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CASE REPORT

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# Combination of low-dose, long-term immunoglobulin and mirtazapine is effective in progressive multifocal leukoencephalopathy caused by JC virus infection

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## Abstract

**Background** Progressive multifocal leukoencephalopathy (PML) is an often fatal disease of the central nervous system caused by opportunistic infection of John Cunningham Polyomavirus (JCV). There's still no antiviral therapeutic strategy which was generally recognized as effective. The prognosis may differ in patients with different pathological mechanisms and treatments. We aim to report the effectiveness of combined treatment of low-dose, long-term immunoglobulin and mirtazapine in a pathologically proved PML case.

**Case presentation** A patient presented with progressive acalculia, right-left confusion and visual neglection was recorded. She received 10-year immunosuppressive therapy for dermatomyositis. White matter lesions located in bilateral parietal lobe and callosum area symmetrically in MR scanning. JC virus analysis and brain biopsy in left parietal lobe were performed. The number of JCV copies was 2595 in CSF and 282,809 in brain specimen. Abundant foamy macrophages and the lymphatic cells were obvious in immunohistochemistry staining. Few SV-40 positive JC infected cell and more CD4 + and CD68 + cells were predominant. Immunosuppressive drugs were terminated after being diagnosed as PML for positive JCV and pathological characteristics. In addition, immunoglobulin (5 g/day) and mirtazapine (45 mg/day) were used. JC virus in CSF decreased to 0 after treatment for 4 months and was still negative in June 2023. The clinical symptoms improved, and white matter lesions recovered significantly.

**Conclusions** We demonstrated that the combination treatment of IVIG and mirtazapine was effective in PML. Low-dose, long-term immunoglobulin might regulate the immune status in our case with controlled inflammatory reaction instead of destructive virus spreading. The therapy may be a prospective option for PML.

**Keywords** Progressive multifocal leukoencephalopathy, JC Polyomavirus, Immune reconstitution, IVIG, Methotrexate

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## Background

Progressive multifocal leukoencephalopathy (PML) is a rare, debilitating and often fatal disease of the central nervous system. It is an opportunistic infection caused by John Cunningham Polyomavirus (JCV) in patients with severe immunosuppressive status or undergoing immunotherapy [1]. Drug-associated immunosuppression can also trigger PML. The medication classes suspected of initiating PML include antineoplastic agents, immunosuppressants (such as methotrexate), and corticosteroids [2]. Human immunodeficiency virus (HIV) infection has accounted for the vast majority of PML cases (~80%) in the published manuscript. PML also developed in patients with hematological malignancy, with identifiable immunosuppressed state, being treated with MS disease-modifying drug (like natalizumab and rituximab) and some more rare autoimmune diseases as polymyositis/dermatomyositis (PM/DM). Among the few reports of PM/DM related PML, 7 patients died while 3 patients improved [3]. There's still no antiviral therapy available for JCV infection or PML, and survival depends on immune reconstitution [4]. Controlled inflammatory response is necessary for good prognosis while overreaction of inflammation is destructive during immune reconstitution [4, 5]. Here, we reported the effectiveness of combined treatment of low-dose, long-term immunoglobulin (IVIG) and mirtazapine in a case that was diagnosed as PML.

## Case presentation

A 45-year-old female presented to our hospital on May 23rd, 2022, with progressive acalculia, right-left confusion and visual neglection for over one month. She regularly received immunosuppressive therapy (prednisone 5-40 mg/ Qd, methotrexate 10 mg Qw and hydroxychloroquine 0.2 mg Bid) for 10 years and a short period of thalidomide for treatment of amyopathic dermatomyositis with TIF1γ IgG (+). At the time of presentation, the patient was on methylprednisolone (MP) 8 mg qd and hydroxychloroquine 0.1 g bid. Gerstmann syndrome, memory impairment and bilateral agnosia were significant with Montreal cognitive assessment (MoCA) score of 10. HIV was negative. Lymphopenia was noted with the decreased absolute lymphocyte count of 530/ ul (normal: 1000–3300) and a preserved CD4/CD8 ratio of 3.9. The initial pressure of lumbar puncture was 210 mm$H_2O$. Cerebrospinal fluid (CSF) analyses were in normal ranges. Lesions in bilateral cerebral white matter, white-gray matter junction of parietal lobe and corpus callosum were predominant in cranial magnetic resonance imaging (MRI). Hypointensity on T1-weighted images, hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, hypointensity in the center part and slightly high intensity at the peripheral region on diffusion-weighted image (DWI), and no enhancement on post-gadolinium T1-weighted images. The enhancement around the periphery of lesions became prominent after treatment for about 4 months in Nov. 2022 and returned to no-enhancement in the 1-year follow up in June 2023 (Fig. 1). Positron emission tomography with computed tomography (PET/CT) showed no evidence for tumor. Her symptoms still worsened, and the lesions expanded after treating with MP 1000 mg qd and IVIG 20 g qd for 5 days.

