Renal Replacement Therapy

CASE REPORT

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A case of progressive multifocal leukoencephalopathy in a post-kidney transplant patient with improvement after discontinuation of immunosuppressive drugs and combination therapy with mefloquine and mirtazapine

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Abstract

Background Progressive multifocal leukoencephalopathy is a rare disease, but the prognosis is very poor, especially in the immunosuppressed state with a non-HIV background, and there is no established treatment.

Case presentations A 49-year-old patient who had undergone a renal transplant and was receiving prednisolone and mycophenolate mofetil treatment was admitted for peritoneal dialysis initiation. While hospitalized, he experienced aphasia and other percutaneous symptoms. Magnetic resonance imaging of the brain revealed a subcortical demyelinating lesion. JC virus DNA was identified in cerebrospinal fluid, and he was diagnosed with progressive multifocal leukoencephalopathy. Immunosuppressant was ceased, and he was treated with mefloquine and mirtazapine. The patient subsequently underwent a head MRI scan, confirming lesion reduction, improved activities of daily life, and survival.

Conclusions Progressive multifocal leukoencephalopathy is commonly observed in patients with compromised immune systems, which was the case for this patient due to long-standing immunosuppressive medication usage and end-stage renal failure necessitating dialysis.

Keywords Progressive multifocal leukoencephalopathy, Immunosuppression, Mirtazapine, Mefloquine

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Background

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the reactivation of JC virus (JCV) in individuals with impaired cellular immunity. Various risk factors have been associated with PML, such as human immunodeficiency virus (HIV) infection, hematologic malignancies, autoimmune diseases, and organ transplantation with immunosuppressive therapy. The typical clinical course of PML involves a subacute progression of neurological symptoms leading to a spontaneous rash within a few months [1]. Unfortunately, there is currently no established treatment for this condition, and non-HIV PML patients have a median survival of only 3 months with a very poor prognosis [2, 3].

In this context, we report a case of a patient who suffered from PML and required peritoneal dialysis due to impaired transplant renal function. However, the patient achieved a favorable outcome following the discontinuation of immunosuppressive drugs and a combination therapy with mefloquine and mirtazapine.

Case presentation

The patient is a 49-year-old man who had undergone kidney transplantation with his mother as a donor 30 years ago because of renal failure caused by chronic urinary tract infection due to vesicoureteral reflux disease. He was most recently treated with 5 mg prednisolone and 500 mg mycophenolate mofetil (MMF) per day. However, the patient's renal function gradually declined. Simultaneously, mild memory loss began to appear; however, it did not interfere with his daily life. He was admitted to the hospital for induction of peritoneal dialysis, which was started on the same day. He complained of difficulty speaking and was found to have higher brain dysfunction, mainly aphasia, approximately one week after hospitalization (day 0 of diagnosis).

At the time of diagnosis, his body temperature was 35.8 °C, blood pressure was 120/89 mmHg, pulse rate was 85/min, and oxygen saturation was 99% on room air. Neurological examination revealed disorientation and aphasia, with dysgraphia, dyslexia, and dysarthria. The laboratory data at the time of diagnosis are presented in Table 1. Blood tests showed renal dysfunction due to end-stage renal failure and hypogammaglobulinemia (IgG, 599 mg/dL; normal range: 870–1,700 mg/dL), and the HIV antibody test was negative. Cerebrospinal fluid (CSF) examination showed normal cell count, protein, and glucose levels. Brain magnetic resonance imaging (MRI) showed irregular high-intensity lesions mainly in the subcortical white matter from the left frontal lobe to the temporal lobe in fluid-attenuated inversion recovery

Table 1 Results of laboratory examination at diagnosis of progressive multifocal leukoencephalopathy

Complete blood (cell) count		**Cerebrospinal fluid test**	
WBC	5500/μL	Appearance	Clear
Segmented neutrophils	80%	Cell count	1/μL
Lymphocytes	9.0%	Polymorphs	100%
Monocytes	10%	Protein	43 mg/dL
Eosinophils	1.0%	Glucose	51 mg/L
Hemoglobin	6.7 g/dL	Oligoclonal band	(–)
Platelets	30.8×10^4/μL	Culture	Negative
Biochemistry and infection		JCV DNA quantification	8825 copies/mL
Total Protein	5.3 g/dL		
Albumin	3.0 g/dL		
BUN	54 mg/dL		
Creatinine	4.9 mg/dL		
Glucose	107 mg/dL		
AST	13 U/L		
ALT	8 U/L		
LDH	123 U/L		
CRP	2.12 mg/dL		
IgG	599 mg/dL		
sIL-2R	1845 U/mL		
HIV (Ag/Ab) /CLIA	Negative		

WBC: white blood cell; BUN: blood urea nitrogen; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CRP: C-reactive protein; sIL-2R: soluble interleukin-2 receptor; HIV (Ag/Ab): human immunodeficiency virus (antigen/antibody); JCV: JC virus; DNA: deoxyribonucleic acid

(FLAIR) images (Fig. 1A). PML was suspected based on the clinical course and imaging findings. Later, polymerase chain reaction (PCR) assay for JC virus (JCV) in the CSF yielded positive results (8825 copies/mL), which confirmed the diagnosis of PML.

