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Original Communication

Title:

Usefulness of ^{11}C -methionine-positron emission tomography for the diagnosis of progressive multifocal leukoencephalopathy

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease of the brain caused by the JC virus that occurs mainly in immunocompromised patients. The prognosis is very poor. As the lesion looks like non-specific leukoencephalopathy, making a diagnosis at the early stage is very difficult. We report 3 PML cases in which there was a mismatch between ^{11}C -methionine-positron emission tomography (MET-PET) uptake and ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) uptake. All 3 cases demonstrated the hyper-uptake of MET around the white matter lesions and hypo-uptake of FDG inside the lesions. We speculate that the infection had ended inside the white matter lesions of these patients, while JC virus infection was ongoing around the lesions, resulting in the increase of methionine metabolism, and the glucose metabolism was reduced or intermediate because inflammatory cells infiltrate PML lesions rarely. Two patients who were diagnosed and treated with mefloquine while the JC virus was at a low level in the cerebrospinal fluid are still alive. We suggest the usefulness of MET-PET for the early diagnosis of PML and early treatment with mefloquine.

Introduction

Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease of the brain caused by the JC virus (JCV) and occurs mainly in immunocompromised patients. The prognosis is very poor. As the lesion resembles non-specific leukoencephalopathy, it is difficult to make a diagnosis at the early stage of the disease. We report 3 PML cases in which there was a mismatch between ^{11}C -methionine-positron emission tomography (MET-PET) uptake and ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) uptake in and around the lesions. We suggest this mismatch may be useful for the early diagnosis of PML.

Subjects and Methods

Case series: We report 3 PML cases without human immunodeficiency virus (HIV) infection from July 2012 to December 2013.

Case 1: A 51-year-old man was admitted to our hospital in July 2012 because of gait impairment. He reported dizziness and gait impairment from April 2012, when he was followed for chronic hepatitis B infection and hepatic cell carcinoma. Ataxia of the four extremities was detected and a cerebellar lesion was observed on magnetic resonance imaging (MRI). His positive neurological findings were

slurred speech, left spastic hemiparesis (MMT 4), and ataxia of the four extremities. He could not stand by himself. He had a slight hepatic function disorder and was positive for the hepatitis B virus surface (HBs) and hepatitis B virus e (HBe) antigens. Hepatitis C virus (HCV) and HIV antibodies were negative. His cerebrospinal fluid (CSF) showed a cell count of 2 cells/ μ L, protein level of 27 mg/dL, and glucose level of 60 mg/dL. The polymerase chain reaction (PCR) for JCV was negative. A brain biopsy from the left middle cerebellar peduncle resulted in a diagnosis of glioma. The pathological findings revealed swollen oligodendrocytes on hematoxylin-eosin staining, demyelination on Klüver-Barrera staining, and staining using anti-agnoprotein and anti-VP1 antibodies was positive, which was consistent with PML (Fig 1a–d). Mefloquine therapy was initiated. His symptoms improved and he was able to ride in a wheelchair in December 2013.

Case 2: An 80-year-old male was admitted to our hospital because of right hemiparesis, aphasia, and dysarthria. He underwent chemotherapy including rituximab for primary thyroid MALT lymphoma in June 2011. He had slight weakness of his right upper and lower extremities in October 2012. His symptoms worsened and a brain MRI showed white matter lesions of the right frontal and parietal lobes. He was admitted to our hospital in February 2013 because the

white matter lesion enlarged and his symptoms worsened further.

His positive neurological findings on admission were motor aphasia, right unilateral spatial neglect, dysphagia, and right hemiparesis. He had a slight elevation of serum soluble interleukin 2 (IL-2) receptor (654 U/mL). He was negative for the HBs antigen and HCV and HIV antibodies. His CSF showed a cell count of <1 cell/ μ L, protein level of 31 mg/dL, and glucose level of 85 mg/dL.

