INTERNAL MEDICINE

□ CASE REPORT □

PET Imaging of ^{18}F-FDG, ^{11}C-methionine, ^{11}C-flumazenil, and ^{11}C-4DST in Progressive Multifocal Leukoencephalopathy

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Abstract

The use of positron emission tomography (PET) imaging in progressive multifocal leukoencephalopathy (PML) has rarely been reported. We herein report a set of PET images in a 63-year-old patient with PML. In PML lesions, the uptake of ^{18}F-fluorodeoxyglucose, ^{11}C-methionine, ^{11}C-flumazenil, and [methyl-^{11}C]4'-thiothymidine was decreased, increased, decreased, and unchanged, respectively. These results suggest that glucose metabolism decreased, protein synthesis increased, neuronal integrity decreased, and the DNA synthesis and cellular proliferation of host cells were not activated in PML lesions. These results may reflect very little infiltration by inflammatory cells and active infection with JC virus in this case.

Key words: progressive multifocal leukoencephalopathy, positron emission tomography, ^{18}F-FDG, ^{11}C-methionine, ^{11}C-flumazenil, ^{11}C-4DST

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease caused by the human polyomavirus, JC virus (JCV), in immunocompromised patients. The histopathological hallmarks of PML are the triad of demyelination, oligodendrocyte inclusion bodies, and bizarre astrocytes (1, 2). JCV replicates in the nuclei of infected oligodendrocytes, which become greatly enlarged and develop intranuclear eosinophilic inclusions known as oligodendrocyte inclusion bodies. The toxic and lytic effects of JCV are exerted on oligodendrocytes, leading to demyelination in the central nervous system. JCV also infects astrocytes, which have a bizarre appearance when infected and are unlikely to permit the replication of JCV.

Positron emission tomography (PET) is a molecular imaging technique to image and measure fundamental biological processes ranging from transcription and translation of DNA to signal transduction of cellular communication and the synthesis and metabolism of substrates that perform cellular functions *in vivo* (3). PET imaging is therefore able to provide crucial information for understanding the physiology and pathophysiology of a living human being, for clinical diagnoses, and for the selection and assessment of therapy in clinical use, some of which the histopathological approach hardly provides. However, the use of PET imaging in PML has rarely been reported.

The aim of this case report was to assess the underlying pathophysiology in a living patient with PML by performing a set of PET scans using ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{11}C-methionine, ^{11}C-flumazenil, and [methyl-^{11}C]4'-thiothymidine (^{11}C-4DST). The ^{18}F-FDG uptake provides an index of glucose metabolism (4). The ^{11}C-methionine uptake, which is influenced by the intracellular metabolism of the amino acid, provides an index of protein synthesis (5). ^{11}C-flumazenil binds to benzodiazepine receptors that are localized exclusively to neurons and dendrites (6), and its up-

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take provides an index of neuronal integrity. ^{11}C-4DST is incorporated into DNA when DNA is synthesized, and its uptake provides a direct index of cellular proliferation (7).

Case Report

The patient with PML

The study was conducted in accordance with the Helsinki Protocol and was approved by the Ethics Committee of the Tokyo Metropolitan Institute of Gerontology. After a detailed explanation of the study, the patient provided his written informed consent. The PET data used in this study were collected for research purposes.

The patient was a man 63 years of age at the time of PET scanning. He had developed acute myeloid leukemia in his 40s. After undergoing autologous peripheral blood stem cell transplantation, he experienced complete remission for about 13 years, after which he developed angioimmunoblastic T-cell lymphoma at 61 years of age. Computed tomography showed enlarged lymph nodes in the deep cervical region, axilla, mediastinum, mesentery, and surrounding abdominal aorta. About a year and a half after starting chemotherapy, the patient was referred to the neurology department with a month-long history of progressive visual disturbance at 62 years of age. A neurological examination showed only a bilateral reduction in visual acuity. Magnetic resonance imaging (MRI) revealed white-matter lesions in the bilateral occipital lobes, while T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted images showed hyperintensity, and T1-weighted images showed hypointensity (Fig. 1A-E). The results of gadolinium enhancement were negative. These MRI findings were typical of PML (8). As PML was suspected, chemotherapy was stopped. However, the visual disturbance experienced by the patient worsened.

Two months after his first visit to the neurologist, he was diagnosed with PML after the detection of 574 copies/mL of JCV in the cerebrospinal fluid using real-time polymerase chain reaction (PCR). The MRI findings at this time showed enlarged PML lesions that included the gray matter with cortical laminar necrosis and negative gadolinium enhancement (Fig. 1F-J). Three months after his first visit to the neurologist, his bilateral visual acuity was almost completely impaired. Real-time PCR detected 78,340 copies/mL of JCV in the cerebrospinal fluid. He then underwent a set of PET scans.

