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Progressive multifocal leukoencephalopathy successfully treated with mefloquine and literature review

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Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection due to reactivation of John Cunningham virus (JCV). The diagnosis depends on evidence from clinical, imaging, and virologic studies. When the cerebrospinal fluid shows a negative polymerase chain reaction result, brain biopsy is required to confirm the diagnosis. PML has no standard treatment except for immune reconstitution. The anti-JCV effect of mefloquine, however, is supported by some studies, and if brain biopsy is difficult, a mefloquine trial can be considered. We describe a case of possible PML successfully treated with mefloquine.

Keywords: Progressive multifocal leukoencephalopathy, JC virus, Mefloquine

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare fatal infection caused by John Cunningham virus (JCV) that usually occurs in immunocompromised patients. Since any area of the brain can be involved, PML shows diverse clinical features. The diagnostic criteria of PML are comprised of evidence from clinical, imaging, and virologic studies [1].

PML has no approved treatment except for immune reconstitution. Although *in vitro* studies and some case reports suggest an anti-JCV property of mefloquine [2-22], the efficacy of mefloquine for JCV is controversial [23,24]. We describe a possible PML case with negative cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for JCV that was successfully treated with mefloquine.

Case Report

A 52-year-old male patient visited the emergency department with a 2-week history of positional vertigo, a 3-day history of tinnitus, ear pressure, and hearing loss in the left ear. He denied other neurologic symptoms. He had a history of coronary stent insertion for myocardial infarction and living-donor kidney transplantation for end-stage renal disease of unknown etiology. He was taking prednisolone 5 mg daily with mycophenolate mofetil 360 mg twice a day.

Neurologic examination revealed Weber lateralization to the right side, bilateral nasolabial fold blunting, and truncal ataxia. However, other cranial nerves, motor, sensory, and cerebellar function tests, and the otoscope examination were unremarkable. The initial impression was multiple cranial nerve palsy. Brain magnetic resonance imaging (MRI) revealed bilateral facial nerve enhancement (left > right) and subtle flu-

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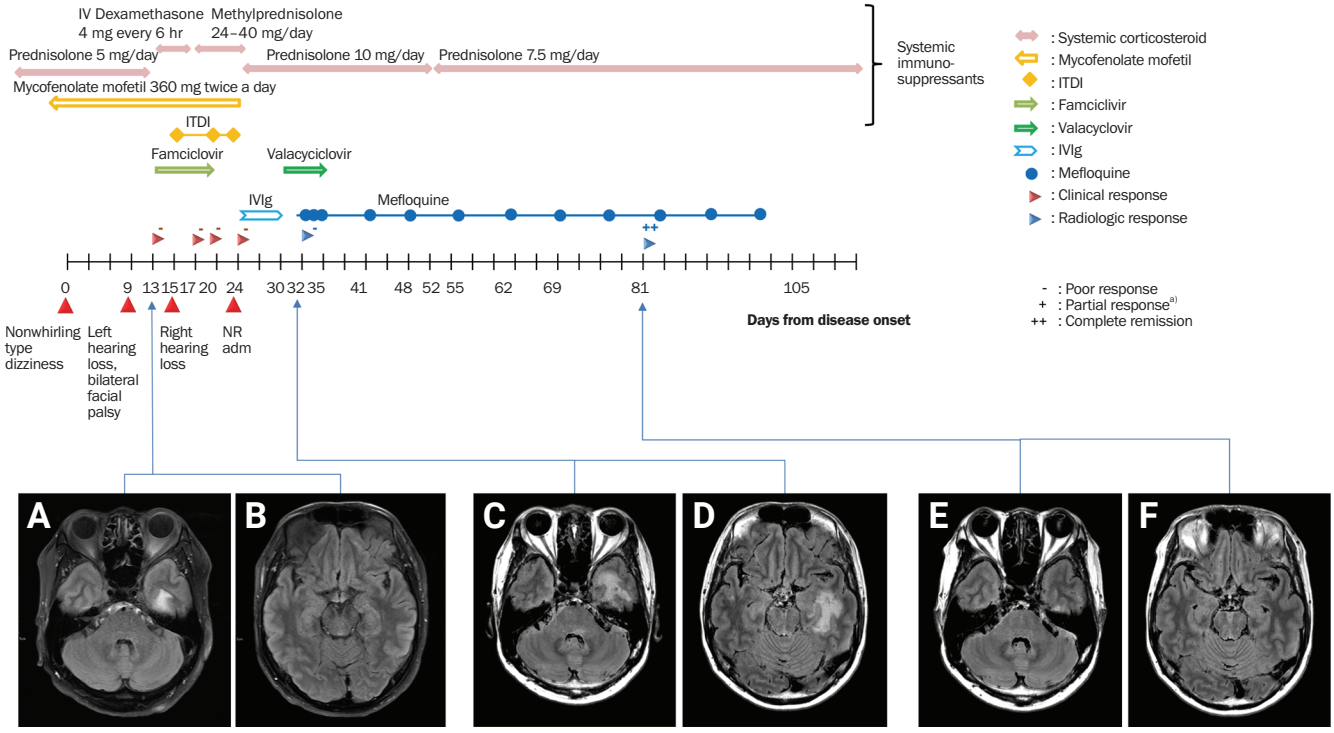
id-attenuated inversion recovery (FLAIR) hyperintensity and T1 hypointensity in the left temporal white matter (Figure 1A and B).

