Case Report

Early Magnetic Resonance Detection of Natalizumab-Related Progressive Multifocal Leukoencephalopathy in a Patient with Multiple Sclerosis

Guglielmo Manenti, Simone Altobelli, Marco Nezzo, Marco Antonicoli, Erald Vasi, Luca Neroni, Roberto Floris, and Giovanni Simonetti

Department of Diagnostic and Molecular Imaging, Interventional Radiology and Radiation Therapy, Fondazione Policlinico "Tor Vergata", Viale Oxford 81, 00133 Rome, Italy

Correspondence should be addressed to Guglielmo Manenti; gu.manenti@gmail.com

Received 22 January 2013; Accepted 19 February 2013

Academic Editors: T. Chakera, A. Komemushi, and M. Leonardi

Copyright © 2013 Guglielmo Manenti et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Diagnosis of progressive multifocal leukoencephalopathy is usually based on the clinical presentation, on the demonstration of the brain lesions at the magnetic resonance imaging examination, and on the detection of the JC virus DNA in the cerebrospinal fluid with high sensitive polymerase chain reaction. The role of magnetic resonance imaging specifically in natalizumab-associated progressive multifocal leukoencephalopathy is strengthening, and it is gaining importance not only as an irreplaceable diagnostic tool but also as a surveillance and risk stratifying tool in treated patients. While other imaging techniques such as computed tomography lack sensitivity and specificity, magnetic resonance performed with morphological and functional sequences offers clinicians the possibility to early identify the stage of the disease and the emergence of an immune reconstitution inflammatory syndrome after natalizumab blood removal plasmapheresis.

1. Case Report

A 44-year-old man with a 12-year-history of multiple Sclerosis (MS) was treated with interferon therapy till June 2009 when it was decided to introduce natalizumab (Tysabri; Biogen Idec, Weston, MA, USA) due to symptomatology worsening (reduction in walking autonomy) which quickly regressed after three months of therapy. In December 2011, the patient reported a memory and concentration deficit and presented several episodes of verbal aggression, mood changes, and suicidal thoughts. The patient was admitted at the Neurology Department of our Institution for further clinical and radiological examinations. A magnetic resonance (MR) scan on a 3T scanner (Philips Achieva 3T) was performed using the following sequences: T1 and T2 weighted, fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), T1 post-gadolinium (Gd), and single- and multivoxel point resolved spectroscopy (PRESS). The MR exam showed a wide subcortical lesion with an irregular shape which involved the semioval center underneath the frontal lobe of the left hemisphere with a minor involvement of subcortical white matter of the right hemisphere and of the anterior commissure (Figure 1). The lesion showed a high signal intensity on T2-weighted and FLAIR images, low signal on T1-weighted images, no contrast-enhancement (CE) after endovenous gadolinium administration (Figure 2), no restricted diffusion (Figure 3), elevated lactate and myoinositol levels, and an increase of choline with a reduction of creatine (reversed ratio) and NAA (N-acetyl-aspartate) in both monovoxel and multivoxel spectroscopies (Figure 4). Due to magnetic resonance imaging (MRI) findings, it was decided by the clinicians to abrupt Natalizumab therapy and perform the spinal tap. A low JCV DNA burden was found in the cerebrospinal fluid (CSF) with high sensitive polymerase chain reaction (PCR). Subsequently, it was decided to start plasmapheresis (PLEX) treatment to obtain the complete drug removal. At the followup with MR, in February 2012, no signs of
Table 1: Differential diagnosis of PML.

