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Short communication

Failure of mefloquine therapy in progressive multifocal leukoencephalopathy: Report of two Japanese patients without human immunodeficiency virus infection

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ABSTRACT

Although progressive multifocal leukoencephalopathy (PML) cases showing responses to mefloquine therapy have been reported, the efficacy of mefloquine for PML remains unclear. We report on the failure of mefloquine therapy in two Japanese patients with PML unrelated to human immunodeficiency virus. One of the patients was a 47-year-old male who had been treated with chemotherapy for Waldenström macroglobulinemia, and the other was an 81-year-old male with idiopathic $CD4^+$ lymphocytopenia. Diagnosis of PML was established based on MRI findings and increased JC virus DNA in the cerebrospinal fluid in both patients. Mefloquine was initiated about 5 months and 2 months after the onset of PML, respectively. During mefloquine therapy, clinical and radiological progression was observed, and JC virus DNA in the cerebrospinal fluid was increased in both patients. Both patients died about 4 months and 2 months after initiation of mefloquine, respectively. Further studies are necessary to clarify the differences between mefloquine responders and non-responders in PML.

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a brain disorder caused by JC polyomavirus, which causes death in one-half of patients within 1 year [1]. Primary infection usually occurs during childhood and is often asymptomatic. The initial site of JC virus (JCV) infection is thought to be the tonsils, and it is then carried by lymphocytes to the kidneys and bone marrow. Reactivation of JCV occurs due to severe cellular immunodeficiency, and the virus crosses the blood–brain barrier (BBB) and infects oligodendrocytes, causing widespread demyelinating lesions. A recent study revealed promyelocytic leukemia nuclear bodies as an intranuclear target of JCV [2].

A study of 9675 cases of PML between 1998 and 2005 showed that 82% of patients had human immunodeficiency virus (HIV), 8.4% hematologic malignancies, 2.83% solid organ cancers, and 0.44% rheumatologic diseases [3]. Recently, a new category of PML patients has emerged among patients treated with immunomodulatory medications including natalizumab, rituximab, and efalizumab. PML may also occur in patients with minimal or occult immunosuppression including idiopathic $CD4^+$ lymphocytopenia [4]. In Japan, the proportion of hematological malignancies or rheumatologic diseases as underlying diseases is relatively high, whereas that of HIV infection is low [5,6].

The estimated probability of survival at 1 year is reported to be 52% in HIV related PML [1] and variable in PML unrelated to HIV among reports. Some patients with PML do survive for extended periods of time after diagnosis [7,8]. Survival in PML is influenced by the presence of JCV-specific cytotoxic T-lymphocytes, $CD4^+$ cell counts, or JCV DNA levels [1,9]. One study reported that estimated 1-year survival was 48% in patients with HIV related PML with $CD4^+$ cell counts $<200/\mu l$ at PML diagnosis compared to 67% in those with $CD4^+$ cell counts $>200/\mu l$ [1]. Another study showed that JCV DNA levels >4365 copies/ml of cerebrospinal fluid (CSF) correlated significantly with shorter survival in patients with HIV related PML not receiving highly active antiretroviral therapy (HAART) [9].

To date, although antiviral drugs such as cytarabine and cidofovir show activity against JCV *in vitro* [10,11], large clinical studies have failed to establish the efficacies of these drugs in the treatment of PML [12–14]. The reason for this may be that these drugs are not able to cross the BBB and accumulate throughout the entire brain parenchyma at a dose sufficient to suppress JCV proliferation [15].

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In 2008, mefloquine, an anti-malarial drug, was reported to show activity against JCV *in vitro* [15]. Since then, there have been at least 5 reported cases of PML in which mefloquine was effective [16–20]. In contrast, a recent mefloquine trial of 24 patients with PML (21 HIV-positive and 3 HIV-negative) reported failure in reducing JCV DNA levels in the CSF [21], although it is pending publication. Because there have been no reports describing the details of PML patients demonstrating mefloquine treatment failure, we report two HIV-negative patients with PML in whom mefloquine was not effective.

2. Case reports

2.1. Case 1

A 47-year-old male presented with progressive left hemiparesis. The patient had been treated with chemotherapy including rituximab for Waldenström macroglobulinemia for six years in our hospital. The interval between the last administration of rituximab and occurrence of hemiparesis was about 1 month. Diffusion weighted images (DWI) of brain MRI about 3 months after the onset of hemiparesis demonstrated high intensity areas with internal low intensity areas in the white matter of the right frontal lobe. The apparent diffusion coefficient (ADC) values of the lesion were increased. Because serum IgM had been prominently elevated (around 5000 mg/dl) in association with Waldenström macroglobulinemia, we presumed that the hyperviscosity syndrome resulted in brain infarction.

