumab is 0.04 per 1000 patients.⁷ There have been 4 reported cases of PML during the first 12 doses of natalizumab. Because the patient had no history of prior immunosuppression, he carried a risk for PML of less than 1 in 1000 between dose 1 and 24. However, after 24 doses, his risk of PML increased to 2.5 in 1000.⁷ Because the patient's disease was previously well controlled with interferon beta-1a with no further MS relapses and a low Expanded Disability Status Scale score at 5 years, the risk vs benefit ratio for natalizumab treatment could have been considered too high after the 24th dose.

A positive DNA test result in CSF is diagnostic for PML whereas DNA testing in urine or blood is not useful. JC viremia does not necessarily occur concomitantly with PML and has conversely been seen in 1.3% of healthy immunocompetent individuals as well as in 10% to 15% of HIV-positive patients without PML.⁸ Likewise, JCV DNA can be detected in the urine of 18% to 30% of healthy individuals.⁹ Importantly, CSF JCV DNA copy numbers were less than 500/mL in 10% to 15% of HIV-positive patients without PML.⁸ The assay with the best sensitivity is offered as a free diagnostic service by the University of Duesseldorf (Germany), Karolinska Institute (Sweden), and Erasmus Medical University Centre in Rotterdam (the Netherlands).

The risk vs benefit ratio of natalizumab treatment should be regularly reevaluated in each patient as it changes with duration of therapy. When clinical suspicion for PML is high in the setting of negative test results, it may be reasonable to hold natalizumab treatment and to repeat CSF and MRI testing after several weeks. The brain MRI should be carefully reviewed by an experienced neuroradiologist and by the treating neurologist for subtle changes concerning for PML. The JCV DNA copy number in the CSF may be absent or low in many cases of natalizumab-related PML and appropriate testing with a sensitivity of less than 50 copies/mL is recommended.

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