He was admitted to the otorhinolaryngology department with the initial impression of Ramsay-Hunt syndrome. The patient received intravenous dexamethasone 4 mg every 6 hours for 4 days, oral methylprednisolone 40 mg for 10 days, and famciclovir 500 mg for 7 days. Intratympanic dexamethasone was administered three times in the left ear and twice in the right ear, but the administration aggravated the patient's bilateral sensorineural hearing loss.

He was referred to the neurology department and was admitted with the impression of encephalitis of infectious or autoimmune etiology. CSF examination showed marginal pleocytosis (leukocytes, 8 cells/μL; lymphocytes, 75%; others, 25%) with a normal protein level (39 mg/dL) and negative results for the Gram stain, bacterial culture, and cryptococcal antigen (Table 1). Valacyclovir 1,000 mg twice a day for 1 week and intravenous immunoglobulin G (IgG) 2 g/kg over 5 days were prescribed. The corticosteroid dose was tapered to oral prednisolone 10 mg daily. CSF PCR revealed a positive result for Epstein-Barr virus (EBV) and negative results for mycobacteria, cytomegalovirus, herpes simplex virus, varicella zoster virus (VZV), and JCV. The result of serum JCV PCR was positive. EBV viral capsid antigen (VCA) IgG was positive, but EBV VCA IgM was negative. Early antigen and EBV nuclear antigen tests were not conducted (Table 1).

After 2 weeks of antiviral treatment, follow-up brain MRI showed FLAIR hyperintensity and T1 hypointensity in the subcortical white matter of the left temporal lobe and dorsal pons (Figure 1C and D). The imaging findings suggested lymphoproliferative disease or PML. Whole-body positron emission tomography was performed to rule out the possibility of lymphoproliferative disease and revealed no abnormal hypermetabolism, which would suggest malignancy. In the meantime, an initial workup that included ganglioside antibodies, antinuclear antibody, antineutrophil cytoplasmic an-

Figure 1 Hyperintensity in the subcortical white matter was seen in the fluid-attenuated inversion recovery sequence of the brain magnetic resonance imaging.



Left inferior temporal gyrus **(A)** and left superior temporal gyrus **(B)** on the initial image; and left inferior **(C)** and superior temporal gyrus and left dorsal pons **(D)** before mefloquine treatment. Decreased hyperintensity in the left temporal areas **(E**, inferior; **F**, superior**)** after mefloquine treatment.

IV, intravenous; ITDI, intratympanic dexamethasone injection; IVIg, IV immunoglobulin G.

[a)]Clinical improvement with remnant neurologic deficit.

Table 1 Laboratory results of blood and cerebrospinal fluid of the patient

Lab finding	Initial visit	Second admission	6 wk after mefloquine	Normal range
Blood				
White blood cell (/μL)	4.78	8.51	7.98	4–10
Hemoglobin (mg/dL)	9	8.3	13.8	12–16
Platelets ($\times 10^3$/μL)	214	196	365	130–400
Absolute neutrophil count (/μL)	3824	7829	1.3	1–5
C-reactive protein (mg/L)	0.06	0.01	0.02	0–0.5
Sodium (mEq/L)	138	139	133	135–145
Potassium (mEq/L)	4.2	4.5	3.8	3.5–5.5
Albumin (g/dL)	3.6	3.0	4.4	3.3–5.2
Glucose (mg/dL)		216		70–110
EBV PCR		Positive	NA	
JCV PCR		Positive	Negative	
VZV PCR		Negative	NA	
Cerebrospinal fluid				
Cell count (/μL)	NA	8	NA	0–5
Polymorphonuclear cell (%)		0		
Lymphocytes (%)		75		
Other cells (%)		25		
Protein (mg/dL)		39		15–45
Glucose (mg/dL)		69		40–70
FTA-ABS		Nonreactive		Nonreactive
JCV PCR		Negative		Negative
EBV PCR		Positive		Negative

