Progressive multifocal leukoencephalopathy with extended natalizumab dosing

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A 53-year-old man with an 18-year history of multiple sclerosis (MS) was treated with natalizumab for 7 years. Two years prior to presentation, natalizumab treatment interval was increased to every 6 weeks in attempt to reduce the risk of PML. Medical history was notable for cutaneous T-cell lymphoma status-post CHOP chemotherapy. JCV serology was positive (index 2.8). He presented to our tertiary referral center for consultation due to 8 months of progressive left-sided paresthesias, 4 months of right arm clumsiness, and several weeks of expressive aphasia. Neurologic examination was consistent with these symptoms. Serial brain MRIs demonstrated progressive development of a subcortical, multifocal T2/fluid-attenuated inversion recovery hyperintensity in the left frontoparietal white matter (figure 1). Subtle but definite MRI abnormalities were present in the same area 12 months prior. His clinical course and MRI findings prompted urgent evaluation for PML.

Two lumbar punctures demonstrated normal routine studies and negative cytology. JCV PCR performed at Mayo Medical Laboratories was negative for both samples,¹ but JC multiplex quantitative PCR of the second sample at the NIH revealed 10 copies/mL.² After obtaining informed consent, a research 7T MRI was obtained using T2* and T1/MP2RAGE sequences, including gadolinium administration. This MRI revealed marked cortical thinning associated with T1/T2 hypointensity at the origin of PML development. There was typical subcortical T2 hyperintensity suggestive of PML (figure 2).

Based on the patient's clinical presentation, MRI, and positive CSF JCV PCR, the diagnosis of PML was established (figure e-1, links.lww.com/CPJ/A23). He was treated with 5 courses of plasmapheresis, followed by mirtazapine and maraviroc. Over the next month, aphasia worsened, and MRI demonstrated expansion of lesions with gadolinium enhancement (figure e-2). Immune reconstitution inflammatory syndrome (IRIS) was diagnosed and treated with IV methylprednisolone. Four months after plasmapheresis, expressive aphasia and hand dyscoordination had improved, and IRIS had nearly completely resolved. Expanded Disability Status Scale score was 3.0.

Discussion

This case highlights several aspects of natalizumab-related PML. First, new MRI lesions in patients receiving natalizumab therapy should prompt immediate consideration of PML, even in the absence of new or worsening symptoms. Typically, natalizumab treatment should be suspended until it is certain that new lesions do not represent PML.

At the earliest stages, PML lesions can be subtle and evolve slowly over time. Careful comparison to previous studies is important. In this case, there was evidence of PML on MRI 1 year prior to diagnosis. This finding illustrates the sensitivity of MRI in detecting PML, as MRI changes typically predate symptoms.

PRACTICAL IMPLICATIONS

Progressive multifocal leukoencephalopathy (PML) should be immediately considered in the setting of neurologic decline or new brain MRI lesions in patients on natalizumab. Extended interval dosing does not prevent PML, but may prolong its clinical and imaging evolution, and contribute to low CSF JC virus (JCV) copy number. 7T MRI appears to be a useful tool in identifying subtle radiographic abnormalities suggestive of PML.

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Figure 1 Serial T2/fluid-attenuated inversion recovery (FLAIR) images demonstrate progressive multifocal leukoencephalopathy (PML) development

Serial T2/FLAIR images (A–F) over the 22 months prior to clinical presentation show the protracted evolution of left frontal lobe PML lesions. Subtle lesions were present as early as 12 months prior to presentation (C, arrows), and became more obvious 6 months prior to clinical presentation (D, arrows). Contrast enhancement was present in the lateral T2 lesion at the time of presentation and 3 months earlier (images not shown).

Third, a low copy number of JCV in CSF can make the diagnosis of PML challenging.³ Although commercially available JCV PCR assays are considered sensitive, many can only detect 200 copies/mL,⁴ so negative results do not exclude PML. Some assays provide detection at 10 copies/mL or lower and should therefore be considered when PML is suspected.^{1,2}

Extended natalizumab dosing (intervals greater than the Food and Drug Administration–approved 4 weeks) has been proposed to reduce the risk of PML,⁵ although it is not fully protective since 12 cases of PML were recently reported during extended interval dosing.^{6,7} Extended interval dosing may permit increased immune surveillance in the CNS compared to conventional dosing, therefore reducing the risk of PML. The JCV copy number in our case was low, and the clinical and imaging course of PML was more insidious than is typically seen in natalizumab-related PML. Although one case is not sufficient to draw conclusions, this case raises the question of whether extended interval dosing may contribute to a more protracted and subtle presentation, and further emphasizes the challenges of diagnosing PML in this setting.

Finally, this case illustrates the potential utility of ultra-high-field imaging in PML diagnosis. T2* sequences showed marked

cortical thinning and hypointensity within the cortex, and T1/MP2RAGE images showed marked subcortical hypointensity. The cortical T2* hypointensity was located at the suspected origin of PML development and may indicate regions of severe cortical damage similar in appearance to laminar necrosis. This observation suggests that the higher spatial resolution of 7T MRI may help distinguish new PML lesions from new MS lesions, although further studies are needed to confirm this finding. Sinnecker et al.⁸ utilized 7T MRI to differentiate MS activity from PML in a case report. They did not observe the T2* and T1/MP2RAGE findings we report here, but overwhelming IRIS could have precluded that observation. In addition, previously reported milky way–like lesions were not observed, suggesting that those findings may be related to IRIS.

Author contributions

L.E. Baldassari: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. S.E. Jones: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, obtaining funding. D.B. Clifford: drafting/revising the manuscript, analysis or interpretation of data. R.J. Fox: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

Figure 2 1.5 vs 7T MRI at the time of progressive multifocal leukoencephalopathy (PML) diagnosis

Comparison of 1.5 and 7T MRI at the time of PML diagnosis reveals marked cortical thinning in the area affected by PML, and this thinning is more obvious on T1 sequences obtained with 7T MRI (white arrow). In addition, hypointensity was evident on T2* sequences in the area affected by PML (white asterisk). 7T MRI allowed better visualization of subcortical T1 hypointensity and T2* abnormalities compared to 1.5T imaging.

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