Inflammatory natalizumab-associated PML: baseline characteristics, lesion evolution and relation with PML-IRIS

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ABSTRACT

Background and objective Natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML) patients may show imaging signs suggestive of inflammation at diagnosis (“inflammatory PML”), reminiscent of PML-immune reconstitution inflammatory syndrome (PML-IRIS). We investigated the imaging characteristics of inflammatory NTZ-PML lesions and PML-IRIS to determine differentiating and overlapping features.

Methods We scored the presence, localization and pattern of imaging characteristics of inflammation on brain MRI scans of inflammatory NTZ-PML patients. The imaging characteristics were followed-up until the occurrence of PML-IRIS.

Results 10 out of the 44 NTZ-PML patients included showed signs suggestive of inflammation at time of diagnosis. The inflammation pattern at diagnosis was similar to the pattern seen at PML-IRIS, with contrast-enhancement representing the most frequent sign of inflammation (90% at diagnosis, 100% at PML-IRIS). However, the severity of inflammation differed, with absence of swelling and low frequency of perilesional edema (10%) at diagnosis, as compared to the PML-IRIS stage.

Conclusion Patterns of inflammation at the time of PML-diagnosis and at the PML-IRIS stage overlap, but differ in their severity of inflammation. This supports histopathological evidence that the inflammation seen at both stages of the same disease share a similar underlying pathophysiology, representing the immune response to the JC virus to a variable extend.
INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a serious side effect of immunosuppressive therapies particularly seen in multiple sclerosis (MS) patients treated with natalizumab (NTZ, Biogen Inc, Cambridge, MA, USA), a humanized monoclonal antibody against the α4-integrin adhesion molecule.[1,2] PML is an opportunistic infection of the central nervous system (CNS) caused by reactivation and replication of JC virus (JCV), characterized by a lytic infection of oligodendrocytes, astrocytes and neuronal cells.[3-5]

PML risk mitigation programs during therapy with NTZ recommend regular clinical assessment, laboratory tests (eg, JCV serostatus), and magnetic resonance imaging (MRI), aiming at improving the benefit-risk ratio of a drug with a known high clinical and MRI efficacy in MS.[6-9]

In NTZ-treated MS patients, brain MRI can detect opportunistic infections such as PML at very early stages, even prior to the development of clinical symptoms suggestive of PML coining the term presymptomatic or asymptomatic PML.[10-14] However, the detection of PML at an early stage can be challenging since the imaging findings can be subtle, fluctuating and difficult to interpret.[15-19] In comparison to classical, human immunodeficiency virus (HIV) associated cases of PML, NTZ-PML displays a higher frequency of MR imaging signs suggestive of inflammation at time of diagnosis, including contrast-enhancement and punctuate lesions with a perivascular distribution pattern, reported in approximately 30% of the patients [11,15,16]. Such lesions can be the most prominent initial imaging sign at the time of PML diagnosis, even in asymptomatic NTZ-PML, reflecting inflammation in the perivascular spaces and thereby unmasking the opportunistic infection.[19-22] These observations have led to the term “inflammatory PML”, thereby differentiating these PML cases from those without any signs of inflammation, termed “classical PML”. [18,23,24] It has been suggested that the inflammation in NTZ-PML is caused by the mode of action of a drug that is classified as a selective immune suppressant, with a partial maintenance of immune functions in the central nervous system.[25]
“Inflammatory PML” shares several imaging and histopathological characteristics with PML-immune reconstitution inflammatory syndrome (IRIS). [20,21] PML-IRIS is characterized by a clinical deterioration despite partial or full recovery of the immune competence in previously immune-compromised patients. [22,26-30] Inflammatory PML and PML-IRIS often are not clearly separated, and terminology is partly conflicting in published literature. In “inflammatory PML”, lytic infection by JCV is supposed to be the leading cause of structural brain damage, and inflammation a rather desirable side action of a still partly functioning immune system limiting the further spread of, and supporting the destruction by the virus. In contrast, during PML-IRIS, the immune reactions, initiated by the JCV replicating but then spreading and becoming an independent factor of tissue destruction, is believed to overshoot and become the leading cause of structural brain damage. Thus, the correct interpretation and recognition of the two distinct variants of inflammation could affect management and treatment of patients with PML. [31,32]