<table>
<thead>
<tr>
<th>CT</th>
<th>MRT</th>
</tr>
</thead>
</table>
| **PML**                                 | (i) Hypointense in T1 and hyperintense in T2, single lesion, round or oval, (majority of cases) lesion or multifocal white matter lesions  
(ii) Signal at DWI sequences depends on the age and activity of the lesion but is often restricted  
(iii) Abnormal fractional anisotropy values on DTI  
(iv) At MRS, lesions are characterized by an increased choline, elevated lactate, variable myoinositol, decrease of N-acetylaspartate, and increased choline/creatinine ratio |}

| **CNS lymphoma**                        | (i) Lesion appears at MRI with intermediate-to-low signal intensity on T1-weighted images and either isointense or hypointense signal on T2-weighted images  
(ii) Diffusion is often restricted  
(iii) Elevated lipid peaks and high Cho/Cr ratios on MRS  
(iv) The intense homogeneous enhancement is the hallmark of primary CNS lymphoma |

| **Ischaemic infarct**                    | (i) CT typically shows a high-density (70%) lesion in a central hemispheric location, which often reaches or crosses the midline  
(ii) Intense and homogeneous CE is the hallmark of primary CNS lymphoma |

| **ADEM**                                | (i) T2W and FLAIR images usually show multiple regions of hyperintensity at the gray-white junction, in the brainstem, cerebellum, and basal ganglia  
(ii) Solid or ring enhancement can be seen  
(iii) There can be variable diffusion restriction  
(iv) Spectroscopy can show low NAA |

| **EBV-induced encephalitis**             | (i) CT results may be negative  
(ii) Low-density parenchymal lesions  
(iii) Brain atrophy |

| **Toxoplasmosis**                        | (i) On T1-weighted MRI, the lesions are hypointense relative to brain tissue  
(ii) On T2-weighted MRI, foci of infections are usually hyperintense  
(iii) Ring enhancing may be present after Gd administration  
(iv) Active lesions are often surrounded by edema  
(v) Elevated lactate and lipid |

| **Early stage brain abscess**            | (i) Central low-density core  
(ii) Iso-hyperdense ring  
(iii) Peripheral low density (edema)  
(iv) Ring enhancement |

| **MS relapse**                           | (i) High signal on T2-weighted and FLAIR MRI sequences  
(ii) When actively inflamed, often enhanced with gadolinium contrast |
IRIS (immune reconstitution inflammatory syndrome) were identified in agreement with the regression of the symptomatology. In May 2012, another MR examination was performed at 5 months from the abruption of the therapy which showed the slight reduction of the lesion extension, of choline and lactate levels, and no CE after Gd administration.

2. Discussion

Progressive multifocal leukoencephalopathy (PML) is caused by JC virus (JCV), identified in 1971, which is a nonenveloped, double-stranded DNA virus (5,1 kilobases) in the family of Polyomaviridae. Its DNA codes for six nonstructural proteins, three capsid proteins (VP1, VP2, VP3), and contains a noncoding region which acts as a transcription regulatory region that may affect the viral cellular tropism [1–4]. The JCV, after a primary replication, may reach the blood through the bone marrow and kidney affecting CD-34 cells, B lymphocytes progenitors, and uroepithelial cells. Immunosuppression and lack in CD8+ immunity response, along with the natalizumab-associated increase of peripheral blood levels of CD-34 and B lymphocytes progenitors that act like virus carriers and the increase in their nucleus levels of transcription factors such as SPI-B which promotes viral DNA replication, seems to be related to the colonization of the CNS and the development of PML [22]. Natalizumab-related PML shows unclear gender and age predilection. Diagnosis of PML in patient undergoing natalizumab therapy resides in an accurate clinical examination which can demonstrate the typical triad of symptoms (cognitive impairment, visual deficit, and motor dysfunction), MR examination and laboratory results which can confirm the diagnosis by the identification of JC virus DNA in CSF or in the brain tissue with PCR [23]. Neuroimaging today is