We discontinued MMF on the day after diagnosis. On the 22nd day after diagnosis, the prednisolone dose was reduced to 4 mg/day. On the 41st day after diagnosis, seizures and right hemiplegia were observed. Brain MRI in FLAIR images showed an edematous expansile lesion (Fig. 1B). On the 46th day after diagnosis, we prescribed mirtazapine (15 mg daily). On the 82nd day after diagnosis, we also prescribed mefloquine (275 mg daily for 3 days, followed by 275 mg once a week), after approval by the hospital committee (approval number FR20210001, date of approval: August 16, 2021). On the 97th day after diagnosis, his CSF JCV DNA PCR was negative, and on the 176th day after diagnosis, brain MRI showed that the lesion had stopped enlarging and was shrinking (Fig. 1C). His activities of daily living were temporarily reduced to the point of requiring wheelchair mobility (Barthel Index 60 out of 100, Lawton Instrumental Activities of Daily Living Scale 1 out of 5). Following treatment, his activities of daily living improved sufficiently for him to walk with a cane (Barthel Index 100 out of 100, Lawton Instrumental Activities of Daily Living Scale 2 out of 5), and his aphasia also improved.

Discussion and conclusions

This report details the case of a patient who developed PML after undergoing renal transplantation and being on peritoneal dialysis. The patient ceased taking immunosuppressive agents and was successfully treated with a combination therapy of mefloquine and mirtazapine. Two significant factors emerged from this case. Firstly, the patient developed PML while experiencing a decline in the transplanted kidney's renal function, necessitating the need for renal replacement therapy. Secondly, following the initiation of mefloquine and mirtazapine treatment and a decrease in the dosage of immunosuppressive drugs, the JCV PCR test of the spinal fluid turned negative, and both the clinical and imaging findings improved.

In this case, both chronic renal failure during the induction phase of dialysis and the use of post-transplant immunosuppressive medications could have contributed to the patient's immunosuppressive state. It is known that renal insufficiency and uremia can impair humoral and cellular immune functions [4]. While PML cases resulting solely from chronic renal failure are uncommon, they have been observed in the past [5, 6]. The incidence of PML in post-transplantation cases is also rare, with a reported occurrence of only 0.027% in patients with kidney transplantation [7].

Blood transfusion frequency before transplant, panel reactive antibody levels exceeding 20%, and the use of anti-rejection medications during the first year are demonstrated as risk factors for PML [7]. In the present case, the transplant took place 30 years ago, and it remains unclear whether these risk factors were present due to the unavailability of his medical records at the time of transplantation.

BK virus nephropathy can cause transplant renal dysfunction and leads to loss of transplant renal function at a high rate. Reactivation of BK virus in urine has been observed in 33–49% of renal transplant recipients, independent of the duration of transplantation [8]. This case was not tested for the presence of BK virus in the urine; therefore, it is unclear whether there was an association between the graft, BK virus, and graft loss. Additionally, the patient's condition at the time prevented a graft kidney biopsy. However, since patient's urine output was relatively well maintained, peritoneal dialysis could be initiated. The treatment for PML consisted of reducing steroids reduction and discontinuing MMF.

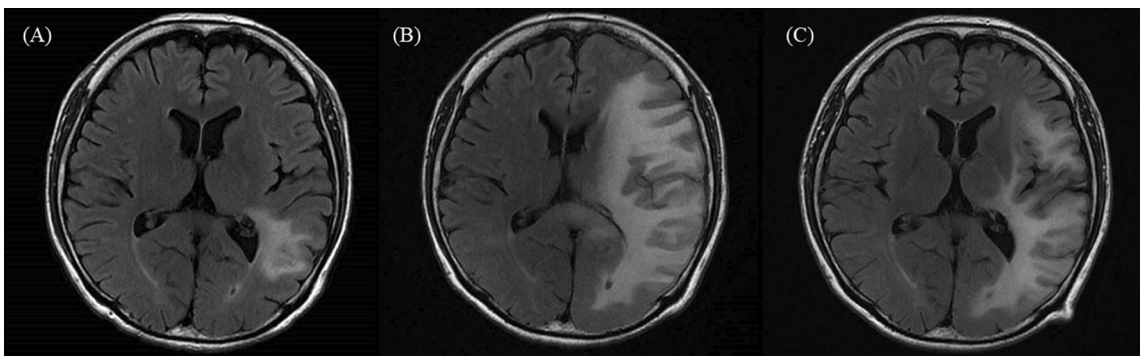

Fig. 1 Magnetic resonance images of the head of the present case. **A** At the time of diagnosis. **B** At onset of seizures 41 days after the diagnosis. **C** 176 days after the diagnosis and 130 days after initiation of the treatment with mirtazapine

This approach aligns with the treatment for BK virus nephropathy, making it plausible that successful outcomes would have been achieved even if the patient had BK virus nephropathy.