Systematic data on the lesion evolution of inflammatory PML lesions, and criteria for separation from PML-IRIS are lacking. The aim of this study was to investigate characteristics of inflammatory PML and PML-IRIS, including the lesion evolution in patients with and without signs of inflammation at time of diagnosis.
PATIENTS AND METHODS

Standard protocol approvals, registrations, and patient consents

Brain MRI is included in the standard patient care of NTZ-treated MS patients for treatment efficacy assessment and safety monitoring purposes. We retrospectively collected clinical, laboratory and imaging data from NTZ-PML patients. We obtained a waiver from our local institutional review board stating that the requirements of the Medical Research Involving Human Subjects Act did not apply and that official IRB approval was not mandatory. Written informed consent was obtained from all participants for the use of the clinical, laboratory and imaging data for research and teaching purposes.

Study design, patient selection

This retrospective study used routine brain MR images for the diagnosis and follow-up of PML lesions in NTZ-treated MS patients. We obtained data from 67 natalizumab-associated PML patients, 25 of whom were derived from the Dutch-Belgian natalizumab-associated PML cohort and 42 patients referred by other institutions to our center for second opinion and research purposes. Figure 1 gives detailed information on the patient selection and inclusion process. MR images were collected in the Digital Imaging and Communication in Medicine (DICOM 3) file format. All MRI scans from the first observation of PML lesions through follow-up until and including PML-IRIS stage were collected. Only patients fulfilling the following criteria were analyzed for the purpose of this study: 1. Availability of T2-weighted and contrast-enhanced T1-weighted images at the time of diagnosis, and during PML follow-up. 2. MR images of sufficient quality, suitable for diagnostics purposes (i.e., no movement artefacts or bad repositioning etc.). 3. Sufficient data available at diagnosis and during the clinical course to enable assessment of the detection of imaging findings suggestive of PML-IRIS.[33]
Image analysis and interpretation

All MRI scans were analyzed on a digital workstation in consensus by two raters (MPW, MTW) with special expertise in the field of inflammatory diseases of the CNS. Brain MRI scans were screened for signs suggestive of inflammation at the time of PML diagnosis, before immune reconstitution (“inflammatory PML”).

Imaging characteristics suggestive of inflammation were categorized as recently described [33]: 1. Occurrence of contrast enhancement in the brain. 2. Occurrence of lesions showing new signs of mass effect and/or perilesional edema. Per definition: subtle perilesional edema can present without any mass effect or swelling. 3. Occurrence of new punctate T2 lesions with a perivascular spread. The characteristics of contrast-enhancement were further classified according to the localization (in the center of PML lesions, in the border of PML lesions, outside of PML lesions with a perivascular spread, or outside of PML lesions without a perivascular spread), and the enhancement pattern (punctuate, homogeneous, patchy).

In patients showing signs of inflammation at the time of PML diagnosis, the evolution of MRI findings were assessed on follow-up MRI scans up to, and including PML-IRIS stage. Patients were considered to fulfill the PML-IRIS stage when both clinical deterioration, and new or progressive imaging signs of inflammation were noted on MRI after NTZ cessation.[23,26,27,33] The MRI analysis on the follow-up visits included: 1: Lesion evolution of the main PML lesions (size increase, decrease, stable). 2. contrast-enhancement: increase, decrease or stable contrast-enhancement of pre-existing lesion, new contrast-enhancing lesion, change of the enhancement pattern. 3. New small T2 lesions with a perivascular distribution pattern 4. New mass effect and/or edema.

MRI protocols

Since the PML cases were collected from different centers, the image acquisition parameters including pulse sequences, head coils and magnetic field strengths (1.5T and
3T) and parameters related to spatial resolution were heterogeneous and based on local MRI protocols. In all patients the MRI protocol at the time of first PML lesion detection and during follow-up, including the PML-IRIS stage, consisted of T2-weighted, T2-fluid attenuated inversion recovery (FLAIR), and post-contrast T1-weighted MR images. In 17 patients, pre-contrast T1-weighted images were also available during follow-up. Based on the multi-center data acquisition, the scan intervals of follow-up MRI after the diagnosis of PML were not standardized and ranged from 1 to 4 weeks.
RESULTS