About 4 months after the onset of hemiparesis, the patient was admitted to our hospital because a convulsion occurred in the left upper and lower limbs. At that time, the patient did not receive any immunosuppressive therapy. On admission, neurological examination revealed upper limb-dominant left hemiparesis, and Babinski's sign and Chaddock's reflex on the left. MRI on admission demonstrated lesion expansion and extension to the right parietal and insular white matter, right putamen, right internal capsule, right thalamus, corpus callosum, left frontal white matter, and midbrain. There was no edema or gadolinium-enhanced lesions. Peripheral blood tests showed white blood cell count (WBC): 3790/μl (normal range: 4500–9000), hemoglobin: 10.4 g/dl (normal range: 13–16), and platelet count: 3.7×10^4/μl (normal range $15–30\times10^4$), indicating pancytopenia. C-reactive protein (CRP) was below 0.1 mg/dl. Testing for HIV was negative. On the next day of admission, a nasogastric feeding tube was inserted because of dysphagia. Four days after admission, CSF examination demonstrated cell count: 1 cell per 3 μl, total protein: 97 mg/dl, and glucose: 67 mg/dl. PCR was positive for JCV DNA in the CSF and detected 1200 copies/ml of DNA. A diagnosis of PML was established based on MRI findings and increased JCV DNA in the CSF.

After diagnosis, the patient developed right hemiparesis and apraxia of speech. Brain MRI 18 days after admission demonstrated lesion expansion and extension to the left insular white matter and left putamen (Fig. 1A). The JCV DNA copy number in the CSF was increased to 4300 copies/ml. $CD4^+$ cell count of the peripheral blood was 219/μl (normal range: 500–1300). Nineteen days after admission, about 5 months after the onset of PML, mefloquine was initiated at a dose of 275 mg/day orally for 3 days, followed by 275 mg once a week [17]. We used Mephaquin Hisamitsu tablets (Hisamitsu Pharmaceutical, Tosu, Japan), which show maximum concentration (C_{max}) of 3.1 μM, time at which C_{max} is observed (T_{max}) of 5.2 h, and terminal half-life (T1/2) of 400.1 h when 1100 mg of drug is once administered. Treatment with mefloquine was approved by the Ethics Committee in our hospital. We obtained written, informed consent from the patient's family. We also used 1 mg/day of risperidone, a 5HT2A receptor blocker at the same time. After initiation of mefloquine, we observed no symptoms suggestive of mefloquine neurotoxicity such as nausea, dizziness, sleep disturbances, anxiety, and psychosis [22]. Eight days after initiation of mefloquine, the JCV DNA copy number in the CSF was increased to 150,000 copies/ml, and the dose of mefloquine was returned to 275 mg/day for 3 days per week (Fig. 2).

However, the JCV DNA copy number in the CSF 22 days after initiation of mefloquine was increased to 850,000 copies/ml. Because of severe aspiration pneumonia, tracheotomy was performed 37 days after initiation of mefloquine. Brain MRI 38 days after initiation of mefloquine demonstrated lesion expansion and extension to the right temporal and occipital white matter and pons (Fig. 1B). The JCV DNA copy number in the CSF 50 days after initiation of mefloquine increased to 3,700,000 copies/ml. Changes in the JCV DNA load are shown in Fig. 2. Brain MRI about 3 months after initiation of mefloquine demonstrated lesion expansion and extension to the left temporal and parietal white matter, left internal capsule, left thalamus, and medulla oblongata (Fig. 1C). The patient died of respiratory failure about 4 months after initiation of mefloquine. The total clinical course of PML was about 9 months. Autopsy could not be performed.

2.2. Case 2

An 81-year-old male with a three-week history of gait disturbance presented with muscle cramp in the bilateral upper limbs and was taken to another hospital by ambulance. Past medical history included hypertension, hyperuricemia, chronic heart failure, and chronic renal failure due to renal sclerosis. A diagnosis of brain infarction of the

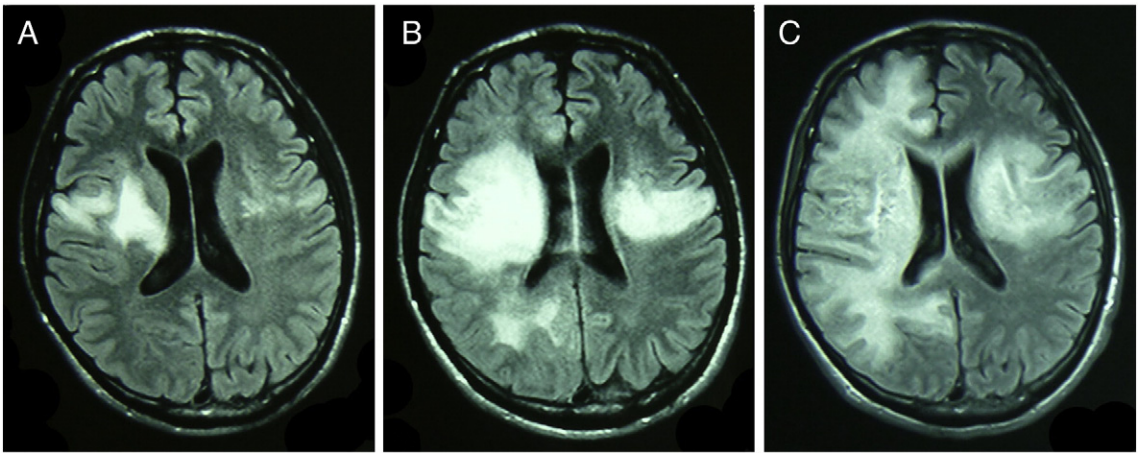

Fig. 1. A. Fluid-attenuated inversion recovery (FLAIR) sequence of brain MRI before initiation of mefloquine demonstrated high intensity areas in the white matter of the bilateral frontal lobes. B, C. FLAIR sequence of brain MRI 38 days (B) and about 3 months (C) after the initiation of mefloquine showed lesion expansion.