We sent CSF and brain specimen for metagenomics next generation sequencing (mNGS) analysis for pathogens. The DNA was extracted and purified from CSF supernatant and brain specimen. The DNA libraries was constructed using QIAseq™ Ultralow Input Library Kit. The concentration and quality of libraries were checked using Qubit and agarose gel electrophoresis. Qualified libraries with different barcode labeling were pooled together, and then sequenced on an Illumina Nextseq platform.

The mNGS analysis was performed to detect pathogens. The result revealed a high load of JC virus with the specific sequence copy of 2595 in CSF and 282,809 in brain specimen. Whole Exome Sequencing for genetic disease genes results were negative.

Brain biopsy was performed in white matter of left parietal lobe for definitive diagnosis. One portion of the obtained specimen was sent for mNGS testing. Another portion was fixed using 10% formalin and was embedded using paraffin, followed by hematoxylin-eosin (HE) staining and immunohistochemistry. The third portion was fixed using 2.5% pentodialdehyde and was embedded for electron microscopy. Immunochemistry staining showed abundant CD4 positive T cells (Fig. 2A) and few CD8 positive T cells (Fig. 2B). CD68 positive macrophages were predominant (Fig. 2C). More importantly, scattered SV40 positive cells were detected by immunochemistry staining (Fig. 2D). Electron microscope, hematoxylin-eosin (HE) staining and immunohistochemistry were performed of the biopsy brain tissue. Electron microscopy showed typical icosahedral viral particles in the intranuclear inclusion bodies (Fig. 2E). Microscopically / histologically, the brain biopsy showed abundant foamy macrophages cells and perivascular cuffs of lymphocytes (Fig. 2F). Finally, the diagnosis of PML was made and the pathological results demonstrated the etiology of inflammatory.

Immunosuppressive drugs were terminated after diagnosis. In addition, low dose IVIG (5 g/day) and mirtazapine (45 mg/day) were used. The combined treatment resulted in a clinical stabilization at 1 year after diagnosis. The CSF JCV decreased to negative after treatment for 4 months and was still negative during the last follow up in June 2023. Area of lesions reduced significantly,

