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【 CASE REPORT 】

Early Pathological JC Virus Lesions in a Patient without Any MRI-based Indications

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Abstract:

A 70-year-old woman with a human T-cell leukemia virus type 1 infection without any focal neurological symptoms showed age-related atherosclerotic changes in the white matter without any suspicious signal changes suggestive of progressive multifocal leukoencephalopathy (PML) based on the findings of MRI. Viral polymerase chain reaction (PCR) revealed 6,700 copies/mL of the JC virus genome in the cerebrospinal fluid (CSF). An immuno-pathological examination of the autopsied brain revealed JC virus capsid proteins, and *in situ* hybridization confirmed a JC virus infection, indicating that an active infection begins at the radiologically indistinguishable phase of PML. An early JC virus infection is probably associated with small, scattered demyelinating lesions around the cortico-medullary area of the cortex.

Key words: JC virus, progressive multifocal leukoencephalopathy, viral infection, CSF PCR

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease induced by an opportunistic JC polyomavirus infection of the central nervous system (CNS). Accumulating evidence has indicated that the development of PML is also an adverse effect of the administration of immunomodulatory agents to patients with autoimmune diseases (1). The clinical diagnostic criteria for PML have recently been published (2), and cerebrospinal fluid polymerase chain reaction (CSF PCR) for the detection of the JC virus genome is considered to be an important biomarker. However, the detection of the JC virus in the CSF via PCR is not infallible (3-5). It is rare for patients with a JC virus in the CSF to exhibit a lack of MR image findings compatible with PML. The clinical criteria for PML (2) recommend MR image scanning as the first step of screening for a JC virus infection in the CNS. Knowledge of the distinct pathophysiology of radiologically asymptomatic PML may aid in diagnosing such patients.

Case Report

A 70-year-old Japanese woman was admitted to our hospital with general fatigue and appetite loss. The patient had previously been diagnosed with a smoldering form of adult T-cell leukemia (ATL), but had experienced no symptoms since five years ago. In previous year, positron emission tomography (PET) revealed an abnormal accumulation in multiple lymph nodes of the patient's body, including the spleen. At the end of previous year, treatment was initiated using the modified lymphoma study group 15 method. In next year, the patient successfully underwent umbilical cord blood stem cell transplantation and was discharged in September. Gastric and skin graft-versus-host disease (GVHD) was observed as an adverse effect of the transplantation, resolving after continuous treatment with a combination of cyclosporine and prednisolone.

However, the patient reported experiencing general fatigue

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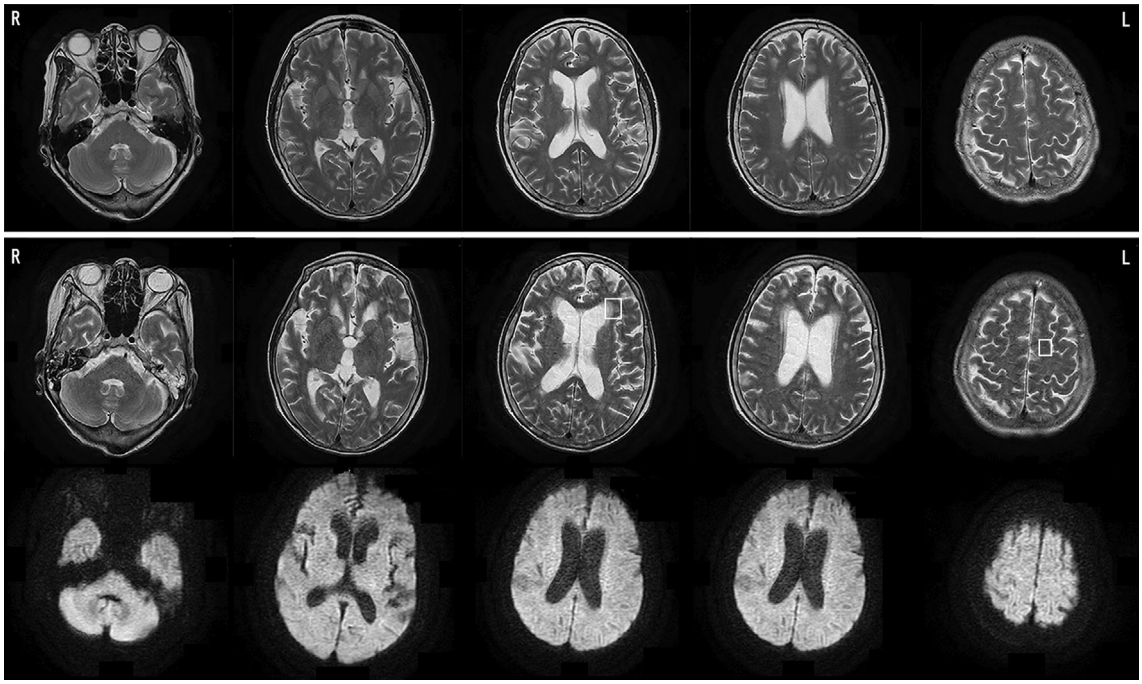