EBV, Ebstein-Barr virus; PCR, polymerase chain reaction; NA, not available; JCV, John Cunningham virus; VZV, varicella zoster virus; FTA-ABS, fluorescent treponemal antibody absorption.

tibody, angiotensin-converting enzyme level, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein IgG, vitamin B12, and folate level showed that these levels were normal. He was diagnosed with possible PML. Because of the patient's poor response to the antiviral agent and the results of his extensive diagnostic workup, we excluded other differential diagnoses, including VZV leukoencephalopathy, central nervous system (CNS) vasculitis, and lymphoproliferative diseases.

Nevertheless, the corticosteroid was tapered to prednisolone 10 mg equivalent, brain MRI showed increased extent of the FLAIR hyperintensity lesion, and pure-tone audiometry (PTA) showed progressive bilateral sensorineural hearing loss. Since steroid tapering was not sufficient to halt disease progression, mefloquine 250 mg/day for 3 days was introduced and maintained at 250 mg every week. After mefloquine treatment, his neurologic deterioration stopped, and no other focal neurologic deficit, other than the presenting sensorineural hearing loss, appeared. In the 6-week follow-up MRI, previous white matter lesions were markedly decreased, and serum JCV PCR was negatively reversed (Figure 1E and F). Initially, we planned maintenance treatment with mefloquine to continue until radiologic remission or confirmed recovery of hearing. However, the maintenance therapy of mefloquine 250 mg/week was administered for only 8 weeks due to the patient's refusal. At his nadir, he was only able to follow simple commands, but after treatment, his sensory aphasia improved to almost normal and his cognitive function improved to independent activities of daily living. A change in his hearing deficit, however, was not assessed due to the patient's refusal for PTA follow-up.

Discussion

PML is prevalent in immunocompromised patients. Although JCV infects more than 50% of the adult population, its replication is suppressed by antigen-specific T cells in immune-competent individuals [1]. In an immune-compromised subject, however, JCV can replicate in oligodendrocytes and astrocytes causing lytic necrosis, which is a key factor in the pathophysiology of PML [25].

No single criterion has been established for the diagnosis of PML. The American Academy of Neurology suggests that cli-

nicians diagnose PML based on evidence from clinical, neuroimaging, and virologic studies [1]. Given these criteria, the definite or probable PML case requires positive CSF JCV PCR or histopathologic evidence in brain biopsy. However, several reports describe negative CSF JCV PCR cases that were finally diagnosed as PML [3,22,26-34]. In a search on PubMed, at least 11 case reports published in English were available, and each case was biopsy-proven [3,22,26-34] (Table 2). Some new diagnostic criteria of PML have been proposed to overcome this limitation [35]. Our case had clinical and imaging features supporting PML and was categorized as possible PML. Other possibilities, like CNS vasculitis and VZV leukoencephalopathy, were excluded through an extensive diagnostic workup. A brain biopsy was required to confirm the diagnosis of PML; nonetheless, brain biopsy was spared in this patient due to its invasiveness and empirically treated as PML.

The only approved treatment of PML is immune reconstruction. This approach is based on the fact that PML is one of opportunity infections. The removal of immunosuppressants in treatment-related PML and antiretroviral therapy in human immunodeficiency virus-associated PML are good examples. Treating PML with immune checkpoint inhibitor is also a similar strategy [36].

Other strategies are based upon *in vitro* studies. Mirtazapine or atypical antipsychotics were expected to inhibit viral entry into cells blocking $5HT_{2A}$ receptors, which is a cellular receptor for JCV. For these medications to be validated as treatment options for PML, their toxicity should be tolerable in the therapeutic range, and the drugs should be delivered to the CNS. *In vitro* studies suggest that mefloquine not only has an anti-JCV property by inhibiting viral DNA replication but also sufficiently penetrates the blood brain barrier [2]. Moreover, these *in vitro* studies are supported by several case reports of PML successfully treated with mefloquine [3-22,37]. In PubMed, at least 21 case reports published in English were available, and these cases even included treatment without additional immune reconstitution therapy [3-22,37] (Table 3). Some clinical studies failed to show the clinical efficacy of mefloquine [23], but some points must be considered. A large clinical trial of PML is difficult due to its rarity. In addition, it seems that *ABCB1/MDR1* gene polymorphism has an important role in pharmacokinetics and efficacy [24], contributing to the negative results of the trial [23].

