CASE REPORT

Longitudinal Monitoring with Multiple MR Techniques in a Case of Progressive Multifocal Leukoencephalopathy Associated with Multiple Myeloma

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Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the brain caused by the JC virus in immunocompromised patients. We report characteristic features of proton MR spectroscopy, 3-dimensional pseudo-continuous arterial spin labeling imaging, and diffusion tensor imaging in a 53-year-old patient with PML. The utility of multi-modal magnetic resonance techniques for longitudinal monitoring was indicated by their reevaluation over time and consideration of their relation to prognosis.

Keywords: *fractional anisotropy (FA), JC virus (JCV), progressive multifocal leukoencephalopathy (PML), proton magnetic resonance spectroscopy (MRS), pseudo-continuous arterial spin labeling (pCASL)*

Introduction

Neurotropic papova JC virus (JCV) causes progressive multifocal leukoencephalopathy (PML), a subacute demyelinating disease of the central nervous system (CNS) in immunocompromised patients.^{1,2} Its definitive diagnosis requires a brain biopsy, but initial diagnosis is usually made on the basis of detection by polymerase chain reaction (PCR) of JCV deoxyribonucleic acid (DNA) in cerebrospinal fluid (CSF). Magnetic resonance (MR) imaging is the conventional method to diagnose PML noninvasively early in its clinical course, and relevant advanced MR techniques have been described.^{3–7} However, few reports involved longitudinal observation of multi-modal MR techniques in PML. In this report, we describe longitudinal findings from 3-dimensional (3D) pseudo-continuous arterial spin labeling (pCASL) imaging, diffusion tensor imaging (DTI), and proton MR spectroscopy (MRS) in a patient with PML.

Case Report

A 53-year-old man with multiple myeloma (IgA-k) and compression fractures of the lumbar vertebrae underwent autologous bone marrow transplantation with cyclophosphamide 2 years previous to this report and started prednisolone therapy one year later. Report of a neurologic examination initially indicated the patient suffered from dementia. He was admitted to our hospital for further evaluation of the deterioration of his memory, visual disturbances, and agnosia. On admission, neurologic examination showed right hemiparesis, right hemianopsia, right upper limb weakness, and aphasia; and analysis of the CSF was positive for JCV DNA (139 copies/mL). At the same time, he underwent initial MR imaging examination with a 3-tesla scanner (Signa 3T HDxt, GE, Milwaukee, WI, USA) that provided conventional images as well as those from the following multi-modal techniques: multi-voxel proton MRS (CSI PRESS); repetition time [TR]/echo time [TE], 1500/144 ms; matrix, 14 × 14; field of view [FOV], 24 × 24 cm; voxel, 15 × 15 × 15 cm³; and single-voxel proton MRS (PROBE-S); TR/TE, 5000/15 ms; matrix, 1 × 1; FOV, 24 × 24 cm; flip angle 90°; voxel, 15 × 15 × 15 cm³; 3D pCASL imaging (3D spiral; TR/TE, 1330/5.1 ms; matrix,

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Fig. 1. Initial magnetic resonance (MR) imaging results (May 2010). (a) T₂-weighted image (T₂WI) shows a focal area of high signal intensity (SI) in the left parietal lobe, mainly in the subcortical white matter. (b) Postcontrast T₁-weighted image (T₁WI) shows less faint gadolinium enhancement. (c) Pseudo-continuous arterial spin labeling (pCASL) cerebral blood flow (CBF) map shows hyperperfusion in the peripheral margin of the lesion in the left parietal lobe. (d) Proton magnetic resonance spectroscopy (MRS) shows a slight increase in the choline (Cho) peak (3.2 ppm) and lactate (Lac) peak (1.3 ppm) below the baseline as well as a decreased N-acetylaspartate (NAA) peak (2.0 ppm).

512 × 8; FOV, 24 × 24 cm; flip angle, 90°); and DTI. Treatment with mefloquine was started soon after detection of JCV DNA, and the patient's symptoms slowed in progression and stabilized a few months after the beginning of treatment. Five months later, follow-up analysis of the CSF was negative for JCV DNA, and neurologic findings showed no remarkable changes. Follow-up MR studies were performed 4 and 8 months after the initial study.

During the initial study (Fig. 1), a conventional T₂-weighted image (T₂WI; fast spin echo (SE); TR/TE, 5000/97 ms; matrix, 512 × 256; FOV, 24 × 19.2 cm; flip angle, 90°) showed high signal intensity in the left parietal white matter and subcortical white matter without mass effect, and the gray matter was spared. An enhanced T₁-weighted image (T₁WI; SE; TR/TE, 650/14 ms; matrix, 512 × 256; FOV, 24 × 18 cm; flip angle, 90°) revealed less enhancement in the lesion. We obtained perfusion-related information by 3D pCASL imaging. At the initial

assessment, this showed hyperintensity on the periphery compared to the core of the PML lesion and normal-appearing white matter on the contralateral side of the brain. The peripheral hyperintensity of the lesion suggested hyperperfusion or hypervolemia, reflecting active inflammation at the early stage of PML. The initial study of proton MRS demonstrated elevation in choline-containing compounds (Cho) at 3.2 ppm, inverted lactate signal (Lac) around 1.3 ppm, and low N-acetylaspartate (NAA) peak at 2.0 ppm. These findings suggest active demyelination and dysfunction of neurons and axons.