Patients

Of the screened 67 natalizumab-associated PML patients, 44 patients were eligible for analysis. Nineteen patients were excluded due to insufficient data available during follow-up of the PML disease course and two were excluded due to insufficient data available at PML diagnosis (inclusion criterion 3). Two patients were excluded due to insufficient quality of the MR images (inclusion criterion 2). Among the included patients, only the 10 patients that showed imaging signs of inflammation at the time of PML diagnosis were selected for the purpose of this study (figure 1). The demographic and clinical information of these 10 patients are presented in table 1, including the diagnostic classification according to PML diagnostic criteria as proposed in a consensus statement from the American Academy of Neurology (AAN) Neuroinfectious Disease Section [34].

With respect to the treatment history before the initiation of natalizumab, in 7 of the 10 patients, exact data on prior immunotherapy for the treatment of MS prior to NTZ-PML development is known. Four were previously treated with interferon beta-1a, one had been treated interferon beta-1a and interferon beta-1b, and two had no prior immunotherapy. Of the remaining three patients, it is known that they were not previously treated with immunosuppressive therapy, but it is unknown whether they had used immunomodulatory drugs.

Imaging characteristics of inflammation at PML diagnosis and during PML-IRIS phase

Global frequency of imaging signs of inflammation

As per definition, all patients analyzed showed signs of inflammation already at time of PML diagnosis, with contrast enhancement seen in 9 out of 10 patients (90%), and perivascular T2 lesions in 6 patients (60%), among whom one did not display contrast enhancement. At the time of PML-IRIS, all patients (100%) displayed contrast enhancement, and the proportion of patients with perivascular T2 lesions increased to 8 out of the 10
patients (80%). Perilesional edema was seen in only 1 patient at time of diagnosis (10%), increasing to 4 (40%) during PML-IRIS. Swelling with mass effect was absent in patients at diagnosis, increasing to 6 (60%) during PML-IRIS.

**Characteristics of contrast enhancement**

At PML diagnosis and during PML-IRIS, contrast enhancement was seen at the border of the PML lesion (8 and 10 patients, respectively), outside of the PML-lesions (6 and 9 patients, respectively), and in the center of the PML lesion (2 and 5 patients, respectively).

Appearance of contrast enhancement was rarely noted to be homogenous (none at diagnosis, 1 during PML-IRIS), but either of punctate (5 at diagnosis, 8 during PML-IRIS), or of patchy (8 at diagnosis, 10 during PML-IRIS). Figures 2 and 3 show examples of different enhancement pattern (punctuate, patchy).

**Individual course of the patients and MRI lesion characteristics**

The individual course of lesion characteristics of the patients is shown in table 2. The clinical presentation including EDSS has not been systematically assessed during and after the PML/PML-IRIS disease course. One single patient (patient number 1) died, all other patients survived PML/PML-IRIS. One patient (patient number 7) stayed asymptomatic during the whole PML/PML-IRIS disease course. One patient (patient number 1) received single course of i.v. corticosteroids (1000 mg/day for three days) directly after the diagnosis of inflammatory PML.

Comparing extent and distribution of contrast enhancement at diagnosis and at the PML-IRIS stage, nine out of ten patients showed new or persisting contrast-enhancement following the same pattern during PML-IRIS as seen at the time of PML diagnosis (seven patients with new contrast-enhancing lesions following a similar pattern and seven patients with persistence of the contrast enhancement from the time of diagnosis). The progression of contrast-enhancement at/during PML-IRIS stages was present in the center/at the border of the main lesion as well as in lesions outside the main PML lesion (Figure 3). In the one
patient showing just perivascular T2 lesion as imaging sign suggestive of inflammation at the time of PML diagnosis, these perivascular T2 lesions started showing additional contrast enhancement, with associated edema and mass effect in other locations during the PML-IRIS phase. Figure 2 and 3 show examples of the inflammatory PML lesion characteristics at baseline and during follow-up.
DISCUSSION