Figure 1. **Sequential MRI over a 10-month period. MRI brain scans without contrast enhancement were performed. Images were acquired on a 1.5 Tesla MRI (Toshiba). The parameters of first and second T2-weighted imaging were as follows: repetition time (TR), 4,080 and 4,460 ms; echo time (TE), 100.608 and 100.928 ms; flip angle, 90° both; slice thickness, 6 mm both; interslice gap, 1.5 mm; field of view (FOV), 100 mm both; number of excitations (NEX), 2 and 1; acquisition matrix, 352×352 or 256×256, respectively. T2-weighted axial MR images obtained 10 months prior to admission (upper panels) reveal slight cortical atrophy and mild age-related white matter hyperintensities. Compared with the previous MRI results, T2-weighted MR images obtained at the time of admission (middle panels) indicate progressive cortical atrophy, mild enlargement of the ventricles, and mild widening of the white matter hyperintensities. Diffusion-weighted MR images [lower panels-TR, 5,600 ms; TE, 83 ms; flip angle, 90°; slice thickness, 5 mm; interslice gap, 6 mm; field of view (FOV), 100 mm; number of excitations (NEX), 1; acquisition matrix, 128×160] demonstrated no abnormal signals. White rectangles in the middle panels indicate the tissue area excised for histological analyses. R: right, L: left**

soon after discharge and was thus re-admitted to the hospital. Although the patient experienced no disturbance of consciousness, she complained of easy fatigability for maintaining sufficient concentration to complete cognitive examinations, but she exhibited no focal neurological disturbance.

MR images of the brain revealed an apparent progressive enlargement of the ventricles during the preceding 10 months (Fig. 1). A slight enlargement of mild ischemic changes was observed in the periventricular white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, although there were no signal changes suggestive of PML, such as punctate lesions, the Milky Way sign, or a scalloped appearance (2, 6, 7), even on diffusion-weighted images (Fig. 1, lower panels). The patient tested negative for HIV, and a CSF examination yielded the following results: 1 cell/μL and 56 mg/dL of total protein. A PCR analysis revealed that the CSF was positive for JC virus DNA (6,700 copies/mL). A pathological examination of the CSF revealed no malignant cells. The patient died of pneumonia nine days after the last MRI examination, and an autopsy was performed 34 hours after the patient's death.

Pathological findings

The total brain weighed 1,335 g, and enlargement of the third ventricle and anterior horns of the lateral ventricles without ventricle obstruction were observed. The brain was fixed in 10% buffered formalin. Specimens for histopathological examination were resected from areas with radiologically normal appearance or mild white matter high-signal lesions according to MRI (Fig. 1, white rectangles). Using low microscopic magnification, numerous small, patchy demyelinating lesions were observed in the cerebral cortex and white matter, predominantly around the corticomedullary junction (Fig. 2A, C), which were associated with infiltration of CD163-positive macrophages (Fig. 2B, E) and an apparent reduction of glial fibrillary acidic protein-positive cells (Fig. 2D). Oligodendroglia-like cells, which were negative for CD45 and glial fibrillary acidic protein, were also observed. These cells exhibited swollen nuclei of various sizes, and some exhibited intranuclear full or dot-

