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CASE REPORT

Successful treatment of HIV-associated progressive multifocal leukoencephalopathy (PML) with mirtazapine, mefloquine, and IVIG combination therapy: a case report

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system caused by reactivation of the polyomavirus JC (JCV). Human immunodeficiency virus (HIV) infection is one of the leading causes of PML which has high morbidity and mortality due to the lack of a proven standard treatment. We found clinical and radiological improvement with the combination of high-dose methylprednisolone, mirtazapine, mefloquine, and IVIG in our patient who presented with neurological symptoms and had diagnosed concurrent acquired immunodeficiency syndrome (AIDS) and PML. To our knowledge, our case is the first HIV-associated PML which responded to this combination therapy.

Keywords HIV · IVIG · JC virus · Mefloquine · Mirtazapine · Progressive multifocal leukoencephalopathy

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system, which is caused by reactivation of the John Cunningham virus (JCV) of polyomaviridae, with high morbidity and mortality. Primer JCV infection occurs in childhood, and the likely modes of transmission are the respiratory tract and the oral route (Kartau et al. 2019). JCV seroprevalence in the population is 50–80% (Bauer et al. 2015). Mostly, JCV remains latent in kidney epithelial cells, bone marrow, spleen, lymph nodes, and lymphocytes (Kartau et al. 2019); in the course of severe cellular immunodeficiency like hematological malignancies, organ transplantation, acquired immunodeficiency syndrome, autoimmune diseases,13 use of immunomodulators (etc. natalizumab in MS), or immunosuppressive agents, opportunistic infection occurs via reactivation (Cortese et al. 2021; Bellizzi et al. 2012). PML was first described in a few cases with hematological malignancies in 1958 (Astrom et al. 1958), and the first human immunodeficiency virus (HIV)-associated PML case was reported in 1982 (Miller et al. 1982). Since 1984, the incidence of PML has increased along with the incidence of HIV, and with the widespread use of antiretroviral therapies (ART), the incidence of HIV-associated PML and mortality rates due to PML have decreased (Engsig et al. 2009). However, HIV infection with CD4 + T cell counts < 100 cells/mm^3 still remains the leading cause of PML (Kartau et al. 2019).

According to the PML diagnostic criteria of the American Academy of Neurology (AAN), it is defined based on clinical (cognitive and behavioral disorders, sensorimotor deficits, hemianopsia, ataxia, and seizures), radiological (hyperintense lesions on T2/FLAIR sections at the cerebral white–gray matter junction, without significant contrast enhancement, and with a mild mass effect) and virological evidence and is classified as definite, probable and possible PML (Berger et al. 2013). Although the definitive diagnosis is made by histopathology, since this method requires invasive intervention, cases with clinically and radiologically suspected PML and with JCV DNA detected in cerebrospinal fluid (CSF) examinations are considered as definitive PML (Berger et al. 2013).