<table>
<thead>
<tr>
<th>CT</th>
<th>MRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(iii) Areas of abnormal enhancement</td>
<td>(iii) Position abutting ventricles (often perpendicular)</td>
</tr>
<tr>
<td></td>
<td>(iv) Luxtacortical position (gray-white junction)</td>
</tr>
<tr>
<td></td>
<td>(v) Involvement of brainstem, cerebellum, or corpus callosum</td>
</tr>
<tr>
<td></td>
<td>(vi) Decrease in NAA and creatine, and increase of choline on MRS</td>
</tr>
</tbody>
</table>
an irreplaceable tool for diagnosis. Computed tomography (CT) lacks sensitivity and specificity demonstrating in PML patients, only nonspecific hypodensities localized in the white matter and sometimes (<10% of cases) a CE of the lesion [24, 25]. At MRI, PML is characterized by single- (majority of cases) or multifocal oval white matter lesions. With disease progression, the lesions may become confluent or grow as a giant white matter plaque. These lesions are hypointense on T1- and hyperintense on T2-weighted images, compared to normal white matter. Common localizations are the parietal and occipital lobes and the corpus callosum while cerebellum, and brainstem involvement is occasionally seen. Usually due to the lack of inflammatory response, no CE is demonstrable but sometimes it is present as a faint peripheral ring. In the majority of cases, there is no mass effect on the contiguous structures [26]. Lesion signal on DWI depends on the age and activity of the lesion: in early ones, diffusion could appear restricted at the borders, while in older it could be increased in the center. Higher B values (>2000) can better depicts lesion borders. PML localizations show abnormal fractional anisotropy values ensuring an earlier identification of the pathology extension on diffusion tensor imaging (DTI). On magnetic resonance spectroscopy (MRS) lesions are characterized by an increased
Figure 2: T1 post-Gd images (Philips Achieva 3T, TR/TE = 500 msec./14 msec, 15 cc Gadobenate dimeglumine, Multihance) in December 2011 (a) and May 2012 (b) of the white matter lesion underneath the frontal lobe of the left hemisphere (arrows) without detectable contrast enhancement in a 44-year-old man with a 12-year history of MS affected by natalizumab-related PML.

Figure 3: DWI ADC map (Philips Achieva 3T, TR = 4500 ms; TE = 112 ms) in December 2011 (a) and May 2012 (b) of the white matter lesion underneath the frontal lobe of the left hemisphere (arrows) with some diffusion restriction in a 44-year-old man with a 12-year history of MS affected by natalizumab-related PML.

Choline, elevated lactate, variable myoinositol, and decrease of N-acetyl-aspartate, although spectra obtained can differ from the center to the border of the lesion. Positron emission tomography/computed tomography (PET/CT) in these patients shows hypometabolic lesions in the majority of cases and results useful in differentiating them from lymphomas. Despite pathology appearance in the different imaging modalities, MRI findings seem to be the most specific, and this imaging technique is going to play a central role not only in the early and sometimes presymptomatic disease diagnosis, but also in the assessment of treatment response and prognosis [27–29]. It is not always possible to obtain a positive result at CSF q-PCR in patient with strong suspicion of PML at clinical and MRI examination. In our case the JCV DNA identification required a highly sensitive PCR as the viral load was low (<500 DNA copies/ml). PML differential diagnosis includes (Table 1) primary CNS lymphoma, ischemic infarct, acute disseminated encephalomyelitis (ADEM), Epstein-Barr virus- (EBV-) induced encephalitis, toxoplasmosis, early stage brain abscess, and MS relapse. Primary CNS lymphoma at CT typically appears as a high-density lesion in a central hemispheric location that often reaches or crosses the midline, characterized at MRI by intermediate-to-low signal intensity on T1-weighted images, and either isointense or hypointense signal on T2-weighted images, restricted diffusion, typical homogeneous CE and elevated lipid peaks and Cho/Cr (choline/creatine) ratio on MRS. Ischemic infarct appears at CT as a low-density lesion occupying a vascular territory with some swelling and at MRI as an area of hyperintensity on FLAIR sequences after 6 hours from onset, abnormally perfused on PWI (perfusion weighted imaging).
Figure 4: MRS (Philips Achieva 3T, TR/TE = 2000/40, increased choline, inverted Cho/Cr ratio, decreased N-acetyl-aspartate between December 2011 (a) and May 2012 (b) of the white matter lesion underneath the frontal lobe of the left hemisphere (arrows) at MRS in a 44-year-old man with a 12-year history of MS affected by natalizumab-related PML. May 2012 MRS showed a decrease in Cho/Cr ratio and increased N-acetylaspartate.