In the present case, although the virologic evidence was not fulfilled, clinical and imaging findings led to the impression of PML. Immunosuppressants were tapered but failed to halt

Table 2 Summary of case report of progressive multifocal leukoencephalopathy with false-negative PCR in CSF

Study	Age (yr) /sex	Presenting symptom	Comorbidity	Treatment	MRI finding	CSF study	Brain biopsy
Kuhle et al., 2011 [26]	48/F	L side hypesthesia and dysesthesia	RRMS	Prednisolone	Compatible with MS Nonenhancing and faintly enhancing ribbon-like lesion	Negative PCR for JCV	Polyomavirus particles on EM
Silverio et al., 2015 [22]	69/M	Progressive dysarthria and R hemiparesis	Follicular lymphoma	Chemotherapy	Multiple confluent foci of FLAIR hyperintensity involving the inferior R and L frontal lobes, as well as periventricular regions	Negative PCR for JCV	Chromatin margination and viropathic change within oligodendrocytes
Babi et al., 2015 [27]	75/F	Progressive L hemiplegia and global decline	Rheumatoid arthritis	Methotrexate, adalimumab	Asymmetric subcortical FLAIR HIS involving R frontoparietal subcortical WM	Negative PCR for JCV	Viral inclusion in enlarged oligodendroglial nucleus
Lee et al., 2019 [28]	44/M	Dysphagia, memory disturbance, Seizure	AIDS	HAART	Multifocal patchy lesions involving subcortical region of both frontal, R temporoparietal, L thalamus, striatocapsular regions	Negative PCR for JCV	Large infected oligodendrocytes with inclusion-bearing dark nuclei High JCV DNA titer of brain biopsy specimen
van der Kolk et al., 2016 [29]	49/M	Aphasia, dyscalculia, hyperesthesia of the R arm, and headache	NA	NA	Large confluating asymmetric white matter hyperintensities lesions in the frontal and parietal lobes	Negative PCR for JCV	Positive PCR for JCV on the biopsy material

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Table 2 Continued

Study	Age (yr) /sex	Presenting symptom	Comorbidity	Treatment	MRI finding	CSF study	Brain biopsy
Kharfan-Dabaja et al., 2007 [30]	51/M	Confusion and disorientation, dysnomia and progressive R upper extremity weakness → seizure → receptive aphasia, R hemiparesis, and cortical blindness	Follicular NHL and secondary myelodysplasia	GVHD prophylaxis with methotrexate, ztacrolimus, alloHCT	T2 hyperintensity in periventricular white matter clustered within the L centrum semiovale	Negative PCR for JCV	Extensive demyelination, presence of naked axons, reactive gliosis, and lipid-laden macrophages Occasional nuclei with a basophilic ground glass appearance, suggestive of inclusions The presence of viral particles typical of the papovavirus group in multiple cells in EM
Chowdhary and Chamberlain 2008 [31]	51/M	Progressive confusion, dysarthria, and visual disturbance	Myelodysplasia and NHL	Allogenic bone marrow transplantation	Multifocal T2HSI lesions including L frontal, parietal, and occipital lobes	Negative PCR for JCV for twice	Multiple enlarged, basophilic nuclei of infected oligodendrocytes intranuclear accumulation of spherical and filamentous viral particles typical of the papovavirus group
Vidarsson et al., 2002 [32]	63/M	Progressive memory loss and R visual disturbances	Follicular lymphoma	Fludarabine, mitoxantrone, dexamethasone	Multifocal T2HSI lesion in L parieto-occipital area	Negative PCR for JCV	Abnormal astrocytes with hyperchromaticnuclei, and oligodendrocytes with enlarged nuclei and "ground glass"' appearance
Landry et al. 2008 [33]	31/F	L facial palsy and L sided weakness	Job's syndrome (HIES) Multiple sclerosis treated with high-dose corticosteroid and plasma exchange	IVIg	Atypical T2HSI pattern	Negative PCR for JCV	Demyelination, myelin-debris-laden foamy macrophages, enlarged nuclei but no definitive intranuclear inclusions in oligodendroglial cells and no bizarre astrocytes Polyomavirus particles in EM finding
Sikkema et al., 2013 [34]	74/F	Progressive symptoms of motor imbalance, fatigue, weight loss, and impaired cognitive function	DLBCL	RCHOP	T2HSI lesions in L thalamus/ mesencephalon, R subcortical frontal lobe	Negative PCR for JCV	Reactive gliosis and in the middle of a cell with a viral nuclear inclusion
Garrote et al., 2015 [3]	50/M	Visual disturbance, diminished muscular strength in the R arm and vesicular-papular lesions in the L ophthalmic branch region of the V cranial nerve	Chronic lymphocytic leukemia	Fludarabine, cyclophosphamide and rituximab	T2 hyperintensity in bilateral parietal and occipital lobules including internal capsule	Negative PCR for JCV	Infiltration of the brain tissue by foamy macrophages and mature lymphocytes with perivascular clustering Loss of myelin in immunohistochemistry Reactive astrocytes with polymorphic nuclei and prominent nucleoli