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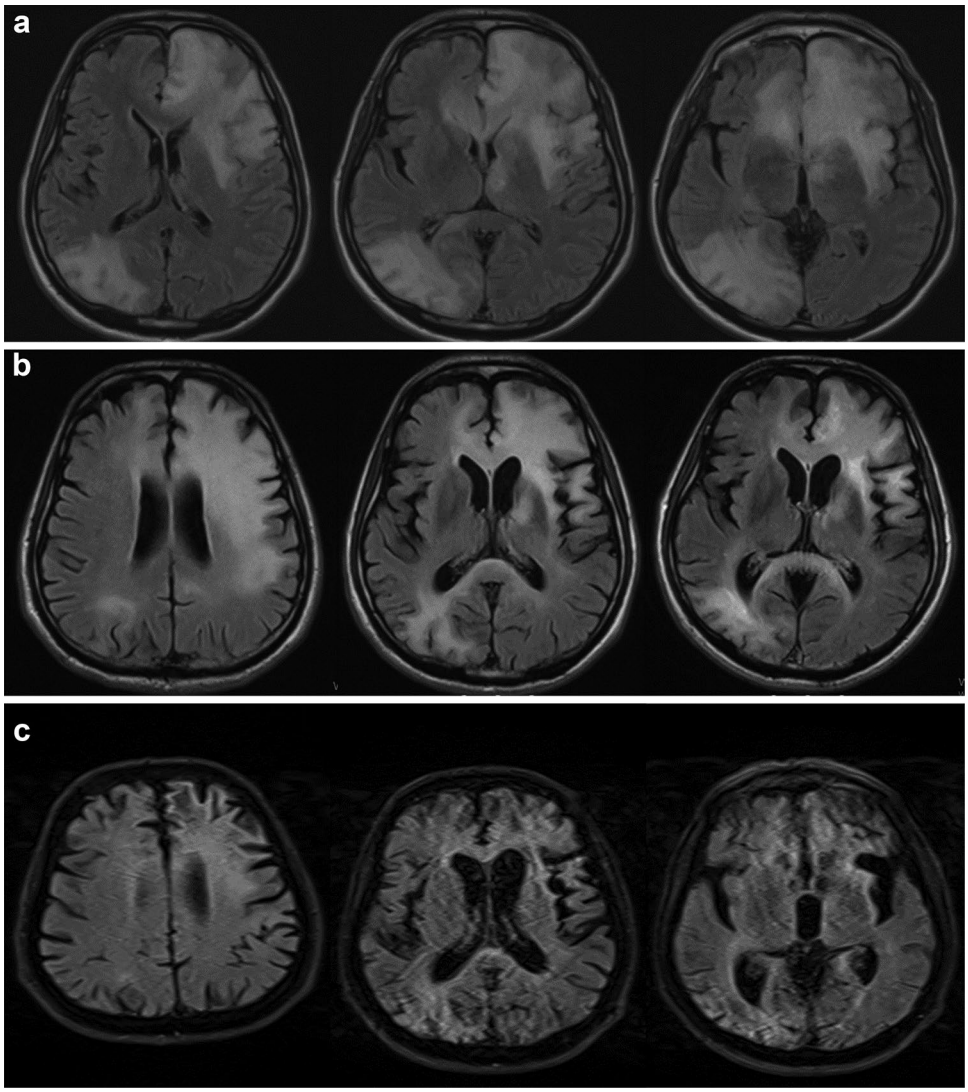


Fig. 1 **a** Cranial MRI findings on the admission day to hospital (12.03.2021). Signal increase in FLAIR sections with no contrast enhancement in bilateral frontal and right parietooccipital regions, millimetric cystic focal vacuolized areas in white matter, and diffusion restriction in cortical regions in the described areas. **b** Follow-up cranial MRI findings on the 3rd month of the treatment (07.06.2021). **c** Follow-up cranial MRI findings on the 6th month of the treatment (20.09.2021). Significant regression observed in large lesions in the left frontal and right parietoccipital regions (hyperintense areas in the FLAIR sequence), while no newly developed lesions detected. However, ventricular enlargement, sulcal prominence, and global atrophy were observed

We aimed to share our treatment success with the combination of high-dose methylprednisolone, mirtazapine, mefloquine, and IVIG; to our knowledge, this is the first HIV-associated PML case who responded to this combination.

Case report

A 58-year-old male without known chronic disease was admitted to emergency department with complaints of decreased oral intake, weight loss, and amnesia in the last 6 months; newly developed confusion; and visual hallucinations described by his relatives. On his initial examination, the patient had urinary-fecal incontinence, global aphasia, and cachexia, in addition to disorientation and limited cooperation. Cranial MRI was performed (Fig. 1a).

As he had cachexia and pancytopenia, during the investigation of the etiology, anti-HIV positivity was detected and confirmed. Since the patient was newly diagnosed with AIDS and had neurological signs and symptoms, lumbar puncture (LP) was performed with the preliminary diagnoses of PML, chronic meningitis, and encephalitis. The test results of the CSF examination and the laboratory results are summarized in Table 1. When the clinical signs, laboratory, and radiological findings were evaluated, he was diagnosed with definitive according to diagnostic criteria of the AAN (Berger et al. 2013).

The patient was started on ART and cotrimaxasol prophylaxis. For the treatment of PML, mefloquine, mirtazapine, i.v. methylprednisolone, and IVIG after pulse steroid were planned and implemented. Dose and duration of all treatments are presented in the timeline (Fig. 2).