and with increased lactate and decreased NAA on MRS. ADEM may appear at CT as scattered low-density areas and at MRI as multiple areas of hyperintensity at the gray-white matter junction demonstrating variable restricted diffusion and a possible ring enhancement. CT in EBV induced encephalitis may document low-density parenchymal lesions characterized at MRI by restricted diffusion and increased myoinositol and choline. Toxoplasmosis is characterized by no pathognomonic lesions at CT, hypointense and hyperintense areas, respectively, on T1- and T2-weighted images with ring
enhancement, edema, elevated lactate, and lipids at MRI. Early-stage brain abscess appearance at CT consists in a lesion with a central low-density core with peripheral iso-hyperdense ring that is enhanced after contrast medium administration and at MRI in a lesion with a hypointense core and peripheral low-intensity area (edema) on T1-weighted vice versa on T2-weighted and FLAIR images, characterized by restricted diffusion and elevated succinate and acetate on MRS. MS relapse is characterized at CT by white matter hypodensities abutting ventricles and at MRI by high signal lesions on T2-weighted and FLAIR images that are enhanced when active on T1-weighted images after Gd administration, with possible involvement of brainstem and Cerebellum and with decreased NAA on MRS. Currently there are no specific antiviral agents to treat PML, although recent findings have shown that Mirtazapine and a lipid ester of Cidofovir (CMX001) may inhibit, respectively, JCV entry and replication in glial cells [30]. The mainstay of PML treatment is immune reconstitution which is obtainable with HAART (highly active antiretroviral therapy) in AIDS related PML or with the drug removal in natalizumab associated disease. Desaturation of the integrin receptors occurs when serum drug level is less than 1 µg/µL. PLEX is needed and strongly recommended in patients that develop PML during natalizumab treatment to accelerate its blood removal. Patients undergoing PLEX should be monitored with clinical and radiological examination to asses PML regression or to early identify the onset of an IRIS. PML prognosis reflects lesions' localization, the ability to achieve an early diagnosis, and the immune reconstitution.

**Abbreviations**

MR: Magnetic resonance  
MS: Multiple sclerosis  
FLAIR: Fluid attenuated inversion recovery  
DWI: Diffusion weighted imaging  
Gd: Gadolinium  
PRESS: Point resolved spectroscopy  
CE: Contrast enhancement  
NAA: N-acetylaspartate  
CSF: Cerebrospinal fluid  
MRI: Magnetic resonance imaging  
PCR: Polymerase chain reaction  
PLEX: Plasmapheresis  
IRIS: Immune reconstitution inflammatory syndrome  
PML: Progressive multifocal leukoencephalopathy  
JCV: JC virus  
AIDS: Acquired immune deficiency syndrome  
VLA-4: Very late antigen-4  
CNS: Central nervous system  
FDA: Food and drug administration  
AFFIRM: Natalizumab safety and efficacy in relapsing remitting multiple sclerosis  
SENTINEL: Safety and efficacy of natalizumab in combination with remicade in the treatment of Crohn's disease  
HRQoL: health-related quality of life  
TOUCH: Tysabri outreach Unified Commitment to Health  
CT: Computed tomography  
DTI: Diffusion tensor imaging  
MRS: Magnetic resonance spectroscopy  
PET/CT: Positron emission tomography/computed tomography  
ADEM: Acute disseminated encephalomyelitis  
EBV: Epstein-Barr virus  
PWI: Perfusion-weighted imaging  
HAART: Highly active antiretroviral therapy  
Cho/Cr: Choline/creatine.

**References**


[23] C. Warnke, T. Menge, H. P. Hartung et al., “Natalizumab and progressive multifocal leukoencephalopathy: what are the causal factors and can it be avoided?” *Archives of Neurology*, vol. 67, no. 8, pp. 923–930, 2010.