In this study, we systematically describe the imaging characteristics of “inflammatory PML” lesions, and we show that the vast majority of these patients continue to show similar signs of inflammation during PML-IRIS stages. Signs of inflammation, in particular contrast-enhancement, seen on brain MRI have been described in approximately 30% of natalizumab-associated PML patients at the time of PML diagnosis, either in symptomatic or asymptomatic disease stages.[11,15,16,35] The pathophysiological background of these imaging signs suggestive of inflammation remained poorly understood for a long time. Recent histopathological data suggested that such inflammation at the time of PML diagnosis might be related to an immune response against the JC virus, similar to, but less severe than, in patients entering the PML-IRIS stage.[23,26,27] PML-IRIS lesions are characterized by inflammatory cell infiltrations including an abundance of CD8+ T cells and numerous macrophages. In addition, surprisingly high plasma cell numbers were reported in natalizumab-associated PML-IRIS by one histopathological case series, not noted in HIV associated PML.[27] Of importance to our study, natalizumab-associated inflammatory PML cases generally share these histopathological findings of PML-IRIS, including the high plasma cell numbers, albeit to a lesser extent.[27] This also refers to specific patterns of inflammation, such as the observation of perivascular cuffing, observed PML-IRIS patients as well as in inflammatory PML patients.[26] Obviously, even in early PML stages, CD8+ cytotoxic T cells are able to attack the JC virus and control the PML disease activity.[36]

In fact, our in-vivo imaging study is in line with these histopathological data. In general, the vast majority of our patients showed a similar imaging pattern of inflammation at the time of PML diagnosis as during the PML-IRIS stage. Although the imaging pattern suggestive of inflammation remained similar during follow-up, the severity of inflammation increased at the PML-IRIS stage including new enhancing lesions, swelling, and perilesional edema. As such, imaging patterns of inflammation at the time of PML diagnosis and at the PML-IRIS stage likely are no distinct entities, but rather differ in their extent of inflammation. This supports experimental evidence that the inflammation seen at both stages of the same
disease may share a similar underlying pathophysiology, representing the immune response to the causative JC virus to a variable extent.[27]

Comparing our present inflammatory PML patients to our recently published ‘classic’ NTZ-PML cohort without any imaging signs of inflammation, the time interval between PML diagnosis and PML-IRIS occurrence was longer for patients with “inflammatory” PML (66.5 days, range: 23-224 [table 1] versus 42 days, range 6-98 days). In addition, one of our inflammatory PML patients received i.v. corticosteroids directly of the diagnosis of inflammatory PML whereas 4 patients of the non-inflammatory PML cohort received corticosteroids < 30 days to PML-IRIS manifestation.[33] It remains unclear if this difference holds up in independent cohorts, and if this is of clinical relevance. However, it could have influenced the patient management.[37]

In general, the investigation of any link between the clinical outcome and the described MRI findings was not the aim of this study. Owing to the rather small size of our study, we were unable to link presence or absence of inflammation at time of PML diagnosis to clinical outcome, warranting larger studies and a prospective, multicentric approach. Furthermore, another open question is if patients with signs of inflammation on imaging should be treated differently as compared to patients with classical PML. Potential differences in the patient management could relate to the early administration of corticosteroids even before the patient is classified as PML-IRIS, or the use of measures of enhancing NTZ clearance depending on imaging characteristics (plasmapheresis/imunoabsorption). Additional biomarkers such as virus specific antibody responses in blood, CSF, or T cell responses that classify and quantify the immune response against JCV at the time of PML diagnosis may potentially be useful tools for individualizing therapeutic regimens.[31,32,38,39]

This study has limitations. First of all, the number of patients in our study presenting with imaging signs suggestive of inflammation with a complete clinical and radiological follow-up until the PML-IRIS stage is rather small. Although these patients are well characterized in terms of patient management, treatment and co-morbidity, we cannot
exclude that some of these aspects could have influenced the clinical and imaging presentation. Further studies including larger numbers of patients are needed to further support our results.

In conclusion, our study demonstrates that an imaging pattern suggestive of inflammation at the time of PML diagnosis in natalizumab-treated MS patients shares imaging characteristics of PML-IRIS in later disease stages. Many of these initial inflammatory PML lesions develop into sites of severe inflammation at PML-IRIS stage. This further supports histopathological and experimental data that this inflammation at the time of PML diagnosis is most likely based on a lymphocytic response against the JC virus due to an incomplete immune suppression during natalizumab treatment.
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Contributors

MPW, MTW collected the data, analyzed the data and wrote the manuscript. FB, SF, BMJU, CW and JK interpreted the data and edited the manuscript. All authors reviewed and agreed on the final versions of the manuscript.