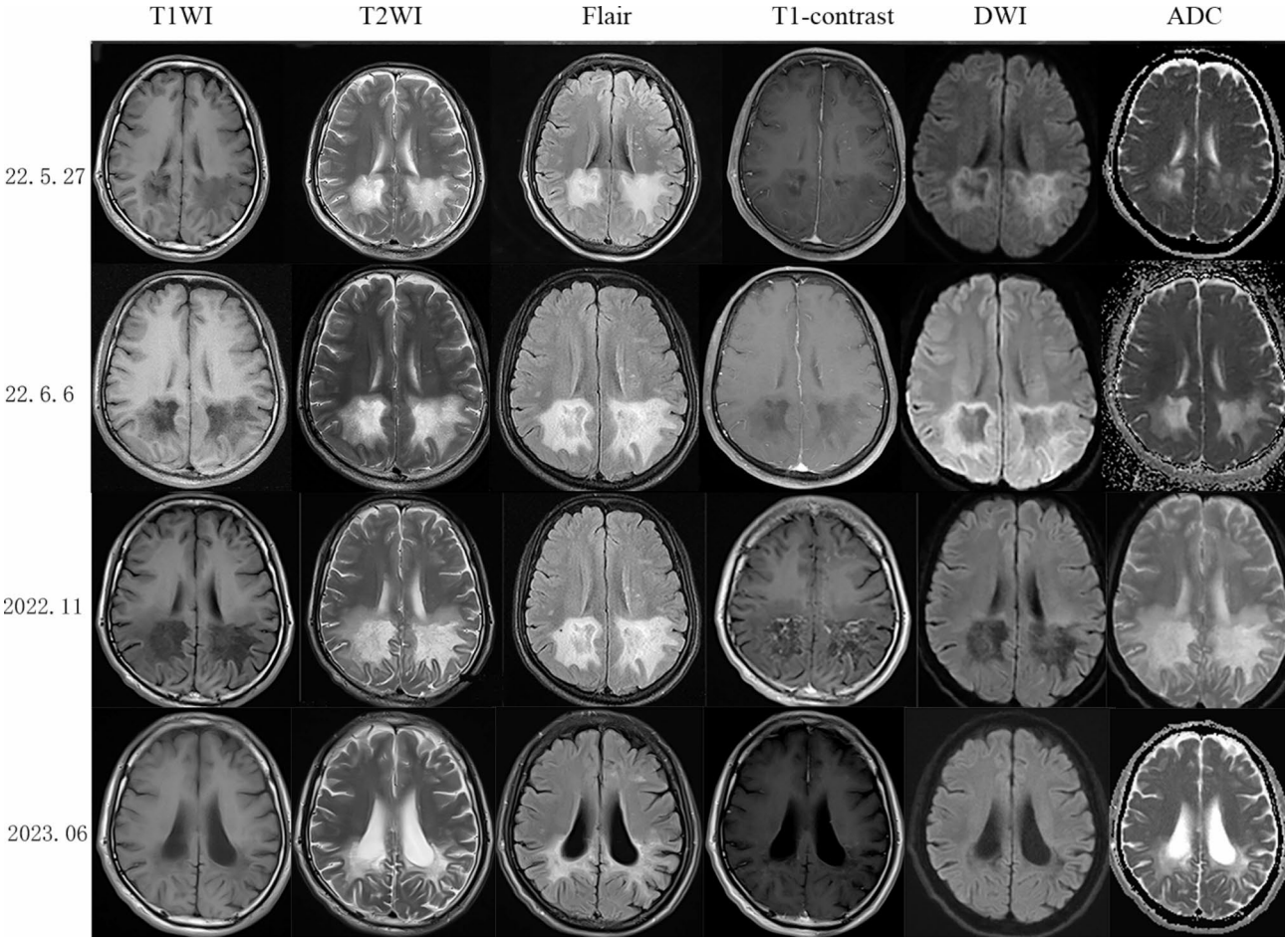


**Fig. 1** The evolution process of white matter lesions on MR scan. We present the results of various MR sequences including T1, T2, fluid-attenuated inversion recovery (FLAIR) , T1-contrast, diffusion-weighted image (DWI) and apparent diffusion coefficient (ADC) from 1 month after onset to 1 year after diagnosis. The lesions locate in bilateral white mater parietal lobe and callosum symmetrically. There's no enhancement on T1-contrast imaging initially. The lesions expanded to the largest range and the white-gray matter junction was involved with scattered enhancement in the edge in Nov 2022. Area of lesions reduced significantly, and the enhancement vanished in Jun 2023. In addition, bilateral lateral ventricle in June 2023 was obvious larger than the previous scanning

and the enhancement vanished in Jun 2023. The clinical symptoms improved significantly (MoCA 10 to 17). The improvement of MoCA reflected in visuospatial/executive functioning (+2), attention (+3), and delayed recall (+2). In addition, the patients can discriminate right from left, walk steadily without agnosia and read more fluently. The ability of calculation also improved and the patient can communicate with others essentially normally. The rash caused by the amyopathic dermatomyositis was also stable.

## Discussion and conclusions

We reported a PML patient who recovered clinically with radiological improvement and JC virus declination after combination treatment of low-dose, long-term IVIG and mirtazapine. These improvements were stable in the 1-year follow-up after diagnosis. The PML case was characteristic of inflammatory reaction after JC infection which was proved by the pathological result. The long-period use of immunosuppressants (MTX and hydroxychloroquine) and MP in our case might lead to immunosuppression condition as a casual etiology of PML. In the previously reported PML cases who took MTX regularly for therapy of rheumatic diseases before onset, the treatment of PML was not specific, and the survival period was less than 9 months [6, 7]. In addition, steroid-induced PML was also reported and it was suggested that prescribers and patients should be informed of the potential associations with corticosteroids, antineoplastic agents, immunosuppressant drugs and PML [2].