The second MR study (Fig. 2), performed 4 months after the initial study, showed on a T₂WI image slight shrinkage of the core hyperintensity but spread of slightly elevated intensities to adjacent white matter in the left frontal lobe. The disappearance of hyperintensity in the periphery of the lesion observed on the initial 3D pCASL image indicated a decrease in active inflammation. The second proton MRS showed a decrease in NAA, which suggested progression of neuronal and axonal damage. The peaks of Cho and Lac remained high in this second study.

The third MR study (Fig. 3), 8 months after the initial study, showed progression of the atrophy in the left hemisphere and slight reduction of the area of hyperintensity in the left parietal lobe. The intensity around the lesion seen on 3D pCASL imaging remained lower than that in the contralateral hemisphere. The third proton MRS showed a slight increase in NAA, but the elevation of the Cho and lactate remain unchanged. Table shows the signal ratios of Cho/creatine (Cr), NAA/Cr, and Lac/Cr. The ratio of NAA/Cr was increased in the third study despite the decrease in the second study. The Cho/Cr and Lac/Cr ratios were decreased.

Diffusion tensor imaging was also conducted 3 times and provided isotropic diffusion-weighted images (DWIs; SE-echo-planar imaging [EPI]; TR/TE, 10000/91 ms; b-value, 1000; number of motion-probing gradients, 6; matrix, 128 × 192; FOV, 24 × 24 cm; flip angle, 90°) and apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps (Fig. 4). An initial DWI showed hyperintensity in the periphery of the lesion and hypointensity in the core; ADC maps of the lesion were increased except at the center of the lesion. The second DWI showed reduction in the hyperintensity in the left parietal lobe but slightly high signal intensity spreading to the left frontal lobe. The previously increased ADC in the lesion was significantly reduced, but slightly increased ADC had spread to the left frontal lobes. The third DWI and ADC maps showed the same tendency of abnormal signal intensity in the white

Fig. 2. Follow-up magnetic resonance (MR) imaging 4 months after the initial evaluation (Sep 2010). **(a)** T₂-weighted image (T₂WI) shows reduced hyperintensity in the core of the left parietal lesion with newly developed focal hyperintensities in the right parietal and left frontal lobes. **(b)** Pseudo-continuous arterial spin labeling (pCASL) shows a marked decrease in peripheral hyperintensity. **(c)** Proton MR spectroscopy (MRS) shows a further decrease in the N-acetylaspartate (NAA) peak; choline (Cho) and lactate (Lac) peaks remain high.

Fig. 3. Follow-up magnetic resonance (MR) imaging 8 months after the initial assessment (Feb 2011). **(a)** T₂-weighted image (T₂WI) shows a slight decrease in the extension of the previous hyperintensities in the bilateral parietal and left frontal lobes with atrophy of the left hemisphere. **(b)** Pseudo-continuous arterial spin labeling (pCASL) shows markedly decreased cerebral blood flow (CBF) in the encephalomalacic region. **(c)** Proton MR spectroscopy (MRS) shows a slight increase in the N-acetylaspartate (NAA) peak without changes in the choline (Cho) and lactate (Lac) peaks.

Table. Volume ratios (%) in the measurement voxel

Evaluation	Cho/Cr	NAA/Cr	Lac/Cr
Initial	3.33	1.27	1.15
4-month follow-up	2.18	0.45	0.76
8-month follow-up	2.14	1.15	0.57

Cho, choline; Cr, creatine; NAA, N-acetylaspartate; Lac, lactate

matter of the left parietal and frontal lobes, with significant diffuse atrophy of the brain. The initial FA map demonstrated a decrease in anisotropy and diffusivity of the left parietal white matter that was also observed in the frontal white matter on follow-up.