PET imaging and results

PET scanning was performed on a SET-2400W scanner (Shimadzu, Kyoto, Japan) in three-dimensional mode at the Tokyo Metropolitan Institute of Gerontology. Static emission data were acquired for 35-41 minutes, 20-30 minutes, 20-40 minutes, and 40-60 minutes after intravenous bolus infusions of ^{18}F-FDG, ^{11}C-methionine, ^{11}C-flumazenil, and ^{11}C-4DST, respectively. The injection doses for the corresponding radioligands were 143 MBq, 327 MBq, 358 MBq, and 532 MBq, respectively.

The PET data were converted into standardized uptake value images and are displayed in Fig. 2. For ^{18}F-FDG and ^{11}C-flumazenil images, in order to determine the areas where the uptake of each radioligand decreased, statistical Z maps were created with the mean and standard deviation values from controls that belonged to a normal database at the institute (Fig. 2F and G). The uptake of ^{18}F-FDG and ^{11}C-flumazenil was found to have widely decreased in the occipital lobe and in the posterior part of the parietal lobe (Fig. 2B and C). The statistical Z maps showed that the magnitude of the decrease in the uptake of ^{18}F-FDG and ^{11}C-flumazenil on the left side was larger than that on the right side (Fig. 2F and G), consistent with the MRI findings. The areas of reduction in the ^{18}F-FDG uptake were more widespread than those for the ^{11}C-flumazenil uptake. This difference between ^{18}F-FDG and ^{11}C-flumazenil images may be explained as follows. First, the ^{18}F-FDG uptake decreased in the gray and white matter, whereas the ^{11}C-flumazenil uptake decreased almost exclusively in the gray matter. Second, as is often observed in patients with epilepsy, the area of hypometabolism extended beyond the focus zone to its neighborhood, whereas the area of lost neuronal integrity localized to the focus zone (9). The ^{11}C-methionine uptake tended to increase in the PML legions (Fig. 2D), whereas the ^{18}F-FDG uptake tended to decrease and gadolinium enhancement was negative. No regions showed an increase in the ^{11}C-4DST uptake (Fig. 2E).

Discussion

We herein report a set of PET images using ^{18}F-FDG, ^{11}C-methionine, ^{11}C-flumazenil, and ^{11}C-4DST in a patient with PML. Although PET studies in PML have rarely been reported, there have been a few studies investigating the uptake of ^{18}F-FDG and ^{11}C-methionine in PML lesions (8, 10). Consistent with those findings, the present study showed that the ^{18}F-FDG uptake had relatively decreased whereas the ^{11}C-methionine uptake had relatively increased in the PML lesions. To our knowledge, this case provides the first findings showing that the ^{11}C-flumazenil uptake had decreased, while the ^{11}C-4DST uptake remained unchanged in PML lesions.

PML lesions initially develop in the white matter with the infection of oligodendrocytes and astrocytes by JCV. Neuronal cells can also be infected with JCV, and more than 50% of patents with PML have lesions in the gray matter (11, 12). In this patient, the PML lesions included the gray matter as well as the white matter, and alterations in the cortical uptake of ^{18}F-FDG, ^{11}C-methionine, and ^{11}C-flumazenil may have been primarily caused by JCV infection in the gray matter. Based on the findings from the PET images, a potential explanation for the underlying pathophysiology is that glucose metabolism had relatively decreased, protein synthesis was relatively active, neuronal integrity had decreased, and human DNA synthesis and cellu-