The negative enhancement in MR scan on admission might be explained by the immunosuppressive condition. The appearance of few enhancements around lesions after treatment may indicate the inflammatory response after immune reconstitution when the copy of CSF JC

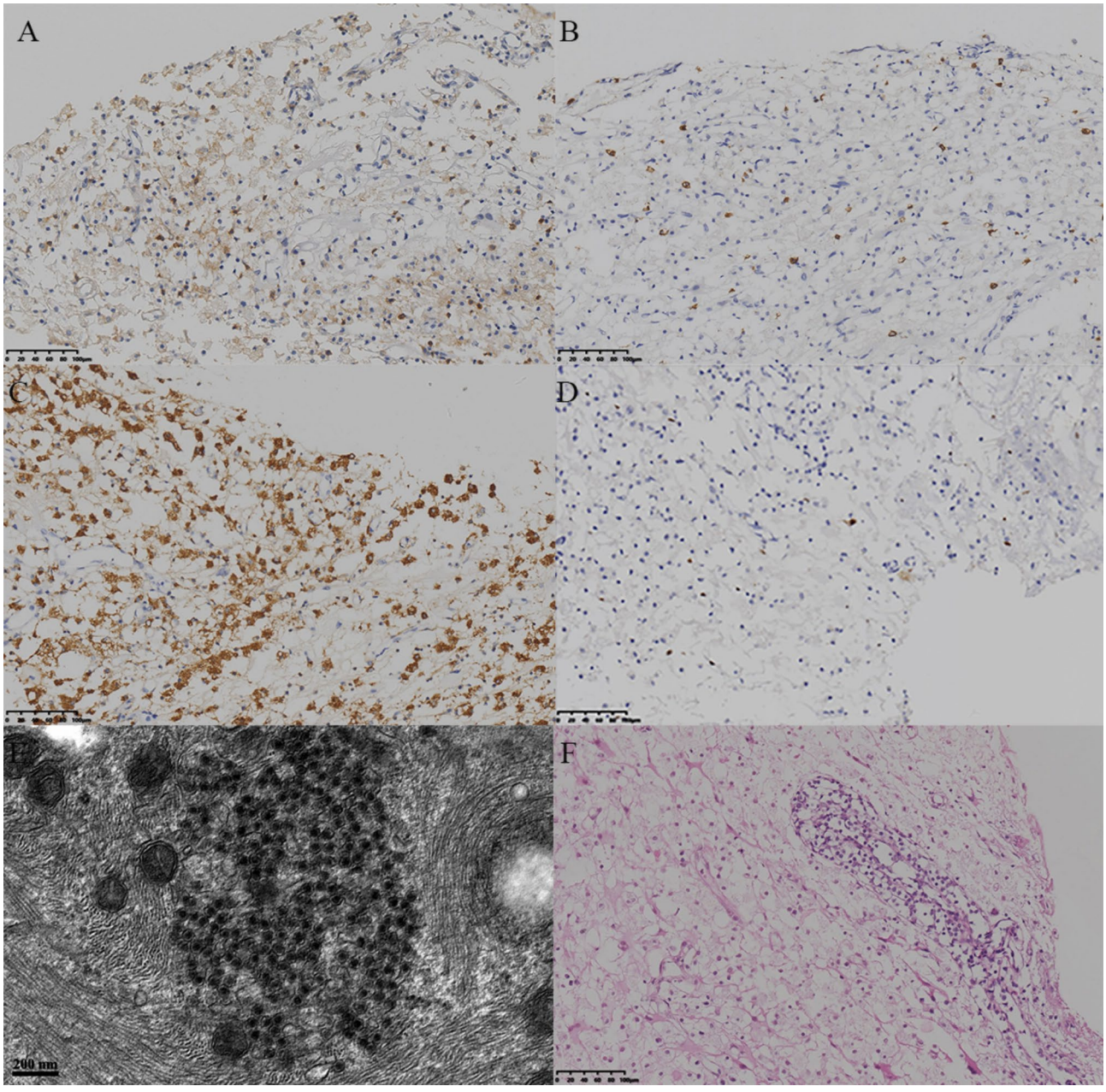


**Fig. 2** Immunohistochemistry of inflammation associated cells and JC virus. **A** Immunohistochemistry staining showed significantly grown number of CD4 + T cells; **B**. Slightly increased number of CD8 + T cell were also shown; **C**. abundant CD68 positive macrophages were predominant; **D**. Immunohistochemistry with monoclonal antibody against SV40 Large T antigen (dilution of 1:100) detects intranuclear accumulation (brown), demonstrating diagnosis of polyoma virus infection; **E**. Icosahedral viral particles in the intranuclear inclusion bodies by electron microscopy; **F**. Abundant foamy macrophages and perivascular lymphocytes were shown on by HE staining

virus reduced to zero [8]. Meanwhile, it returned to no enhancement status in the 1-year follow-up showing the relative immunologically balanced state. The lower number of SV40 positive (JC virus infected) cells and the predominant inflammatory infiltration proved by the predominant CD4+T cells and CD68+macrophages of our case suggested the case is different from classical PML which is catastrophic [9]. The pathological manifestation may differ between HIV-associated classical PML and drug (such as MTX and MP)- associated PML. Macrophages swallowed the lipid droplets which is the product of myelin sheath disintegration and formed abundant foamy cells in our case. Accordingly, the expression of CD68+cells which locate in the lysosome of macrophages were significantly abundant. It was different from the previously reported inflammatory PML cases which indicating predominant CD138+plasma cell [4]. The fatal overshooting immune response is mainly mediated

by predominant cytotoxic CD8+T cell while the appearance of CD8+T cell is also the sign of recovery [10]. The slightly increased CD8+T cell in brain parenchyma and preserved peripheral CD4+/CD8+T cell ratio of the case portended the good prognosis.