Discussion

PML is a subacute demyelinating disease of the brain caused by a papovavirus infection of oligodendrocytes, the cells that produce and maintain the myelin sheaths in the central nervous system.^{1,2} Anstrom and associates first described PML in 1958 in association with chronic lymphocytic leukemia and Hodgkin disease.⁸ Since then, PML has been associated with other immunocompromising conditions, including acquired immunodeficiency syndrome (AIDS), lymphoma, leukemia, systemic lupus erythematosus, and chronic inflammatory diseases, such as sarcoidosis and tuberculosis. PML has also been reported in transplant recipients, most probably because of their immunosuppressive treat-

Fig. 4. Initial and 4- and 8-month follow-up diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), and fractional anisotropy (FA) map images. (a) Initial DWI shows hyperintensity in the periphery and slight hypointensity in the core of the lesion in comparison to the contralateral, normal-appearing white matter. (b) DWI at 4-month follow-up shows a marked decrease in the previous hyperintensity but slightly low signal intensity within the left subcortical parietal white matter and newly developed focal high signal intensities spreading to the right parietal and left frontal lobes. (c) The 8-month follow-up DWI shows marked reduction in the previous hyperintensity in the lesion. (d) ADC maps show a center with increased diffusion rate. (e) ADC map at 4-month follow-up. (f) ADC map at 8-month follow-up shows decreases in the previous hyperintensities in the right parietal and left frontal lobes. (g) Initial FA map shows a marked decrease of anisotropy within the left parietal white matter. (h) and (i) FA maps at 4 months (h) and 8 months (i) show decreases in FA in the left frontal white matter.

ment. Lesions usually occur within 24 months of transplantation.^{9,10} However, PML in patients with multiple myeloma (MM) is rare; only a few cases were reported in the 1970s, and none have been reported since.¹⁰ Characteristic pathologic findings include lytic infection of the oligodendrocytes, which are swollen with enlarged densely basophilic nuclei filled with eosinophilic inclusion bodies. JCV also infects the astrocytes, which are also enlarged and contain numerous enlarged processes. Sometimes enlarged astrocytes contain multilobulated hyperchromatic nuclei that resemble neoplastic cells,

which pathologists refer to as “bizarre astrocytes.”¹¹

Imaging is important and often helpful in the diagnosis of PML. Recent studies showed characteristic MR abnormalities in immunocompromised patients with histopathologically confirmed PML. Conventional MR imaging usually demonstrates asymmetric areas of increased intensity in the white matter on T₂WI and decreased intensity on T₁WI. The parietal lobe is most commonly involved.¹¹ PML lesions generally show no mass effect or contrast enhancement, although faint marginal contrast enhancement has been described. These findings are consistent with those of our case, which was considered to have a clinical presentation typical of PML.

A characteristic feature of our case was the hyperintensity in the periphery of the lesion on the initial pCASL study. This is thought to reflect increased perfusion or blood volume caused by inflammatory changes in the early phase. Recent studies suggest that some cases of PML exhibit more evidence of active inflammation than others.¹² The classic inflammation in oligodendrocytes is seen predominantly at the advancing margin of the lesion, and this inflammation probably causes increased hyper-vascular reactions. Because PML does not usually show vasculitis and breakdown of the blood-brain barrier, the lesion demonstrates no contrast enhancement as opposed to that seen in multiple sclerosis with vasculitis. A previous article reported a patient with PML with a broad decrease in cerebral blood flow in the cortex shown by ^{99m}Tc-ethyl cysteinate dimer (ECD) single photon emission computed tomography (SPECT).¹³ The discrepancy between that report and our case may depend on methodological differences, especially on the characteristics of ECD, which are related to enzyme activity in the tissues. The follow-up studies showed a decrease in perfusion, possibly reflecting a decrease in inflammation. pCASL perfusion studies are considered useful in detecting active inflammation.

In addition, proton MRS in our case exhibited the characteristic changes of metabolism associated with PML. The initial MRS showed an increase in Lac/Cr and Cho/Cr ratios and decrease in the NAA/Cr ratio in comparison with the normal contralateral region, which was consistent with a previous report.³ Our follow-up studies demonstrated decreases in Lac/Cr and Cho/Cr, which may suggest a decrease in pathologic activity that correlated with the suppression of progression of the patient’s symptoms. The reoccurring increase of NAA may suggest some recovery of neurons or specifically axons in the PML lesion. However, this change may have been a technical artifact because the measurement voxel included brain tissue less damaged by necrosis, atrophy, and

shrinkage of the original PML lesion.

DTI provides DWI, ADC, and FA maps that can detect changes in anisotropy and diffusivity of water in neuronal cells and fibers. Most parts of our patient's lesion showed an increase in ADC that reflected vasogenic edema or an increase in mobile water. The second and third DWI and ADC maps showed spread of the lesion to the frontal white matter with shrinkage of the left parietal lesion. FA usually reflects the organized architecture of the white matter and neuronal tracts, and on follow-up in our case, FA had decreased and spread from the left parietal white matter to the left frontal white matter. These findings suggest spread of the disorganization of white matter structures from the parietal lobe to the frontal lobe.

Conclusion

In conclusion, multi-modal advanced MR studies in addition to conventional MR imaging are useful in monitoring the progress or therapeutic response of PML.

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