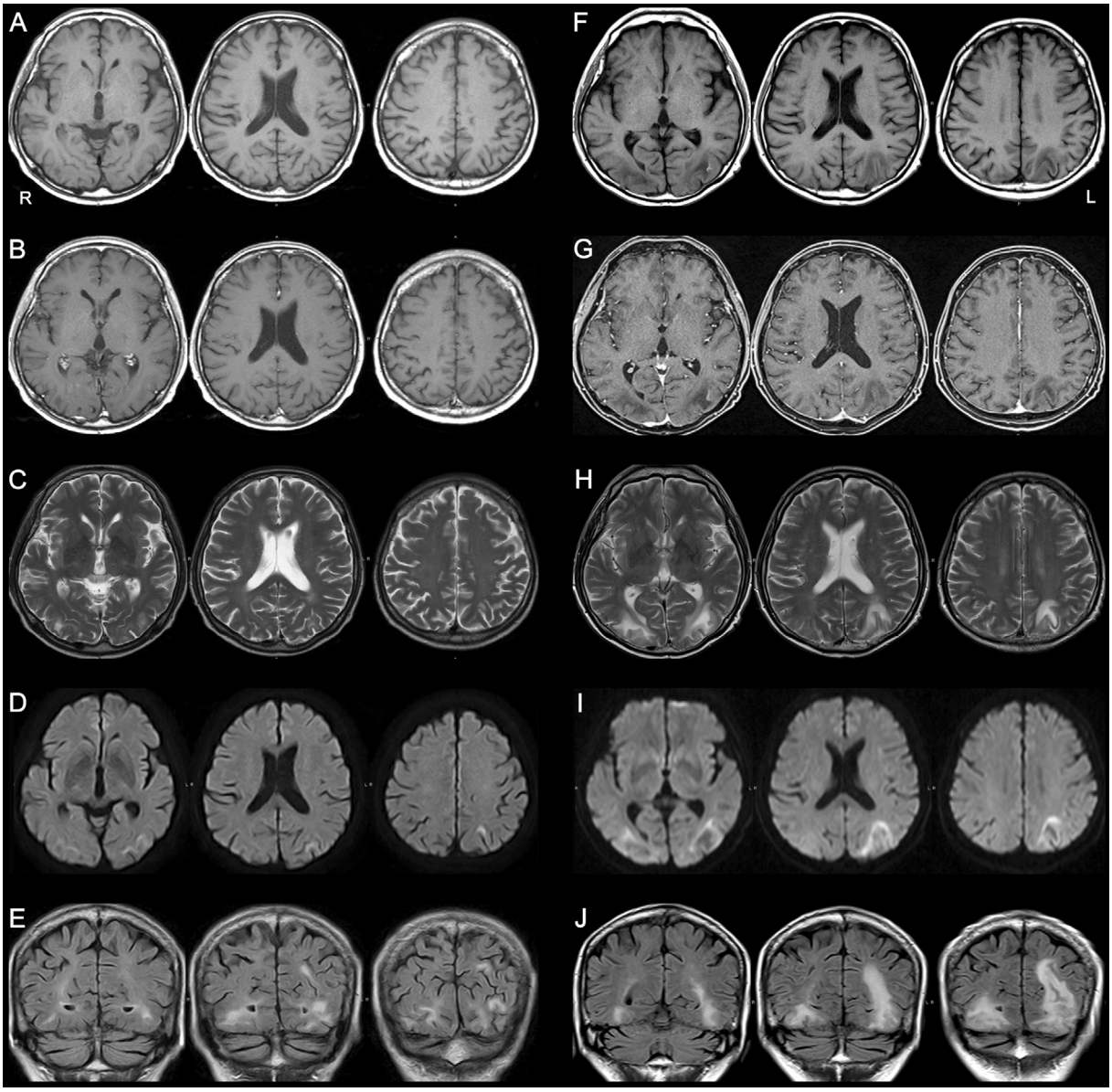

Figure 1. **Magnetic resonance imaging (MRI) at two time points in the clinical course. T1-weighted (A, F), gadolinium-enhanced T1-weighted (B, G), T2-weighted (C, H), diffusion-weighted (D, I), and fluid-attenuated inversion recovery (E, J) images are displayed. A set of MRI scans was performed after a one-month history of progressive visual disturbance (A-E), showing white matter lesions in the occipital lobe without gadolinium enhancement. Two months later, another set of MRI scans was performed (F-J), showing enlarged white matter lesions that included gray matter with cortical laminar necrosis and negative gadolinium enhancement.**

lar proliferation were not activated in the PML lesions. Thus, in this case, the infiltration of inflammatory cells might be very mild, as is observed in most cases of PML (1, 2). Additionally, reflecting active infection with JCV, infected cells might need protein synthesis to replicate JCV within host cells, transform the appearance of cells, or create intracellular inclusions.

The number of PML cases has recently increased as a result of highly efficient immunosuppressive treatments, especially in patients with autoimmune diseases such as multiple sclerosis (13). The handling of PML is extremely precarious at present because the cessation of immunosuppressive treatment during the course of PML can force immune reconstitution, leading to an extremely aggravated immune response against causative pathogens or non-infectious antigens, known as immune reconstitution inflammatory syndrome (IRIS). As IRIS can result in clinical exacerbation associated with high rates of morbidity and mortality, the early diagnosis of IRIS is critically important. Of the four radioligands used in this study, ^{11}C-4DST imaging may be a candidate technique for detecting IRIS at an early stage and for distinguishing the development of IRIS from the exacerbation of PML, as an increased uptake of ^{11}C-4DST reflects the human (not viral) DNA synthesis and cellular proliferation that