Up to now, two therapeutic strategies of PML have been investigated: direct anti viral therapies and indirect strategies designed to restore antiviral immune responses [1]. The antiviral therapeutic agents included nucleoside analogues cytarabine and cidofovir, topoisomerase inhibitor topotecan, 5-HT2A receptor antagonist mirtazapine, and antimalarial agent mefloquine. Their effect on prolonging survival or reducing neurological disability was still a challenge [1, 11]. The indirect strategies were designed to restore antiviral immune responses, including combination antiretroviral therapy (cART) in HIV-related PML, plasma exchange or immunoadsorption in natalizumab-related PML, IVIG, recombinant IL-2, filgrastim, IL-7 as monotherapy, and innovative strategies include T-cell adoptive transfer or immune checkpoint inhibitor therapies [1, 11]. There's still no specific treatment strategy for drug-associated PML such as MTX and MP. Immune reconstruction in a balanced way is the effective strategy while over-reaction might cause destructive inflammatory reconstitution syndrome (IRIS) [1].

Combination of mirtazapine (45 mg/d) and low-dose intravenous IVIG (5 g/d) was effective in our case. Recently, a HIV-associated PML patient was reported to respond to the combination treatment of Mirtazapine and intravenous IVIG together with anti- retroviral treatment of HIV for 6 months and have a good prognosis [12]. The treatment of IVIG was used at 400 mg/kg every day to every week to every month but there's no pathological result. In addition, IVIG at dosage of 300-2,000 mg/kg every 3–4 wk was proved to be effective in 2/9 patients in a study of 91 PML patients [13]. Mirtazapine was effective in 11/34 patients in the same cohort (patients may have received multiple therapies). Mirtazapine as a $5HT_{2A}$ antagonist was proved to blockade 5HT2A receptors and inhibit infection of oligodendrocytes by JC virus in-vitro [14]. The positive effect of Mirtazapine was reported in several cases but without clinical research [1, 2, 5, 6]. High dose of IVIG elicits anti-inflammatory effects while it may innate immune effect cells at low-dose [15]. For the treatment of patients with autoimmune diseases, IVIG was frequently used at high dose (2,000 mg/kg, usually divided into two to five separate days) monthly for several months. However, we used IVIG at low dosage of 500 mg/d for its immune-modularization effects in PML. IVIG is also relevant treatment option for PM and DM.

## Conclusions

Biopsy is helpful for the diagnosis, etiology, and treatment of PML patient. The combination treatment of low-dose, long-term IVIG and mirtazapine might be associated with a favorable outcome in PML patients with characteristic of controlled inflammatory reaction instead of destructive virus spreading.

