Progressive Multifocal Leukoencephalopathy and Relapsing-Remitting Multiple Sclerosis

A Comparative Study

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Objective: To identify clinical and magnetic resonance imaging (MRI) features that distinguish progressive multifocal leukoencephalopathy (PML) from relapsing-remitting multiple sclerosis (RRMS).

Design: Retrospective medical record review.

Setting: Two urban teaching hospitals in Detroit, Michigan.

Patients: Forty-five confirmed PML cases and 100 patients with RRMS.

Main Outcome Measures: Clinical and MRI features distinguishing PML from RRMS.

Results: Overall, monosymptomatic presentations were more common in multiple sclerosis (MS) than PML (85% vs 47%; \( P < .001 \)). However, patients with PML presented more often with hemiparesis (24% vs 5%; \( P = .001 \)) and altered mentation (19% vs 0%; \( P < .001 \)), whereas brainstem (2% vs 18%; \( P = .007 \)) presentations were more common in patients with RRMS. Spinal cord and optic neuritis presentations were seen in 18% and 33% of patients with RRMS, respectively, but not in patients with PML (\( P < .001 \)). Brain MRI scans, available in 35 (78%) PML cases, revealed 7 lesion types. Large, confluent T2-weighted lesions (74% vs 2%; \( P < .001 \)) and deep gray matter lesions (31% vs 7%; \( P < .01 \)) were more frequent in patients with PML than patients with RRMS. Crescentic cerebellar lesions (23% vs 0%; \( P < .01 \)) were seen only in patients with PML. Gadolinium-enhancing (23%), transcallosal (9%), and periventricular (9%) lesions were noted in patients with PML. Brain magnetization transfer ratio (MTR) was low in both PML and MS lesions. However, normal-appearing brain tissue MTR in PML was higher than normal-appearing brain tissue MTR in RRMS (44.15% vs 41.04%; \( P = .002 \)), suggesting that PML may be relatively more focal than MS.

Conclusions: There appear to be differences between the clinical and MRI characteristics of PML and RRMS, which may help distinguish new MS activity from PML. Magnetization transfer ratio studies may provide additional clues in improving early detection of PML in patients with preexisting MS and warrant further investigation.

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been associated with the risk of PML. This includes rituximab, which demonstrated positive results in a phase 2 relapsing-remitting MS (RRMS) study. However, rituximab has been associated with PML in patients with lymphoproliferative disorders and systemic lupus erythematosus. Similarly, other immunosuppressive agents that have been used for MS, including mycophenolate mofetil, methotrexate, azathioprine, and cyclophosphamide, have been associated with PML in the context of rheumatologic disorders or cancer. In the aftermath of NTZ-treated patients with RRMS developing PML, criteria to recognize PML and monitor patients with MS undergoing treatment with NTZ have been proposed. Therefore, we conducted a study with the primary objective of identifying clinical and magnetic resonance imaging (MRI) characteristics of PML that may assist in distinguishing it from RRMS. We also explored magnetization transfer ratio (MTR) imaging in distinguishing PML from MS as a secondary goal of this study.

**METHODS**

The study was approved by the local Human Investigations Committee. We conducted a retrospective medical record review of all PML cases at 2 urban teaching hospitals in Detroit, Michigan, from 1988 to 2006. The medical records were queried with the search term progressive multifocal leukoencephalopathy. PML, and the corresponding International Statistical Classification of Diseases and Related Health Problems, Ninth Revision code. Only cases confirmed by either JCV cerebrospinal fluid polymerase chain reaction or tissue diagnosis (brain biopsy or autopsy) were included in our analysis. Demographic and clinical characteristics of all confirmed cases of PML were obtained from hospital medical records.

All brain MRI scans (n = 35) were reviewed as a group by 4 investigators (A.B., O.K., A.T., and I.Z.) including a neuroradiologist. Brain MRI scans were obtained on 1.0-T (n = 4) or 1.5-T (n = 31) scanners according to the protocol instituted for clinical scans at the 2 hospitals, which typically included axial T2-weighted, fluid-attenuated inversion recovery (FLAIR), and T1-weighted images. Sagittal T2-weighted or FLAIR images were obtained in all but 6 cases. All scans also included postcontrast T1-weighted images acquired after the intravenous administration of 0.1 mmol/kg of gadolinium. Additionally, in 4 patients with PML, brain magnetic transfer (MT) imaging was performed according to previously published techniques to examine brain MT ratio (MTR), which measures changes reflecting injury to myelin and the axonal membrane. Brain MTR was examined globally in the normal-appearing brain tissue (NABT) as well as regionally by placing regions of interest (ROIs) in NABT as well as PML lesions.