PCR, polymerase chain reaction; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; F, female; M, male; R, right; L, left; RRMS, relapse and remitting multiple sclerosis; MS, multiple sclerosis; JCV, JCV, John Cunningham virus; EM, electron microscopy; FLAIR, fluid-attenuated inversion recovery; HIS, high signal intensity; AIDS, acquired immune deficiency syndrome; HAART, highly active antiretroviral therapy; NA; not available; NHL, non-Hodgkin lymphoma; GVHD, graft versus host disease; alloHCT, allogeneic hematopoietic cell transplantation; BMT, bone marrow transplantation; HIES, hyper immunoglobulin E (IgE) syndrome; IVIg, intravenous IgG; DLBCL, diffuse large B-cell lymphoma; RCHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone.

Table 3 Summary of case report of PML successfully treated with mefloquine

Study	Age (yr) /sex	MRI lesion (T2/FLAIR hyperintensity)	Lesion enhancement	Comorbid diseases and treatment	Treatment for PML	Interval between the initial symptom onset and diagnosis (mo)	Clinical outcome
Garrote et al., 2015 [3]	50/M	Bilateral parietal and occipital lobules, and internal capsule	-	CLL treated with rituximab, fludarabine, cyclophosphamide	Mefloquine and dexamethasone	NA	Marked improvement
Shin et al., 2014 [4]	67/M	R Parietal lobe	-	IgAN on prednisone	Mefloquine	NA	Marked improvement
Nishigori et al., 2019 [5]	68/M	Bilateral MCPs, pons and cerebellum	+	RA treated with prednisolone, and methotrexate for 9 years	Mefloquine and mirtazapine	6	Marked improvement
Hamaguchi et al., 2020 [6]	68/M	R MCP and cerebellar hemisphere	+	RA, SLE on prednisolone, tacrolimus	Mefloquine and mirtazapine	5	Marked improvement
Ishikawa et al., 2018 [7]	36/M	Bilateral temporoparietal lobe	-	SLE, HLH on prednisolone, cyclosporin A, rituximab, cyclophosphamide, mycophenolate mofetil	Mefloquine and mirtazapine	3	Marked improvement
Nambirajan et al., 2017 [8]	44/M	Bilateral parieto-occipital subcortical and deep white matter	-	-	Mefloquine and cotrimoxazole	1	Marked improvement
Gofton et al., 2011 [9]	54/F	R cerebellum and brainstem	-	Sarcoidosis on steroid	Mefloquine	6	Marked improvement
Hervás et al., 2015 [10]	51/M	Bilateral MCPs and R frontal subcortical white matter	+	RRMS treated with natalizumab	Intravenous methylprednisolone and mefloquine	1	Marked improvement
Young et al., 2012 [11]	57/M	R BG, thalamus, R frontal WM	+	HIV on HAART	Mefloquine	3	Marked improvement
	39/M	R frontoparietal subcortical white matter	-	HIV on HAART	Mefloquine	NA	Marked improvement
Epperla et al., 2014 [12]	72/M	L frontal lobe	+	CLL s/p splenectomy	Mefloquine and mirtazapine	1	Marked improvement
Sanjo et al., 2016 [13]	53/M	L frontal, parietotemporal and R parietal lobes	+	Follicular lymphoma treated with CCRT	Mefloquine, risperidone, and cytarabine	1.5	Marked improvement
Yoshida et al., 2014 [14]	40/F	R occipital and L frontal lobes	NA	GVHD treated with calcineurin inhibitor and steroid	Mefloquine and mirtazapine	NA	Marked improvement
Yoshida et al., 2015 [15]	66/M	L frontal lobe	-	Chronic hepatitis C after liver transplantation, GVHD on tacrolimus and rapamycin	Mefloquine	NA	Marked improvement
Shirai et al., 2014 [16]	51/M	L MCP and cerebellar lesion	-	Chronic hepatitis B with hepatocellular carcinoma	Mefloquine and methylprednisolone	3	Some improvement
	66/F	R frontal lobe	-	SLE, DM, SSc	Mefloquine and mirtazapine	2	Some improvement
Hirayama et al., 2011 [17]	60/M	Bilateral frontoparietal lobe	-	Sarcoidosis	Mefloquine	4	Marked improvement
McGuire et al., 2011 [18]	74/F	R frontal lobe	+	Idiopathic isolated CD8+ T-lymphocytopenia	Mefloquine and mirtazapine	NA	Some improvement
Ishii et al., 2018 [19]	37/F	Bilateral cerebral peduncles, internal capsule, corpus callosum, and deep white matter of the L frontal lobe and bilateral periventricular area	-	SLE treated with prednisolone, mycophenolate mofetil	Mefloquine	5	Some improvement
Ikeda et al., 2017 [20]	32/F	L frontal lobe	NA	SLE treated with oral prednisolone, tacrolimus and cyclophosphamide pulse	Mefloquine and mirtazapine	1	Marked improvement
Nakayama et al., 2020 [21]	73/F	L MCP, cerebellar hemisphere, brainstem	NA	ET treated with ruxolitinib	Mefloquine and mirtazapine	7	Some improvement