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#### Author contributions

JJL analyzed and interpreted the patient data. Bing L analyzed the pathological results. Zhiyun Yang collected and described the imaging characteristics. Jian Zhang, Yuhua Fan and Shihui Xing collected clinical data in the follow-up and analyzed the NGS results. JSZ was a major contributor in guiding the project and revising the manuscript. All authors read and approved the final manuscript.

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#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

#### Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the first affiliated hospital of Sun Yat-sen University (No. [2023]669).

#### Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/participant.

#### Competing interests

The authors declare no competing interests.

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#### References

1. Cortese I, Reich DS, Nath A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol. 2021;17:37–51.
2. Colin O, Favrelière S, Quillet A, Neau JP, Houeto JL, Lafay-Chebassier C, et al. French Pharmacovigilance Network. Drug-induced progressive multifocal leukoencephalopathy: a case/ noncase study in the French pharmacovigilance database. Fundam Clin Pharmacol. 2017;31(2):237–44.
3. Vulliemoz S, Lurati-Ruiz F, Borruat FX, Delavelle J, Koralnik IJ, Kuntzer T, et al. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. J Neurol Neurosurg Psychiatry. 2006;77:1079–82.
4. Sanjo N, Nose Y, Shishido-Hara Y, Mizutani S, Sekijima Y, Aizawa H, et al. A controlled inflammation and a regulatory immune system are associated with more favorable prognosis of progressive multifocal leukoencephalopathy. J Neurol. 2019;266:369–77.
5. Wattjes MP, Wijburg MT, van Eijk J, Frequin S, Uitdehaag BMJ, Barkhof F, et al. Inflammatory natalizumab-associated PML: baseline characteristics, lesion evolution and relation with PML-IRIS. J Neurol Neurosurg Psychiatry. 2018;89:535–41.

6. Dastmalchi M, Laki J, Lundberg IE, Iacobaeus E. Progressive multifocal leukoencephalopathy in a patient with polymyositis: case report and literature review. J Rheumatol. 2012;39:1299–303.
7. Calabrese LH, Molloy ES, Huang D, Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum. 2007;56(7):2116–28.
8. Küker W, Mader I, Nägele T, Uhl M, Adolph C, Klose U, et al. Progressive multifocal leukoencephalopathy: value of diffusion-weighted and contrast-enhanced magnetic resonance imaging for diagnosis and treatment control. Eur J Neurol. 2006;13:819–26.
9. Baldassari LE, Wattjes MP, Cortese ICM, Gass A, Metz I, Yousry T, et al. The neuroradiology of progressive multifocal leukoencephalopathy: a clinical trial perspective. Brain. 2022;145:426–40.
10. Martin-Blondel G, Bauer J, Cuvinciuc V, Uro-Coste E, Debard A, Massip P, et al. In situ evidence of JC virus control by CD8 + T cells in PML-IRIS during HIV infection. Neurology. 2013;81:964–70.
11. Schweitzer F, Laurent S, Cortese I, Fink GR, Silling S, Skripuletz T, et al. Progressive Multifocal Leukoencephalopathy: Pathogenesis, Diagnostic tools, and potential biomarkers of response to Therapy. Neurology. 2023;101(16):700–13.
12. Cifci B, Yildiz Y, Altin E, Habibi H, Kocer B, Dizbay M. Successful treatment of HIV-associated progressive multifocal leukoencephalopathy (PML) with mirtazapine, mefloquine, and IVIG combination therapy: a case report. J Neurovirol. 2023;29:111–5.
13. Anand P, Hotan GC, Vogel A, Venna N, Mateen FJ. Progressive multifocal leukoencephalopathy: a 25-year retrospective cohort study. Neurol Neuroimmunol Neuroinflamm. 2019;6(6):e618.
14. Elphick GF, Querbes W, Jordan JA, Gee GV, Eash S, Manley K, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. Science. 2004;306:1380–83.
15. Velikova T, Sekulovski M, Bogdanova S, Vasilev G, Peshevska-Sekulovska M, Miteva D, et al. Intravenous immunoglobulins as Immunomodulators in Autoimmune diseases and Reproductive Medicine. Antibodies (Basel). 2023;12(1):20.

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