Clinical and MRI characteristics of the first 100 consecutive patients with clinically definite RRMS from our center database were used as controls for comparison. The patients with RRMS selected as the control group were diagnosed with clinically definite RRMS according to the McDonald criteria and, therefore, more likely to be representative of the current population of patients with newly diagnosed RRMS. Clinical presentations in patients with RRMS were recorded from the onset of initial symptoms.

Statistical analysis was performed using the t test, χ², and the Mann-Whitney U test as appropriate with a 95% level of significance. All P values < .05 were regarded as statistically significant. Data are quoted as mean (SD) unless otherwise stated.

To correct for the multiple comparisons made in our analysis, we applied maximum experimentwise error rate (Hommel method). Adjusted P values are shown in the Tables.

**RESULTS**

**BASELINE CHARACTERISTICS**

Of the 128 medical records of suspected PML cases generated from the query, only 45 were confirmed PML cases included in the analysis. Progressive multifocal leukoencephalopathy was confirmed by positive JCV cerebrospinal fluid polymerase chain reaction in 16 cases (36%) and by brain biopsy or autopsy in 29 cases (64%).

Demographic data are summarized in Table 1. Forty-two of 45 cases (93%) were HIV positive. The 3 non-HIV PML cases (7%) included acute myelocytic leukemia, idiopathic CD4 lymphopenia, and monoclonal gammopathy of unknown significance. Patients with PML presented at an older age than the RRMS cohort (mean [SD], 41 [9] years vs 34 [6.8] years; P = .001). More men (78% vs 29%; P < .0001) and more African American individuals (69% vs 16%; P < .0001) presented with PML compared with the RRMS cohort.

**NEUROLOGICAL PRESENTATIONS**

Clinical presentations at onset are summarized in Table 1. Overall, monosymptomatic presentations were more common in RRMS (85% vs 47%; P < .01). However, patients with PML presented more often with hemiparesis (24% vs 5%; P < .001) and altered mental status (19% vs 0%; P < .0001) than patients with RRMS. Brainstem dysfunction was more common in patients with RRMS than in patients with PML (18% vs 2%; P = .007). Acute spinal cord presentation and optic neuritis occurred in patients with RRMS but not patients with PML (18% vs 0% and 33% vs 0%, respectively; P < .0001). Complete or partial recovery was commonly observed in patients with...
Brain MRI scans were available in 35 of 45 PML cases. Seven PML brain MRI lesion patterns were identified (Figure): (1) large, confluent, and granular T2-weighted hyperintense lesions, (2) T2-weighted hyperintense lesions of deep gray matter structures, (3) crescent-shaped lesions of the cerebellar hemispheres, (4) gadolinium-enhanced T1-weighted lesions, (5) tumefactive lesions, (6) periventricular white matter lesions, and (7) transcallosal lesions.

Compared with patients with RRMS, several brain MRI lesion patterns were seen more commonly in patients with PML (Table 2) including large, confluent, and granular lesions on T2-weighted sequences (74% vs 2%; \(P < .0001\)), deep gray matter involvement (31% vs 7%; \(P < .0001\)), and crescent-shaped cerebellar lesions (23% vs 0%; \(P < .0001\)). In contrast, gadolinium-enhanced lesions (23% vs 54%; \(P = .001\)) and periventricular white matter lesions (9% vs 89%; \(P < .0001\)) were seen less commonly in patients with PML than patients with RRMS. Classic Dawson fingers were seen in 61% of RRMS MRI scans compared with only 1 (2.22%) PML MRI scan (\(P < .001\)). Interestingly, 2 of the 3 PML brain MRI scans that demonstrated periventricular white matter lesions met Barkhof MRI criteria24 for dissemination in space based on the presence of greater than 9 T2-weighted hyperintense lesions, 3 or more periventricular lesions, and the presence of infratentorial lesions. More than half of the PML scans (19 of 35; 54%) contained 2 or more of the lesion types described in Table 2.