He was diagnosed as probable PML because PCR for JCV in the CSF was positive (5.08×10^5 copies/mL). Although mefloquine therapy was initiated, his symptoms worsened and the amount of JCV in the CSF increased to 5.91×10^6 copies/mL.

He died on the 97th hospital day.

Case 3: A 66-year-old female was admitted to our hospital because of left hemiparesis in June 2013. She had been treated with prednisolone and azathioprine since 1991 for overlap syndrome of systemic lupus erythematosus, dermatomyositis, and systemic sclerosis. The weakness of the left extremity occurred in April 2013. No abnormalities were found on brain MRI. Her symptoms worsened and she had difficulty walking in May 2013. Brain MRI revealed a white matter lesion in the right frontal lobe. Her symptoms and MRI findings worsened further in June 2013, so she was admitted to our hospital. Her positive neurological findings were left hemiparesis and mild left unilateral

spatial neglect. She had a slight elevation of serum soluble IL-2 receptor (520 U/mL). She was negative for HBs antigen and HCV and HIV antibodies. Her CSF showed a cell count of 1 cell/ μ L, protein level of 35 mg/dL, and glucose level of 50 mg/dL. She was diagnosed as probable PML because PCR for JCV in the CSF was positive (6.23×10^3 copies/mL). Mefloquine and mirtazapine therapy was initiated. Her hemiparesis improved and JCV became undetectable in the CSF.

Methods: In addition to brain MRI and FDG-PET, we assessed the MET-PET findings of each case, which have been used to evaluate low grade glioma and cerebral inflammatory lesions [1,2]. The MET-PET images were acquired with an EXACT HR+ scanner (Asahi-Siemens Medical Technologies LTD., Tokyo, Japan).

This study was approved by the Institutional Review Board of Hokkaido University.

Results

Case 1: Brain MRI showed a left middle cerebellar peduncle lesion (Fig 2a).

FDG-PET showed low uptake inside the lesion (Fig 2b) and MET-PET showed hyper-uptake around the lesion (Fig 2c).

Case 2: Brain MRI showed leukoencephalopathy in the white matter of the left

parietal lobe (Fig 2d). FDG-PET showed low uptake inside the lesion (Fig 2e) and MET-PET showed hyper-uptake around the lesion (Fig 2f).

Case 3: Brain MRI showed leukoencephalopathy in the white matter of the right frontal and parietal lobes (Fig 2g). FDG-PET showed low uptake inside the lesion (Fig 2h) and MET-PET showed hyper-uptake around the lesion (Fig 2i). After treatment was initiated, the white matter lesion enlarged on brain MRI (Fig 2j) and FDG-PET (Fig 2k). However, the hyper-uptake of methionine decreased (Fig 2l).

Discussion

PML is an infectious multifocal demyelinating disease of the brain caused by JCV infection of oligodendrocytes. No definitive treatment has been established, so the prognosis is very poor. The underlying disorders are various, such as HIV infections, hematopoietic neoplasms, autoimmune diseases, and monoclonal antibodies [3]. Nowadays, the number of monoclonal antibodies related to PML, such as in case 2, is increasing. Especially, neurologists are aware of the risk of PML when immunosuppressive therapy including natalizmab is used to treat multiple sclerosis [4]. Cases in which mefloquine therapy was effective have been reported [5,6].

A summary of our 3 cases is presented in Table 1. In the surviving cases, we were able to initiate mefloquine therapy when the amount of JCV in the CSF was low.