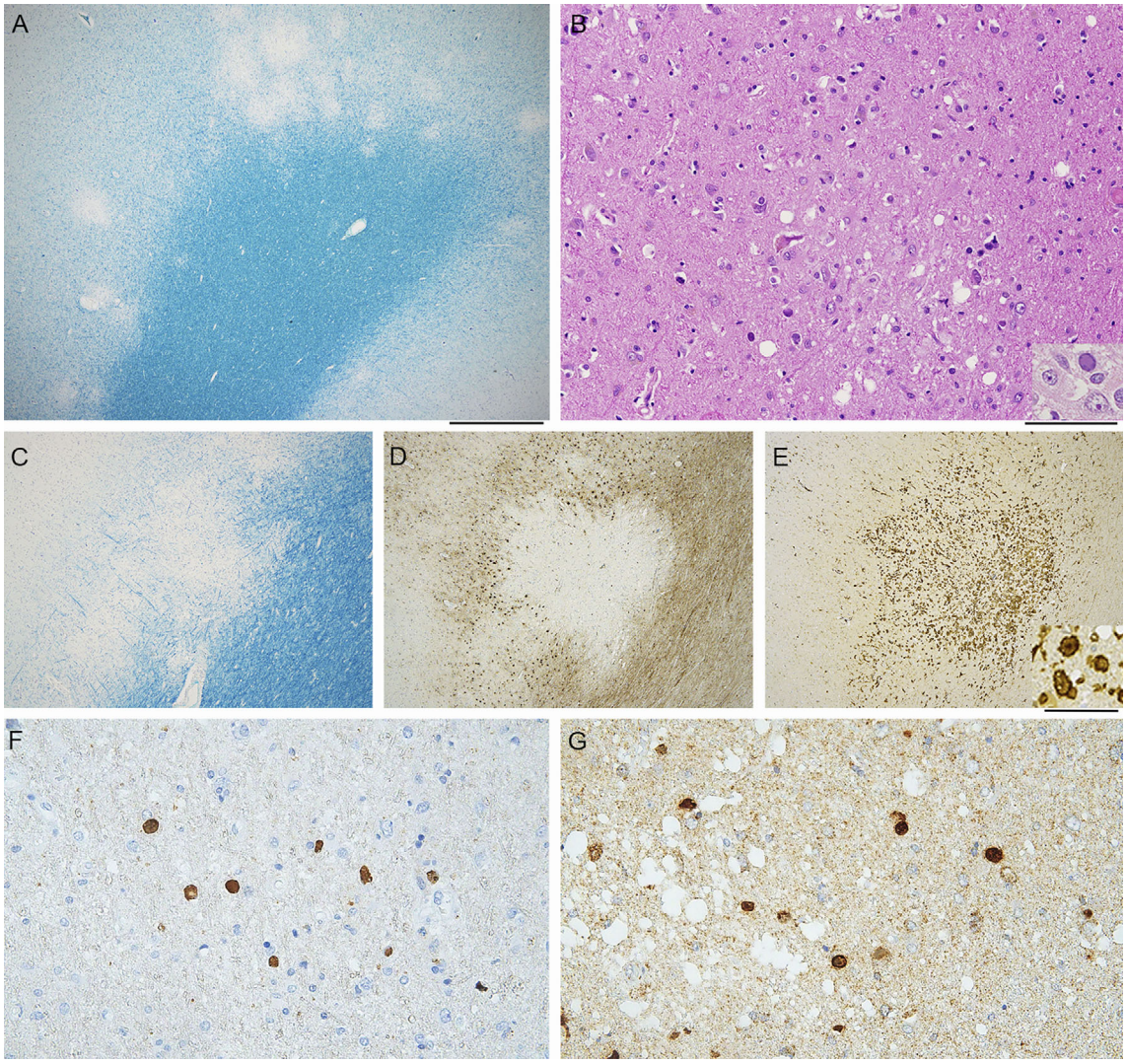

Figure 2. Histopathological findings of demyelinating lesions around the cortico-medullary junction of the cerebrum. Klüver-Barrera (KB) staining (A) of brain specimens shows numerous small-sized, patchy demyelinating lesions in the cerebral cortex and white matter, predominantly at the cortico-medullary junction. Hematoxylin and Eosin staining (B) shows a mildly affected lesion, where oligodendroglia-like cells with swollen nuclei containing full or dot-shaped inclusions can be identified (inset). Serial sections were subjected to KB staining (C), and immunohistochemistry using anti-glial fibrillary acidic protein (GFAP) (D) or anti-CD163 antibodies (E), showing decreased GFAP signals and infiltration of macrophages. Immunohistochemistry with antibodies specific to JC virus capsid proteins VP2/3 (F) demonstrates JC virus-infected cells (browned nuclei). *In situ* hybridization for the detection of JC virus DNA (G) identifies oligodendroglia-like cells to be JC virus-positive (browned nuclei). Scale bar=1,000 μm (A), 100 μm (B, F, G), and 500 μm (C, D, E)

shaped inclusions (Fig. 2B). Immunohistochemistry using antibodies specifically recognizing the JC virus capsid proteins VP1 and VP2/3 (Fig. 2F) yielded positive results (8), and *in situ* hybridization detected JC virus-positive cells around the demyelinating lesions (Fig. 2G). Inflammatory reactions occurred sparsely, and a few CD8-positive anaplastic cells were identified (Supplementary material). Based on these findings, the patient was found to be a pathologically confirmed case of PML.

Discussion

The neuropathological findings represented the condition of the brain at the time of the second MRI, as the autopsy of the patient was performed only 10 days after the MRI. Surprisingly, numerous small, patchy demyelinating lesions were detected around the cortico-medullary junction, infiltrated by numerous macrophages, and these lesions were surrounded by reactive glial cells that expressed JC virus capsid proteins, some of which additionally exhibited intranuclear JC virus inclusions, even on specimens obtained

from areas with a radiologically normal appearance.

Immunologically, the patient was at risk of developing PML due to umbilical cord blood stem cell transplantation, ATL, old age, and the use of cyclosporine and prednisolone for the treatment of GVHD. Viremia and viral mutations likely occurred when the patient was treated with these immunosuppressive agents, thus leading to the virus slowly infiltrating the brain. Alternatively, it may have been present in the brain prior to the treatment, and pathological mutations may have disrupted the immunosurveillance system, causing the virus to spread in the CNS (9). Some malignant cases have been reported to respond to immune-checkpoint inhibitor therapy for immune status enhancement; intervention should be considered in such cases to prevent the onset of PML.