### BRAIN MTR DATA

Brain MTR data were acquired using previously published techniques20,21 and analyzed in a 3-step manner. First, we examined the average brain MTR values in the PML lesions and compared them with MS lesions in patients with RRMS (Table 3). The average MTR values obtained from 6 PML and 12 RRMS cases were 35.7% and 36.08%, respectively (\(P = .72\)). Second, we examined the MTR values obtained from ROIs placed in the NABT in patients with PML and RRMS. The average MTR obtained from 6 ROIs in NABT in patients with PML was significantly higher than the average MTR obtained from 12 ROIs in patients with RRMS (47.2% vs 41.03%; \(P = .001\)). Third, we examined the entire NABT MTR in 4 patients with PML and compared it with 12 patients with RRMS. The average NABT MTR in patients with PML was significantly higher than patients with RRMS (44.15% vs 41.04%; \(P = .002\)).

### COMMENT

Many studies have previously described the clinical and MRI characteristics of PML, in both HIV-positive and HIV-negative populations.1,4,25-28 Cognitive impairment and motor deficits are consistently reported at high frequency. Other presentations, including aphasia and visual-spatial disorientation, dysarthria, incoordination, and sensory abnormalities, are commonly described. Symptom onset is reported as subacute to progressive and recovery of deficits is rare. The PML findings on brain MRI scans are described as bilateral, asymmetric subcortical-predominant lesions that appear hyperintense on T2-weighted and FLAIR sequences and hypointense on T1-weighted sequences. Mass effect is typically absent or mild, but not invariably. When mass effect is observed, it is generally in the context of the immune reconstitution inflammatory syndrome (IRIS).29,30 Patchy, irregular, peripheral postcontrast enhancement has been observed in up to 10% of HIV-associated PML cases26 and more often occurs with IRIS.29,31 Spinal cord and optic nerves are traditionally believed to be spared, although spinal cord abnormalities have been observed at autopsy in PML.32

Compared with RRMS, PML may have a slower symptom onset with more frequent cognitive and behavioral presentations. Unlike RRMS, PML is generally not considered to include optic nerve or spinal cord involvement. In patients with PML, brain MRI scans may demonstrate larger, more diffuse, and less well-demarcated T2-weighted hyperintense lesions that tend to occupy the juxtacortical areas, with relative sparing of the periventricular region. Compared with the homogeneous or ring enhancement frequently seen in MS lesions, PML lesions enhance less frequently and generally in a sparse peripheral pattern, often in the context of IRIS. Moll and colleagues33 recently compared pathologic changes in cortical demyelination in patients with PML and MS, finding intracortical and juxtacortical lesions in both but subcortical lesions only in MS brains. Clinical characteristics were not compared in the study.

In our study, hemiparesis and mental status changes occurred more commonly in PML than RRMS, whereas brainstem dysfunction was less common in PML, consistent with prior observations. Likewise, none of the PML cases in our study presented with a spinal cord syndrome or optic neuritis. Also in accord with prior observations, all PML cases in our study demonstrated disability progression, in contrast to the patients with RRMS, who frequently experienced short-term recovery following a relapse. These clinical findings help confirm differences in clinical presentations of PML and RRMS29,30 and may provide clues in identifying the development of PML in patients with RRMS.

A major focus of our study was to compare brain MRI characteristics of patients with PML and RRMS. We describe 7 patterns of brain MRI lesions in patients with PML. Large, confluent, and granular hyperintense T2-weighted lesions as well as deep gray matter lesions were more commonly seen in patients with PML than patients with RRMS, and crescent-shaped lesions in the cerebellar hemispheres were identified only in patients with PML. This raises the possibility that crescent-shaped cerebellar lesions may represent a unique PML MRI pattern, a finding that requires confirmation in a larger study. Periventricular white matter lesions and Dawson fingers, both common in RRMS, were rarely seen in PML scans. Gadolinium-enhancing lesions were noted in