All 3 cases indicated the hyper-uptake of MET around the white matter lesions and hypo-uptake of FDG inside the lesions. Only one case report from Japan has described the hyper-uptake of MET in a patient with PML[7]. We suggest that the infection had ended inside the white matter lesions of our cases, while JCV infection was ongoing around the lesions, resulting in the increase of methionine metabolism, and glucose metabolism was reduced or intermediate because inflammatory cells infiltrate PML lesions rarely. In case 3, only the MET-PET abnormality improved after treatment. **We hypothesize that the degeneration might have ended in the areas where methionine uptake was increased, so the T2 intensity increased. Moreover, methionine uptake was prevented and PCR for JCV in the CSF was negative. We could not follow up the PET findings of the treated patient (case 1) and the untreated patient (case 2), which is a limitation of this study. We speculate that the reduction of the amount of JCV in case 3 resulted in the improvement of the MET-PET findings.**

We reported 3 cases of PML without HIV infection. The neurological impairments of such patients may improve when the amount of JCV in the CSF is

decreased. The mismatch of MET-PET and FDG-PET uptake may be useful for the early diagnosis of PML, **although these examinations cannot be performed every hospital.**

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Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard: This study was approved by the Institutional Review Board of Hokkaido University.

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Figure legends

Figure 1. The histopathological findings of case 1.

- a. Klüver-Barrera staining ($\times 10$) showing demyelination.
- b. Hematoxylin-eosin staining ($\times 40$) showing swollen oligodendrocytes.
- c. Anti-agnoprotein staining ($\times 40$); and d: anti Vp1 antibody staining ($\times 40$); the oligodendrocytes were positive, which is consistent with PML.