Over the last few years, kidney transplants have become increasingly prevalent, with over 20,000 of them being conducted annually in the USA alone. The median graft survival for donated kidney transplants is 11.7 years, while living donor kidney transplants have a median survival rate of 19.2 years. These procedures are typically conducted on patients between the ages of 34 and 54 [9, 10]. As the number of transplants continues to increase worldwide, this case of PML may provide an important insight into the diagnosis of diseases other than uremia and cerebrovascular disease when the patient presents with unexpected neurological symptoms during the induction of dialysis at the time of graft loss.

Presently, immune reconstitution is the only treatment considered effective for non-HIV-PML, and no established therapy exists for this disease. In cases of drug-related PML caused by the use of biological agents or immunosuppressive drugs, reducing or discontinuing the drug and considering plasma exchange are recommended. Non-HIV-PML patients often have favorable outcomes when immunosuppression is reduced [11]. In this case, our patient had a positive outcome, which we attribute to the discontinuation of immunosuppressive drugs.

The inhibitory effects of mefloquine and mirtazapine on JCV are promising, and further studies are needed to confirm their effectiveness as a treatment for PML [12, 13]. In addition, it is important to note that these drugs have potential adverse effects and may interact with other medications, which should be taken into consideration when prescribing them to PML patients. Close monitoring and careful consideration of the risk–benefit ratio are necessary when using these drugs for the treatment of PML.

To the best of our knowledge, 60 cases in 52 studies have been reported in English papers using both mefloquine and mirtazapine for non-HIV-PML (Additional file 1: Table S1) [14–65]. In summary, as for background diseases, 15 cases of multiple sclerosis, 12 cases of hematologic malignancies such as lymphoma, 8 cases of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, 7 cases of sarcoidosis, and 7 cases of immune deficiency have been reported mainly. There was one case of a dialysis patient [15]. It should be noted that patients treated with natalizumab or ocrelizumab for multiple sclerosis have different symptoms and course at the onset of the disease and adjuvant treatment from other background diseases because of the medical behavior of monitoring JCV during the course of the disease [14, 25, 27, 32, 35, 37, 38, 42, 49, 60]. The range of onset age was 19–85 years. Regarding the time from the onset of background disease to the diagnosis of PML, the longest period was 40 years in a case of Takayasu arteritis; however, many reports do not specify this time [22]. There have been reports of a wide variety of initial symptoms, including asymptomatic cases with neurological disease in the background and incidentally detected cases as well as cases with motor disturbance, headache, visual disturbance, and amnesia as the initial symptoms. In most cases, immunosuppressive drugs and other drugs used for the background disease were discontinued. Dose of mefloquine and mirtazapine were prescribed in the range of 250–375 mg/week and 15–60 mg/day, respectively. Most reports did not report or reported no side effects, but pancytopenia was reported in one case and hepatotoxicity in one case [38, 44]. Regarding prognosis, 37 patients reported improvement or survival of more than one year and 13 reported mortalities of less than one year. Considering that the reported median survival for PML with non-HIV background disease is three months, these medications may be effective, but the possibility of publication bias in reporting cannot be denied; therefore, it is possible that early deaths were not reported.

We reported a case study of a patient who developed PML after experiencing graft loss and requiring peritoneal dialysis. Thankfully, the discontinuation of immunosuppressive drugs and a combination therapy of mefloquine and mirtazapine resulted in long-term survival for the patient. As renal transplant recipients will inevitably experience graft loss, it is crucial to remain vigilant for the development of PML during the course of the disease and when dialysis is required again. Treatment, including the use of mefloquine and mirtazapine, should be initiated promptly upon the onset of PML.

Abbreviations

DNA	Deoxyribonucleic acid
MRI	Magnetic resonance imaging
PML	Progressive multifocal leukoencephalopathy
JCV	JC virus
HIV	Human immunodeficiency virus
MMF	Mycophenolate mofetil
CSF	Cerebrospinal fluid
PCR	Polymerase chain reaction

Supplementary Information

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Additional file 1: Table S1. Summary of case reports treated with mefloquine and mirtazabine for non-HIV progressive multifocal leukoencephalopathy.

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Availability of data and materials
The datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This single case report was ethically approved by the institutional research board at Showa University (IRB approval number CR2023005-B).

Consent for publication
Informed consent for publication was obtained from the patient and his family included in the study.

Competing interests
The authors declare that they have no competing interests.

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