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Figure. The 7 identified progressive multifocal leukoencephalopathy brain magnetic resonance imaging lesion patterns. A, Large, confluent, granular T2-weighted lesions (arrows). B, Deep gray matter involvement (arrow). C, Crescent-shaped cerebellar lesion. D, Gadolinium-enhancing lesions (arrow). E, Tumefactive lesion (arrow). F, Multiple sclerosis-like appearance. G, Transcallosal lesion (arrow). All brain magnetic resonance images are axial T2-weighted except for part D, which is an axial T1-weighted image acquired after the intravenous administration of gadolinium.
approximately one-fourth of PML scans. We cannot rule out the possibility that a percentage of the HIV-positive patients with PML had IRIS at the time of their MRI scan, contributing to MRI gadolinium enhancement. However, 2 of the 3 HIV-negative patients with PML also had gadolinium-enhancing lesions. These findings support observations made by Huang et al,27 suggesting that brain MRI gadolinium enhancement may be seen in HIV-negative patients with PML, cautioning that the presence of gadolinium enhancement should not preclude PML. All but one of the enhancing PML brain lesions in our cohort demonstrated subtle contrast enhancement largely limited to the rim of the lesion. This appearance is quite different than most RRMS lesions, which typically tend to demonstrate a homogeneous pattern of enhancement.34 One PML lesion did contain an open ring-enhancing lesion, similar in appearance to ring-enhancing MS lesions35 seen in 6% of the RRMS cohort in our study.

Magnetization transfer imaging has received considerable attention as a novel imaging technique to detect and quantify microstructural changes associated with myelin tissue and axonal injury.30 It is based on the exchange of magnetization between protons bound to macromolecules (myelin) and those in free water. This allows the calculation of MTR that reflects the efficiency of such an exchange before and after the application of an off-resonance saturation pulse. Low MTR indicates a reduced capacity of the macromolecules in brain tissue to exchange magnetization with the surrounding water molecules, indicative of damage to myelin or to the axonal membrane. Postmortem studies have shown that MTR is strongly associated with the percentage of residual axons and the degree of demyelination both in T2-visible lesions and the NABT.37 Previously, brain MTR measured from T2-visible PML lesions and the NABT of patients with PML has been shown to be significantly low compared with age-matched controls.30,36 However, no study has been done comparing the brain MTR of PML with RRMS. We examined MTR of T2-visible lesions as well as NABT in PML and RRMS. Relative to normal tissue, lesions in both disorders demonstrated low MTR values, consistent with the underlying demyelinating pathology, but without any significant difference between the 2 groups. In contrast, NABT MTR, examined by ROI or globally, was significantly lower in RRMS than PML. Both regional and global reductions in the NABT MTR of patients with RRMS compared with relatively normal MTR in the NABT of patients with PML suggest that PML may be a more focal disease than RRMS. Nonconventional brain MRI studies have demonstrated diffuse and subtle tissue damage in otherwise NABT in RRMS even early in the disease course.30,41 These observations could have significant implications by potentially detecting PML when it is relatively more focal. Chen et al42 recently used voxel-based MTR to characterize the evolution of demyelination and remyelination in gadolinium-enhancing MS lesions, finding a significant decrease in MTR at the time of enhancement and partial recovery over the next 4 months, followed by apparent stabilization. In contrast, MTR of T2-visible PML brain lesions has been found to be very low and did not change significantly during a 9-month follow-up.38,39 These MTR differences may reflect the different underlying pathophysiology of demyelination in the 2 conditions; whereas MS lesions are related to inflammation that may later resolve, JCV infection of oligodendrocytes is believed to lead to cell death. When evaluating a new brain MRI lesion in a patient with MS considered at risk for PML, one could use serial voxel-based MTR to discern whether the lesion is from MS (reversible inflammatory demyelination) or PML (irreversible infectious demyelination). Monthly brain MTR evaluation using a voxel-based approach demonstrating