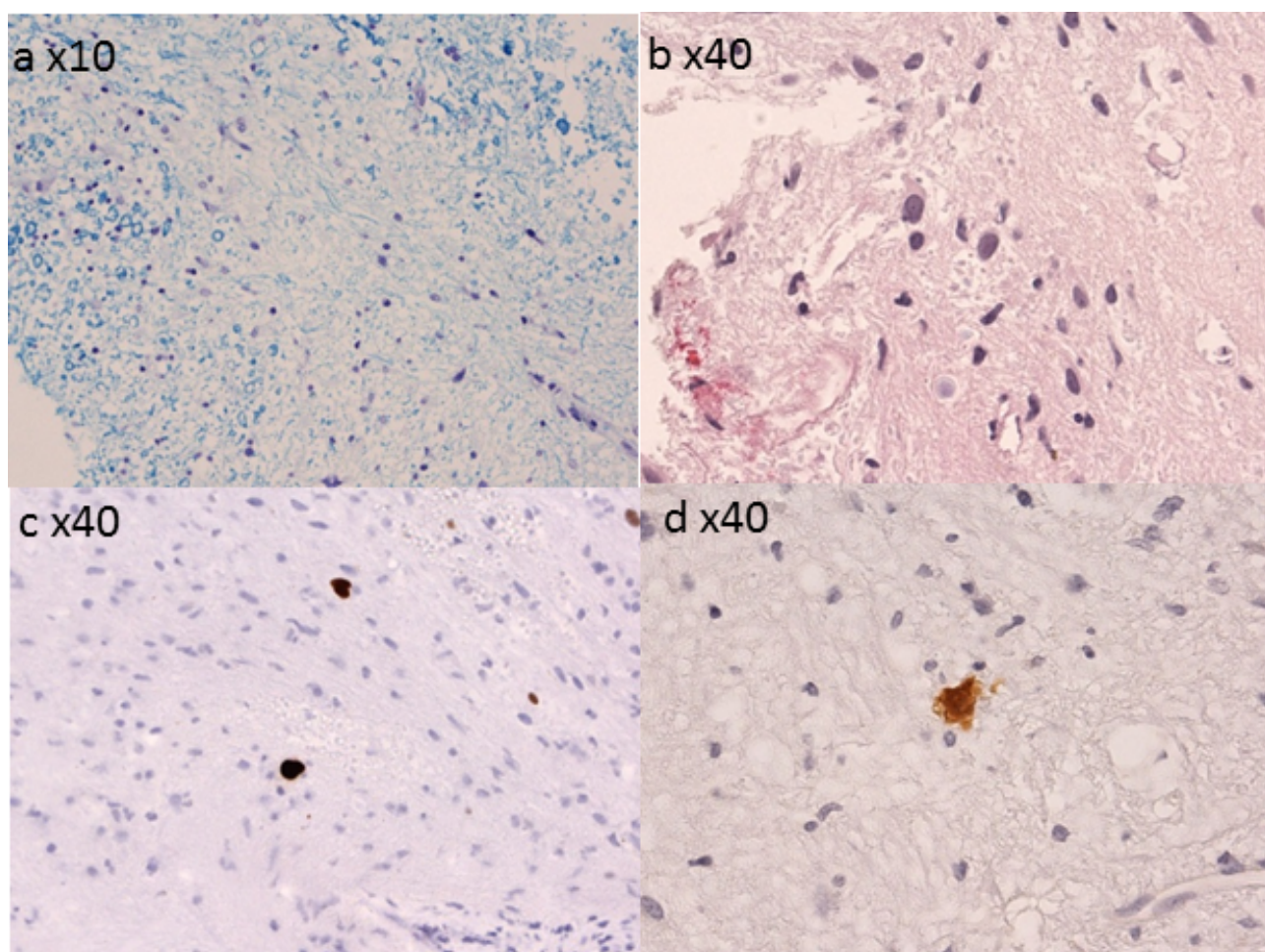


Figure 2. Neuroradiological findings

Neuroradiological findings of case 1 (a–c).

- a. Brain MRI image on admission (T2-weighted image, TR = 4,438 ms, TE = 100 ms) showing leukoencephalopathy of the left middle cerebellar peduncle.
- b. FDG-PET on admission. FDG uptake is decreased inside the lesion.
- c. MET-PET on admission. Methionine uptake is increased around the lesion.

Neuroradiological findings of case 2 (d–f).

- d. Brain MRI image on admission (T2-weighted image, TR = 4,540 ms, TE = 96 ms) showing leukoencephalopathy of the left parietal lobe.
- e. FDG-PET on admission. FDG uptake is decreased inside the lesion.
- f. MET-PET on admission. Methionine uptake is increased around the lesion.

Neuroradiological findings of case 3 (g–l).

- g. Brain MRI image on admission (T2-weighted image, TR = 4,540 ms, TE = 96 ms) showing leukoencephalopathy of the right frontal lobe.
- h. FDG-PET on admission. FDG uptake is decreased inside the lesion.
- i. MET-PET on admission. Methionine uptake is increased around the lesion.
- j. Brain MRI image on admission (T2-weighted image, TR = 4,160 ms, TE = 85 ms) still showing leukoencephalopathy of the right frontal lobe.
- k. FDG-PET after the initiation of treatment. FDG uptake is decreased inside the lesion, similar to that observed on admission.
- l. MET-PET after the initiation of treatment. The hyper-uptake of methionine is

reduced.