At the follow-up examination, 1 month later, he was conscious, cooperative with simple commands, but his motor aphasia had continued. HIV RNA PCR was detected as 50 copies/ml and CD4: 87 cells/mm^3. Follow-up cranial MRI was planned for the patient at 3rd month (Fig. 1b) and 6th

Table 1 Laboratory and cerebrospinal fluid test results

Laboratory test results	
Anti-Toxoplazma lgG	Positive
Anti-Toxoplazma lgM	Negative
Anti-Rubella lgG	Negative
Anti-CMV IgM	Negative
Anti-CMV lgG	> 500 Positive
CMV PCR	Negative
HSV-I IgG	Positive
HSV-II IgG	Negative
Borrelia lgM	Negative
Borrelia lgG	Negative
Brucella tube agglutination	Negative
RPR-VDRL	Negative
TPHA	Negative
FTA-ABS IgM (FTA-ABS)	Negative
FTA-ABS IgG (FTA-ABS)	Negative
Interferon gamma release assay test (IGRA)	Negative
HIV RNA PCR	1,575,000 copies/ml
CD4	76 cells/mm^3
CD8	543 cells/mm^3
CD4/CD8	0.14
CSF test results	
Cell count	99 leukocyte (%95 polymorphonuclear)
Biochemıstry	Lactate dehydrogenase (LDH) — < 25 U/L Glucose — 58.3 Mg/Dl Protein — 70.63 Mg/Dl
Ziehl–Neelsen staining, Tuberculosıs Culture, Tuberculosis PCR	Negative
HSV-I PCR and HSV-II PCR	Negative
Meningoencephalitis Multiplex PCR	Negative
VDRL-RPR	Negative
CSF Culture	Negative
JC virus PCR	**Positive (850 copy /ml)**
Cryptococcus neoformans Antigen	Negative*

*Meningoencephalitis Multiplex PCR (Escherichia coli K1, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Cytomegalovirus(CMV), Enterovirus, Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), Human herpesvirus 6 (HHV-6), Human parechovirus, Varicella zoster virüs (VZV), Cryptococcus neoformans/gattii)

month (Fig. 1c) of the treatment, and his cranial MRI findings were significantly improved.

Discussion

Although there is no proven and standard treatment for PML, case reports and clinical studies in the literature have reported monotherapy or combination regimens of agents like mirtazapine, mefloquine, cidofovir, recombinant interleukin-7, interferon alpha, IVIG, and methylprednisolone for the treatment of PML, as in our case (Graf et al. 2021; Vulliemoz et al. 2006; Owczarczyk et al. 2007; Moenster et al. 2012; Soleimani-Meigooni et al. 2017).

JCV infection in oligodendrocytes is dependent on the serotonin 5HT2A receptor; therefore, 5HT2A antagonists such as mirtazapine may be effective in the treatment of PML. Clinical and radiological improvement was achieved at the 7th month of ART and mirtazapine treatment in a 20-year-old patient followed up with HIV-related PML (Mullins et al. 2018). In addition, immunosuppressive therapy–related PML cases which responded to combination of mirtazapine with another agent like cytarabine, cidofovir, or interferon alfa were reported (Vulliemoz et al. 2006; Owczarczyk et al. 2007).

Brickelmaier et al. showed mefloquine, an antimalarial agent, inhibited the replication of JCV in an in vitro study (Brickelmaier et al. 2009), but it was found to be insufficient for the treatment of