Competing interest

MPW has received consultancy fees from Biogen, Novartis and Roche. FB serves as a consultant for Bayer-Schering Pharma, Sanofi-Aventis, Biogen, Teva, Novartis, Roche, Synthon BV, Genzyme, Jansen Research. JK has accepted consulting fees from Merck-Serono, TEVA, Biogen, Genzyme, and Novartis. BMJU has received consultancy fees from Novartis, Merck Serono, Biogen and Danone Research. MTW does not report any competing interest. The VUmc has received financial support for research activities from Bayer Schering Pharma, Biogen, Glaxo Smith Kline, Merck Serono, Novartis, and Teva. JE received
consultancy fees and/or lecture fees from Biogen, Genzyme, Teva, Merck and Novartis. The authors had full editorial control of the manuscript and provided their final approval of all content.

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References


**Legends to the figures:**

**Figure 1**

Flow chart illustrating the patient selection and inclusion process.

**Figure 2**

T2 and T1 weighted images (with contrast administration) at the time of PML diagnosis (top row) and at the time of PML-IRIS stage (bottom row). The images at diagnosis (“inflammatory PML”) show a subcortical and cortical lesion in the right frontal lobe showing contrast enhancement (C, D) in addition to punctuate T2 lesions following a perivascular distribution that also enhance on T1 after contrast administration (A, B). These inflammatory PML lesions show different enhancement pattern such as punctuate (B) and patchy (D). At the time of PML-IRIS manifestation the PML lesions have increased in size and the contrast enhancement of the main PML lesion (H, I) as well as in and around the perivascular T2 lesions (F, G) has also markedly increased. In addition, there are now signs of edema with mass effect around the PML lesions (F, H).

**Figure 3**

Fluid attenuation inversion recovery (FLAIR), T2 and T1 weighted images (with contrast administration) at the time of PML diagnosis (top row), and at the time of PML-IRIS stage (bottom row). At the time of diagnosis there are multiple contrast enhancing punctuate T2
lesions (punctuate enhancement pattern) with a perivascular distribution visible (A – C). At PML-IRIS manifestation there is a massive increase in the number of contrast enhancing perivascular lesions and persistence of the contrast enhancement from the time of diagnosis (D – F). The increase of punctuate lesions in number and size includes enhancing lesions in the main PML lesions as well as outside of the main PML lesion (F). In addition, the main PML lesion had increased in size.
Table 1: Demographic and clinical characteristics of the included patients

<table>
<thead>
<tr>
<th>Demographic and clinical information of the study participants</th>
<th>Median [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female), n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 [23 – 55]</td>
</tr>
<tr>
<td>Natalizumab treatment duration (doses) at PML diagnosis</td>
<td>44 [12 – 63]</td>
</tr>
<tr>
<td>Interval first inflammatory PML MRI scan until last natalizumab administration, in days for patients in whom natalizumab was continued because inflammatory PML lesions were not recognized as PML lesions; four cases</td>
<td>38 [3 – 172]</td>
</tr>
<tr>
<td>Interval last natalizumab administration until first inflammatory PML MRI (five cases)</td>
<td>20 [3 – 36]</td>
</tr>
<tr>
<td>Asymptomatic* at the time of PML diagnosis*, n (%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Symptomatic at the time of PML diagnosis, n (%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>“Definite PML*** at the time of PML diagnosis*, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>“Probable PML*** at the time of PML diagnosis*, n (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>“Possible PML*** at the time of PML diagnosis*, n (%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>“Not PML*** at the time of PML diagnosis*, n (%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>“Definite PML*** during the observational period*, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>“Probable PML*** during the observational period*, n (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>“Possible PML*** during the observational period*, n (%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>“Not PML*** during the observational period*, n (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients who received corticosteroids prior to PML diagnosis</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients who received corticosteroids directly after PML diagnosis</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Interval between PML diagnosis and PML-IRIS in days during follow-up</td>
<td>66.5 [23 – 224]</td>
</tr>
</tbody>
</table>

PML=progressive multifocal leukoencephalopathy, IRIS= immune reconstitution inflammatory syndrome.