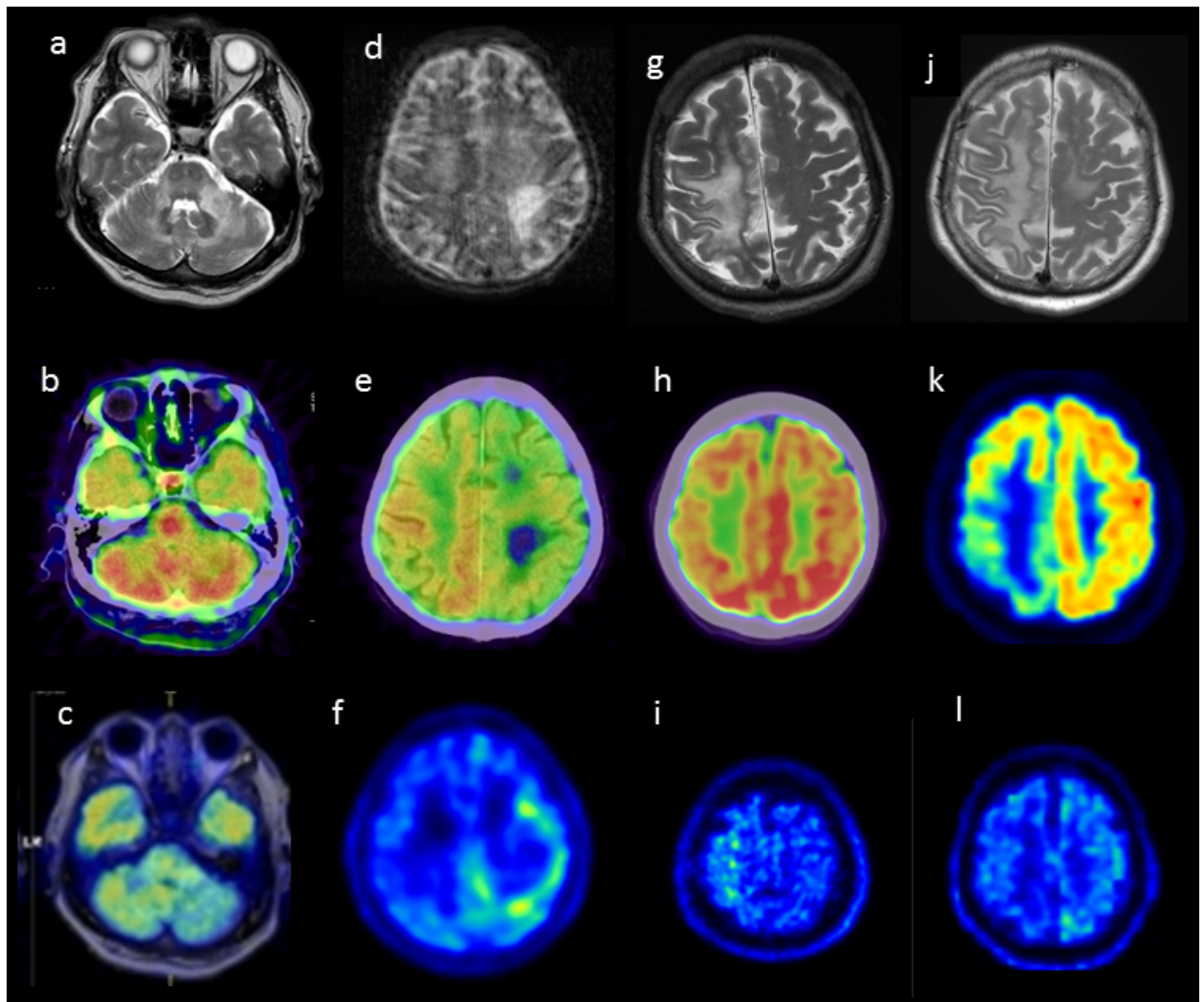


Table 1. Summary of our 3 cases

	Case 1 51 y.o. male	Case 2 80 y.o. male	Case 3 66 y.o. female
Diagnosis	Definite PML	Probable PML	Probable PML
Background	HBV	MALT lymphoma	SLE + DM + SSc
Immunosuppressant.	None	Chemotherapy including rituximab	PSL + AZT
CSF JC virus			
on diagnosis	Under the detection limit	5.08×10^5 copies/mL	6.23×10^3 copies/mL
after treatment	Unexamined	5.91×10^6 copies/mL	Under the detection limit
Treatment	Mefloquine mPSL	Mefloquine	Mefloquine Mirtazapine
Modified Rankin-Scale	5	5	5
before treatment			
after treatment*	4	6	4

*We were able to initiate mefloquine therapy in the survivors when the amount of JC virus in the CSF was low.

mPSL; methyl predonisolne AZT; azathioprine, SLE; systemic lupus erythematosus, DM; dermatomyositis, SSc; systemic sclerosis