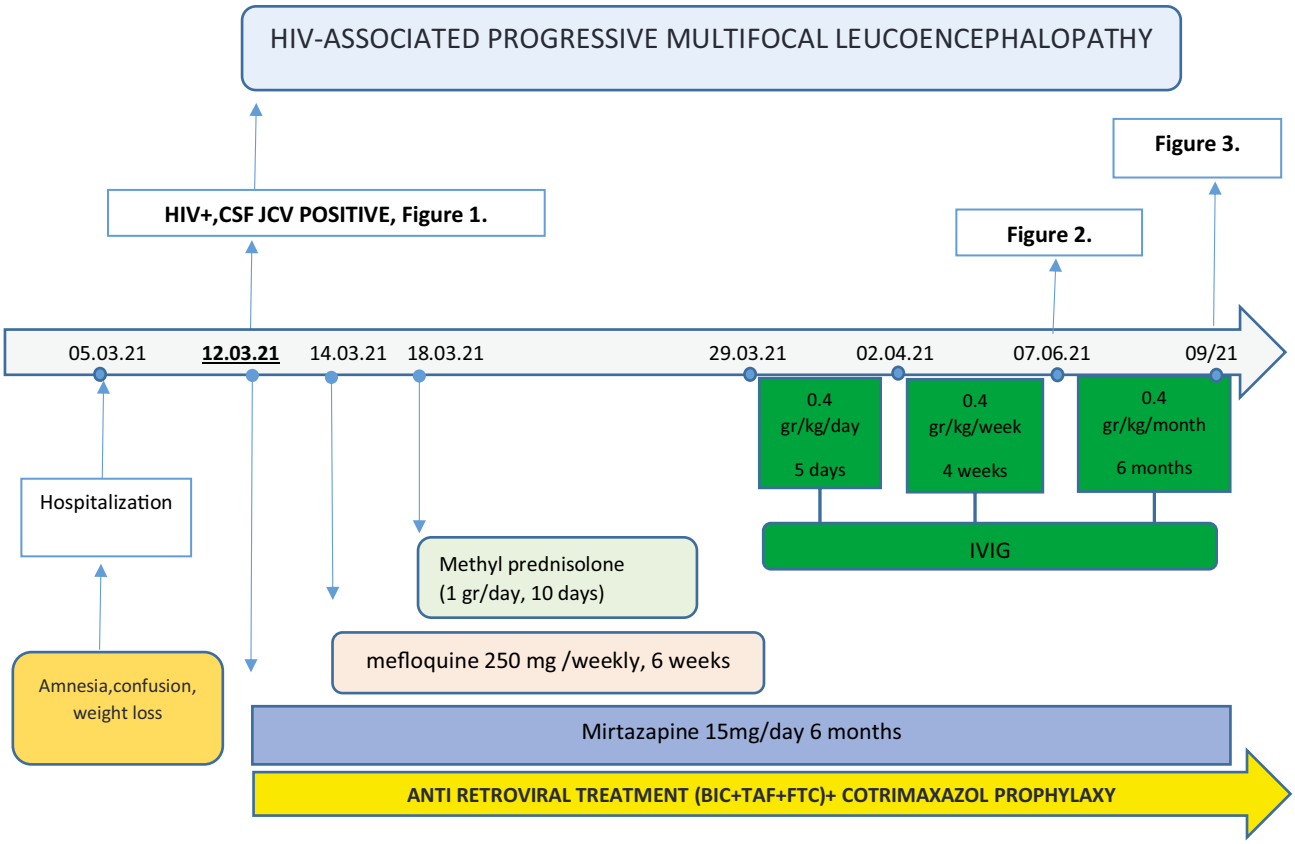


Fig. 2 Timeline

PML in reducing CSF JCV DNA in a randomized study and the study was terminated early (Clifford et al. 2013). An idiopathic CD4 lymphopenia–associated PML case clinically improved with mirtazapine and mefloquine combination treatment (Nambirajan et al. 2017). Tacrolimus-related PML was detected in a 68-year-old male patient followed up with a diagnosis of lupus, and clinical improvement was demonstrated, and JCV DNA became negative in the CSF with 6 months of mirtazapine and mefloquine treatment (Hamaguchi et al. 2020).

IVIG was successfully used in cases of thymoma-associated PML, while the surveillance rates were reported to be higher with the IVIG + mirtazapine combination, then IVIG alone (Cortese et al. 2021). JC granule cell neuropathy (JCV-GCN) was detected in a patient who was followed up with iatrogenic lymphopenia and presented with ataxia. After the treatment of mirtazapine, mefloquine, IVIG, high-dose methylprednisolone, and recombinant IL-7, the patient's ataxia and CSF findings improved (Soleimani-Meigooni et al. 2017).

We found clinical and radiological improvement in a HIV-related PML case with the treatment of high-dose methylprednisolone, mirtazapine, mefloquine, and IVIG, addition to HAART, in the 6th month of diagnosis. Our case is the first HIV-associated PML which responded to this combination. PML should be kept in mind in the differential diagnosis of patients with neurological signs and symptoms due to the increasing use of mAbs, widespread use of organ transplantation, and in the HIV pandemic era. Furthermore, in vitro and randomized studies and also new drugs are needed for the treatment of PML.

Author contribution All authors contributed to study conception and design. BC and YY collected the data. BC, YY, EA, and HH wrote the first manuscript draft. All authors were involved in the care of the patient. All authors participated in the interpretation of the data. All authors read and approved the final manuscript.

Data availability The data associated with the paper are not publicly available but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval No ethics committee approval was needed.

Conflict of interest The authors declare no competing interests.

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