* data missing for one patient.
* Asymptomatic PML is defined as no symptoms suggestive of PML

** “Definite PML”: all patients had a clinical presentation and imaging findings suggestive of PML as well as JCV DNA in the CSF detected by PCR. “Probable PML”: all patients were asymptomatic, had MRI lesion(s) suggestive of PML and JCV DNA in the CSF detected by PCR. “Possible PML”: all patients had clinical symptoms suggestive of PML and MRI lesion(s) suggestive of PML but no JCV DNA detected in the CSF. “No PML”: all patients had MRI lesion(s) suggestive of PML but no clinical symptoms suggestive of PML, no JCV DNA has been detected in the CSF.

# According to American Academy of Neurology (AAN) PML diagnostic criteria [27]
<table>
<thead>
<tr>
<th>Patient</th>
<th>PML diagnosis (n=10)</th>
<th>PML-IRIS stage (n=10)</th>
<th>Findings at PML-IRIS phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Persistence of enhancement seen at Dx</td>
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<tr>
<td>1</td>
<td>Contrast enhancement in border of the PML lesions and enhancing perivascular T2 lesions</td>
<td>Persistent enhancing lesions from PML diagnosis. New enhancing lesions with a similar pattern.</td>
<td>y</td>
</tr>
<tr>
<td>2</td>
<td>Contrast enhancement in the center and border of the PML lesions</td>
<td>Persistent enhancing lesions from PML diagnosis. New enhancing lesions with a similar pattern and enhancing perivascular T2 lesions.</td>
<td>y</td>
</tr>
<tr>
<td>3</td>
<td>Contrast enhancement in the border of the PML lesions and enhancing punctuate T2 lesions adjacent to the</td>
<td>Enhancement from time of diagnosis disappears during follow-up. New contrast enhancing lesions following-same pattern as at diagnosis, plus</td>
<td>n</td>
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<tr>
<td></td>
<td>main PML lesion</td>
<td>swelling with mass effect.</td>
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<tr>
<td>4</td>
<td>Punctuate contrast enhancement adjacent to the main PML lesion and with a perivascular spread</td>
<td>Persistent enhancing lesions from PML diagnosis. New enhancing lesions in the border of the PML lesions, plus swelling with mass effect.</td>
<td>y</td>
</tr>
<tr>
<td>5</td>
<td>Contrast enhancement in the border of the PML lesions and adjacent to the PML lesions</td>
<td>Persistent enhancing lesions from PML diagnosis. New enhancing lesions with a similar pattern and new enhancing lesions in the center of the PML lesions plus swelling with mass effect.</td>
<td>y</td>
</tr>
<tr>
<td>6</td>
<td>Contrast enhancement in the center, border and outside of the PML lesions, enhancing punctuate T2 lesions and perilesional edema</td>
<td>Persisting enhancement and edema. New enhancing lesions with a similar pattern and swelling with mass effect.</td>
<td>y</td>
</tr>
<tr>
<td>7</td>
<td>Contrast enhancement in the border and outside of the PML lesion with enhancing perivascular T2 lesions</td>
<td>Persisting enhancement. New enhancing lesions with a similar pattern and new enhancing lesions outside of PML lesions, and new perilesional edema and swelling with mass effect.</td>
<td>y</td>
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<tr>
<td>8</td>
<td>Contrast enhancement in the border of the PML lesion with enhancing perivascular T2 lesions</td>
<td>Enhancement from time of diagnosis disappears during follow-up. New contrast enhancing lesions following same pattern as at diagnosis and new enhancing lesions in the center and outside of the PML lesion, plus perilesional edema.</td>
<td>y</td>
</tr>
<tr>
<td>9</td>
<td>Contrast enhancement in the border of the PML lesion</td>
<td>Slight diminishment of earlier enhancement, new punctuate enhancing lesions outside of the PML lesion</td>
<td>y/n</td>
</tr>
<tr>
<td>10</td>
<td>Perivascular T2 lesions</td>
<td>Contrast enhancement of perivascular T2 lesions and enhancement in border and outside of the PML lesion, plus perilesional edema and swelling with mass effect</td>
<td>-</td>
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</tbody>
</table>