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Table 3 Continued

Study	Age (yr) /sex	MRI lesion (T2/FLAIR hyperintensity)	Lesion enhancement	Comorbid diseases and treatment	Treatment for PML	Interval between the initial symptom onset and diagnosis (mo)	Clinical outcome
Silverio et al., 2015 [22]	69/M	L inferior frontal lobe to corona radiata	-	Follicular lymphoma treated by rituximab, Pulmonary sarcoidosis	Mefloquine and mirtazapine	2	Some improvement
Kurmann et al., 2015 [37]	56/M	L medial thalamus, hypothalamus, mesencephalon, and tegmentum pontis	-	CVID on IVIg	Mefloquine and mirtazapine	2	Marked improvement

PML, progressive multifocal leukoencephalopathy; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; M, male; F, female; CLL, chronic lymphocytic leukemia; NA, not available; R, right; L, left; IgAN, immunoglobulin A nephropathy; MCP, middle cerebellar peduncle; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; HLH, hemophagocytic lymphohistiocytosis; RRMS, relapse and remitting multiple sclerosis; BG, basal ganglia; WM, white matter; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; s/p, status post operation; CCRT, concurrent chemoradiation therapy; GVHD, graft versus host disease; DM, dermatomyositis; SSc, systemic sclerosis; ET, essential thrombocytopenia; CVID, common variable immune deficiency; IVIg, intravenous immunoglobulin.

the disease progression, and mefloquine treatment was administered.

According to pharmacokinetic studies, the biologic half-life of mycophenolate, prednisolone/methylprednisolone, and intravenous Ig were reported as 9 to 17 hours, 12 to 36 hours, and 14 to 35 days, respectively [38-40]. Since 4 half-lives is usually considered sufficient time to reach the steady state, it seems that the half-lives of the corticosteroid and mycophenolate mofetil are too short and the half-life of intravenous Ig is too long to explain our patient's delayed and prolonged treatment response 1 month after onset. Therefore, with all these confounding factors including other immune-related medication changes, it is reasonable to conclude that mefloquine led to improvement of the PML.

Therefore, physicians can learn two points from this case. A negative CSF JCV PCR does not always rule out PML. Moreover, when PML is clinically highly suspicious and brain biopsy is difficult, a mefloquine trial can be considered as an option.

Conflicts of Interest

Kon Chu has been on the editorial board of *encephalitis* since October 2020. He was not involved in the review process of this case report. No other potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Chu K; Data curation: Yoon S, Chu K; Formal analysis: Yoon S, Chu K; Investigation: Ahn SJ, Kim Y; Writing–original draft: Yoon S; Writing–review and editing: all authors.

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