A recent study reported that, among patients with multiple sclerosis diagnosed with natalizumab-associated PML, those with lesions detected early by MRI who remained asymptomatic had a better prognosis (10). However, no previous reports have discussed whether a JC virus infection can be observed in the CNS in minimally symptomatic patients with negative radiological findings and those with positive CSF PCR results. Nonetheless, such cases are defined as possible PML cases based on the clinical diagnostic criteria (2). To our knowledge, the present study is the first to demonstrate that the radiologically asymptomatic phase of PML with minimal symptoms occurs prior to the radiologically symptomatic phase in the course of active JC virus infection in the CNS. Moreover, our findings indicate that an early JC virus infection is associated with small, scattered demyelinating lesions around the cortico-medullary area of the cortex. Thus, it may be beneficial to evaluate the presence of the JC virus DNA in the CSF of patients likely to carry the virus in the CNS during immunosuppressive treatment, even in cases of negative MRI findings, as this would allow physicians to detect the earliest phase possible (i.e., minimally symptomatic and radiologically negative phase). In particular, the high prevalence of JC virus copies in the CSF strongly suggests an active JC virus infection because individuals with false-positive JC virus PCR results in the CSF usually feature copy numbers that are one or two orders of magnitude lower than in this PCR. Early discontinuation of immunosuppressive agents is currently the best treatment available for drug-associated PML because there are no agents that can enhance the immunosurveillance system in patients undergoing immunosuppressive treatment.

In conclusion, this study highlights that an early active JC virus infection begins at the radiologically indistinguishable phase of PML and is associated with small, scattered demyelinating lesions around the cortico-medullary area of the cortex.

This study was approved by the ethics committee of Tokyo Medical and Dental University Hospital. Written informed consent was obtained from the patient's legal representative.

The authors state that they have no Conflict of Interest (COI).

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