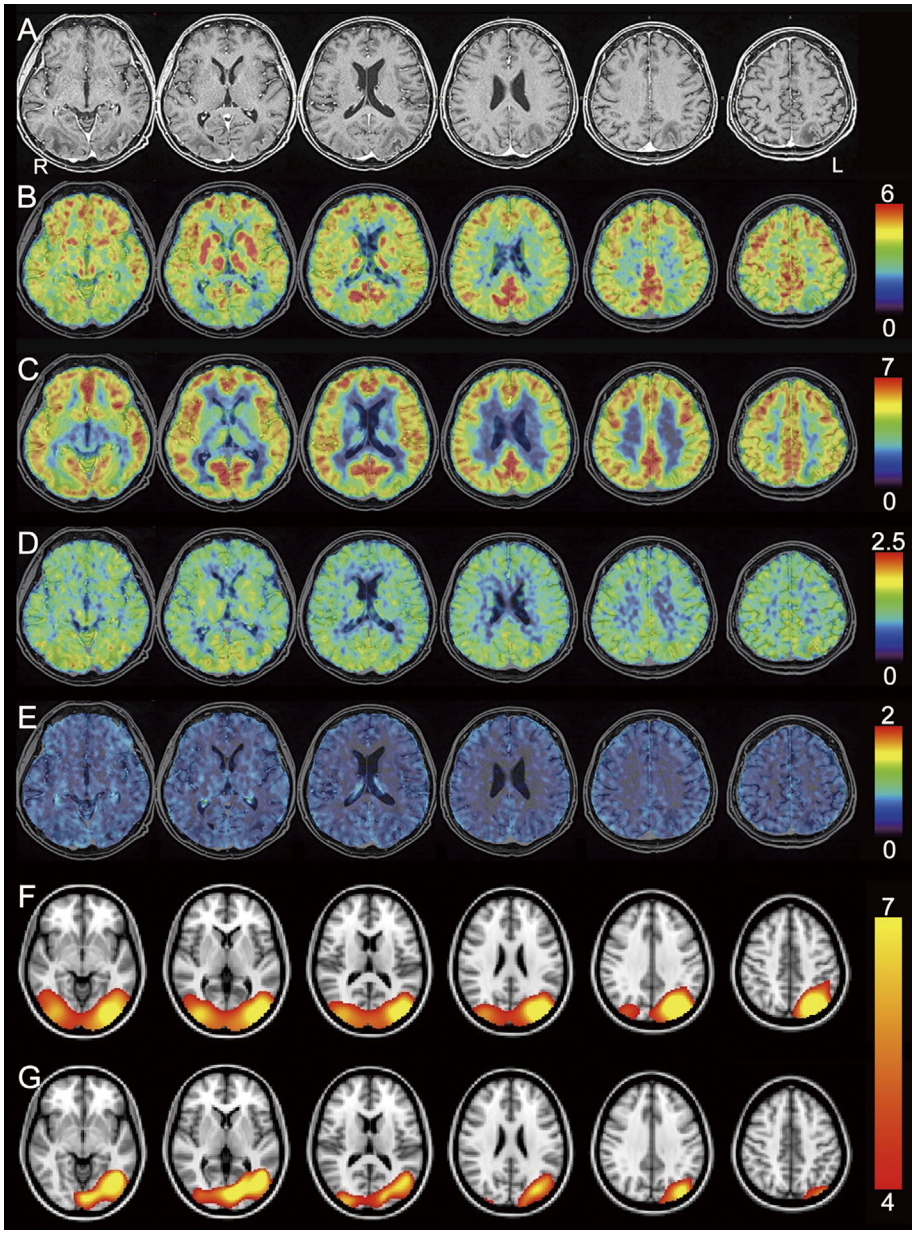

Figure 2. **A set of positron emission tomography (PET) images. Images for ^{18}F-FDG (B), ^{11}C-flumazenil (C), ^{11}C-methionine (D), and ^{11}C-4DST (E) superimposed on an MRI scan (A) are displayed in native space. The MRI scan (A) corresponds to Figure 1G and was used as an anatomical reference for the PET images. One month after conducting MRI (A), a set of PET scans was performed (B-E). Z maps, which are superimposed on a standard brain, represent the regions where the ^{18}F-FDG (F) or ^{11}C-flumazenil (G) uptake had decreased. The rainbow and red-yellow scales represent the magnitude of the standardized uptake values (B-E) and Z scores (F, G), respectively. MRI: magnetic resonance imaging, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose, ^{11}C-4DST: [methyl-^{11}C] 4'-thiothymidine, R: right, L: left**

would occur in the IRIS region, but not in the PML lesions.

One of the limitations of the present study is that this is a care report, and we therefore cannot necessarily expect other patients with PML to follow the same course as the case presented herein. Although we have added the findings from ^{11}C-flumazenil and ^{11}C-4DST images of benzodiazepine receptors and human DNA replication, respectively, to the prior knowledge of PML, future studies with larger sample sizes will be necessary to understand the roles of each radioligand in PML.

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

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