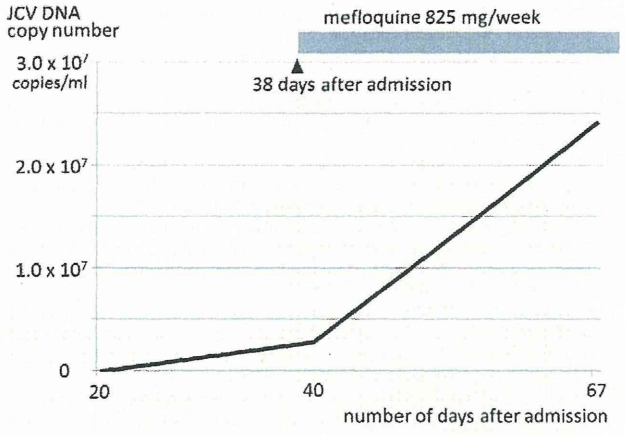

Fig. 4. Changes in the JCV DNA load of case 2 are shown. The JCV DNA copy number in the CSF was increased even after initiation of mefloquine.

diagnosis of PML has been reported to be 5.5 months [25]. Considering that 90% of patients with PML after rituximab therapy die [25], the unfavorable clinical course of our case 1 may be associated with the use of rituximab. In case 2, while $CD4^+$ lymphocytopenia was documented, there were no underlying diseases causing immunodeficiency. However, as PML may occur in patients with minimal or occult immunosuppression [4], idiopathic $CD4^+$ lymphocytopenia may be associated with the occurrence of PML in this patient.

Mefloquine is an anti-malarial drug used both for prophylaxis and treatment of chloroquine resistant *Plasmodium falciparum*. Because mefloquine is highly lipophilic and has a long terminal half-life of more than 1 week [26], a single dose of 15–25 mg/kg is used for treatment and 250 mg/week for prophylaxis. Among subjects administered 250 mg weekly, blood concentrations vary between 1 μM to 5 μM [27]. Mefloquine readily crosses the BBB, where active efflux by the P-glycoprotein membrane transporter prevents its accumulation in the brain [27].

In 2008, mefloquine was reported to show activity against JCV *in vitro* [15]. Brickelmaier et al. showed that mefloquine inhibits viral DNA replication, using quantitative PCR to quantify the number of viral copies in cultured cells. In this study, mefloquine reduced the number of infected cells by 50% or more at a concentration of 3.9 μM [15]. Brickelmaier et al. presumed that efficacious concentrations of mefloquine for PML are achieved in the brains of patients receiving approved doses of the drug [15].

Since the publication by Brickelmaier et al. [15], there have been at least 5 reported cases of PML in which mefloquine was effective [16–20]. The underlying diseases or conditions included sarcoidosis [16], umbilical cord blood transplant [17], HIV infection [18], and systemic lupus erythematosus [19]. $CD4^+$ cell counts in the peripheral blood of patients were described in 3 reports, and were 187/μl [18], 419/μl [17], and 420/μl [16], respectively. JCV DNA loads in the CSF before mefloquine therapy were available in these reports, and were 33,700 copies/ml [16], 535,500 copies/ml [18], and 911,175 copies/ml [17], respectively. The intervals between symptom onset and initiation of mefloquine therapy were about 3 months [17,19], 5 months [18], and 6 months [16,20], respectively. In 4 reports [16–19], the authors stated that PCR for JCV in the CSF became negative after mefloquine therapy. At present, the patients' background or laboratory data common among these cases showing responses to mefloquine therapy is unclear.

In contrast to these cases, 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]. Participants took 250 mg of mefloquine 4 times daily, followed by 250 mg weekly. The failure of this trial and the poor outcome of our patients raise the possibility that the improvement observed in mefloquine therapy in reported PML patients [16–20] may actually reflect the natural favorable course of those patients.

At present, we cannot tell the difference in patient backgrounds or laboratory data between patients showing responses to mefloquine [16–20] and our patients. Regarding the presence of both mefloquine responders and non-responders in PML, Nevin stated that responses to mefloquine may correlate with polymorphisms in the *MDR1* gene coding for P-glycoprotein that affect drug efflux across the BBB [28]. In cases of unsuccessful treatment of PML, active efflux as a result of drug induced upregulation of P-glycoprotein expression in the BBB may be preventing therapeutic concentrations of mefloquine [28]. From this point of view, co-administration of P-glycoprotein inhibitors or substrates such as risperidone may be recommended in the treatment of PML [27]. On the other hand, considering the failure of the mefloquine trial and the poor outcome of our patients, re-evaluation of the anti-JCV activity of mefloquine may be required. If the anti-JCV activity of mefloquine is verified again, further studies are necessary to clarify whether the response to mefloquine in PML is influenced by the presence of HIV infection, $CD4^+$ cell counts, JCV DNA levels in the CSF, blood concentration of mefloquine, interval between disease onset and initiation of therapy, or *MDR1* polymorphism.

Conflict of interest statement

The authors have no conflicts of interest.

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