Table 2. Brain MRI Characteristics in PML and RRMS

<table>
<thead>
<tr>
<th>MRI Pattern</th>
<th>PML (n=35)</th>
<th>RRMS (n=100)</th>
<th>P Value</th>
<th>Adjusted P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large, confluent, granular T2-weighted lesions</td>
<td>26 (74)</td>
<td>2 (2)</td>
<td>&lt;.0001</td>
<td>.0005</td>
</tr>
<tr>
<td>Deep gray matter involvement</td>
<td>11 (31)</td>
<td>7 (7)</td>
<td>&lt;.0001</td>
<td>.0005</td>
</tr>
<tr>
<td>Crescent cerebellar lesions</td>
<td>8 (23)</td>
<td>0</td>
<td>&lt;.001</td>
<td>.003</td>
</tr>
<tr>
<td>Gadolinium-enhancing lesions</td>
<td>8 (23)</td>
<td>54 (54)</td>
<td>.001</td>
<td>.003</td>
</tr>
<tr>
<td>Tumefactive lesions</td>
<td>1 (3)</td>
<td>6 (6)</td>
<td>.07</td>
<td>.084</td>
</tr>
<tr>
<td>Periventricular white matter lesions</td>
<td>3 (9)</td>
<td>89 (89)</td>
<td>&lt;.0001</td>
<td>.0005</td>
</tr>
<tr>
<td>Transcallosal</td>
<td>3 (9)</td>
<td>3 (3)</td>
<td>.067</td>
<td>.078</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis.
<sup>a</sup>Classic Dawson fingers lesions were seen in 61% of RRMS MRI brain scans compared with 2.22% of PML MRI brain scans (adjusted P<.001).
<sup>b</sup>Hommel-adjusted P value.

Table 3. MTR Analysis for PML and RRMS

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean MTR, %</th>
<th>P Value</th>
<th>Adjusted P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML lesions (n=6)</td>
<td>35.7</td>
<td>.72</td>
<td>.81</td>
</tr>
<tr>
<td>MS lesions (n=12)</td>
<td>36.08</td>
<td>.001</td>
<td>.003</td>
</tr>
<tr>
<td>PML NABT ROI (n=6)</td>
<td>47.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS NABT ROI (n=12)</td>
<td>41.03</td>
<td>.002</td>
<td>.004</td>
</tr>
<tr>
<td>PML NABT (n=4)</td>
<td>44.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS NABT (n=12)</td>
<td>41.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MS, multiple sclerosis; MTR, magnetization transfer ratio; NABT, normal-appearing brain tissue; PML, progressive multifocal leukoencephalopathy; ROI, region of interest; RRMS, relapsing-remitting multiple sclerosis.
<sup>a</sup>Hommel-adjusted P value.
varying degrees of remyelination within a suspected lesion would likely suggest that the lesion is secondary to MS. In contrast, consistently low MTR values observed uniformly in all voxels within the suspected lesion would be more likely to be PML. Such an approach may facilitate a timely window of opportunity to intervene, including the use of plasma exchange for rapid removal of the potentially offending agent NTZ as well as initiation of other recently proposed interventions. Nonetheless, this requires further work to evaluate the utility of MTR in a larger cohort.

There are several limitations of our study, including the retrospective and cross-sectional design. Besides a modest sample size, 93% of PML cases were HIV positive, many with AIDS. There was no clinical correlation between the PML brain MRI lesion appearance and the clinical presentation. This could have been because of the relatively small sample size and that brain MRI scans in our study were not obtained according to a standardized protocol. Brain MTR data suggest interesting differences between PML and MS lesions. However, longitudinal studies in a larger number of patients are needed to not only confirm our findings but also study the evolution of PML lesions, regionally and globally. Moreover, there may be technical difficulties in implementing MTR protocols across multiple sites. In our data set, we had access to only 7 spinal cord MRI scans and the presence or absence of spinal cord involvement was judged solely on the basis of clinical presentation. Although we found no PML presentations consistent with a spinal cord syndrome, one such case has been recently reported. It is possible that dedicated spinal cord MRI scans in patients with PML may identify MRI-visible spinal cord pathology at onset.

Our preliminary study identifies differences in clinical and MRI features of PML and MS that confirm prior expert opinions and may assist clinicians in earlier detection of PML in patients with RRMS. Even though effective therapies for PML are lacking, early identification of PML provides the best opportunity to intervene. In the patient with MS, the immediate discontinuation of the medication that may be contributing to the development of PML is of paramount importance. Our study also explored the use of MT imaging as a novel imaging modality. Brain MTR data suggest PML may be relatively more focal than RRMS. This distinction deserves further exploration in a larger study as it may provide critical clues to the evolution of PML in patients with RRMS. Furthermore, serial brain voxel-based MTR may assist in distinguishing the etiology of a new “suspected” T2-weighted brain lesion in a patient with MS at risk for PML. Nonetheless, diagnosing PML against the background of preexisting MS remains challenging and complex, warranting larger multicenter studies to better define the disease, particularly in non–HIV-positive patients.

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