Mirtazapine and Mefloquine Therapy for Non–AIDS-Related Progressive Multifocal Leukoencephalopathy

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the human nervous system caused by the JC virus. We report what is, to the best of our knowledge, the second reported case using a combination of mefloquine and mirtazapine in a patient with non–AIDS-related PML with a good clinical outcome. Conversely, the recent trial of mefloquine in 21 patients with AIDS and 3 without AIDS failed to show a reduction of JC viral DNA levels in the cerebral spinal fluid. However, the positive clinical response seen in our patient after the initiation of this combination therapy suggests that further studies in the form of randomized controlled trials for the treatment of non–AIDS-related PML are warranted.

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by reactivation of the dormant JC virus (JCV) in an immunosuppressed host. The use of antiretroviral therapy in patients with HIV/AIDS has reduced the mortality of patients with PML.[1] There are no approved therapies in non–HIV-associated PML, although in some cases cytarabine, cidofovir, mirtazapine, or mefloquine have been used successfully (Table 1). Here we report a case of non–AIDS-related (B cell chronic lymphocytic leukemia) PML successfully treated with mirtazapine and mefloquine.

CASE REPORT

A 77-year-old man with chronic lymphocytic leukemia (CLL) (CD28 positive, 11q deletion, nonspecific 1:8 translocation, and isolated 13q deletion on bone marrow biopsy) and hypogammaglobulinemia was hospitalized for generalized seizures. Ten months prior to admission he underwent splenectomy for CLL-related splenomegaly. Three weeks before this admission, he was found to have progressive psychomotor slowing and decline in cognitive function. Laboratory studies on admission were significant for a white blood cell count of 18.8 x 10^3 uL with differential cell count of 63% lymphocytes, and human immunodeficiency virus (HIV) was nonreactive. A computerized tomography (CT) scan of the head revealed an area of low attenuation involving the frontal lobe with effacement of the cortical sulci and anterior horn of the lateral ventricle along with vasogenic edema. Magnetic resonance imaging (MRI) showed an abnormal signal in the left frontal lesion with edema and feathered enhancement pattern on post-contrast imaging suggestive of inflammatory or infectious processes (Figure 1A). The patient was started on empiric antibiotics of ceftriaxone intravenously (IV) (2 g every 12 hours) and metronidazole (500 mg IV every 8 hours) for treatment of presumed brain abscess, fosphenytoin for seizures, and dexamethasone for vasogenic edema.

A stereotactic brain biopsy of the left frontal lobe lesion was obtained for definitive diagnosis. Histopathologic evaluation of the tissue sample showed prominent reactive gliosis and frequent bizarre astrocytes (Figure 2). There were florid perivascular lymphocytic infiltrates spreading into the brain parenchyma. The lymphocytes were mostly small sized, along with many large macrophages in the adjacent brain tissue. Immunohistochemical stains and flow cytometry confirmed this is to be exclusively a T-cell lymphocytic infiltrate around vessels and within the parenchyma. Very few B-cells were present. JCV in situ hybridization study was positive (Figure 3). Antibiotics were discontinued when aerobic, anaerobic, and fungal cultures from the left frontal biopsy sample showed no growth.

The patient was treated with mirtazapine (30 mg daily) and mefloquine (250 mg daily for 3 days followed by 250 mg once weekly), as well as tapering the dose of dexamethasone (2 mg twice daily for 7 days, then 2 mg once daily for 7 days). Post

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treatment follow-up in 18 months showed persistent mild improvement in cognitive function and resolution of diffusion abnormality and mass effect on the MRI of the head (Figure 1B). There was persistent, although markedly improved, increased T2 signal at the most posterior and inferior aspects of the left frontal lobe mass effect. The patient improved clinically and remains stable cognitively nearly 24 months on this combination therapy without relapse.

Table 1. Literature Summary–Experimental Therapy Used in Non-HIV/AIDS-Related Progressive Multifocal Leukoencephalopathy (PML)

Study	Regimen used	Condition
Aksamit et al, 2001[2]	5 day course IV cytarabine (2 mg/kg/d)	Non-AIDS related PML
Vulliemoz et al, 2006[3]	5 day course IV cytarabine (2 mg/kg/d) and ongoing treatement with Mirtazapine (30 mg/d)	Dermatomyositis and PML
Verma et al, 2007[4]	Mirtazapine	Polycythemia vera and PML
Owczarczyk et al, 2007[5]	Cidofovir (6 infusions) and Mirtazapine (15 mg/d)	Sarcoidosis and PML
Terrier et al, 2007[6]	Cytarabine and Cidofovir	Systemic Lupus Erythematosus and PML
Raedt et al, 2008[7]	Cidofovir	Sarcoidosis and PML
Yagi et al, 2010[8]	Cidofovir	Heerfordt syndrome and PML
Schroder et al, 2010[9]	Mirtazapine (60 mg/d) and Mefloquine (250 mg daily for 3 days followed by 250 mg once weekly)	Natalizumab and PML

DISCUSSION

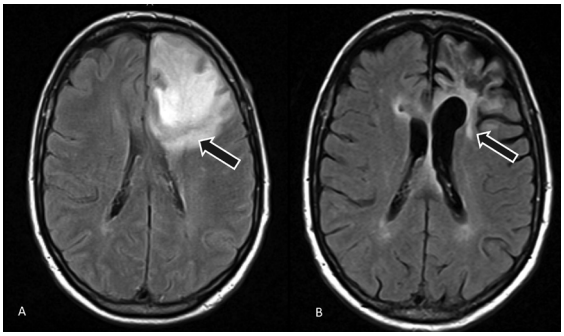
JCV is a double-stranded DNA human polyomavirus that invades oligodendrocytes in the central nervous system white matter, causing demyelination and neurologic deficits. The mechanism of infection is not clearly established, but it is believed to occur through inhalation. Once within the host, the virus remains dormant within the kidney and bone marrow, only to reemerge during periods of immunosuppression when there is impairment of immune surveillance. Once reactivated, the virus is believed to spread by B-lymphocytes to infect astrocytes and oligodendrocytes within the central nervous system by binding to 5-HT_{2A}, 5-HT_{2c}, and dopamine receptors.

In recent years, AIDS has been the underlying immunosuppressive illness most commonly associated with PML.[10] However, a variety of non-HIV immunosuppressive illnesses have been described in patients with PML, including lymphoreticular malignancies of the B-cell type (most commonly chronic lymphocytic leukemia or non-Hodgkin's lymphoma), organ transplantation and immunosuppression associated with rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, or dermatomyositis.[11,12] In general, PML is found in patients who have prolonged immunosuppression for at least 6 months.

In most non-AIDS patients, neurologic abnormalities are focal, predominately in the cerebral hemispheres. The ratio of cerebral to brainstem involvement is estimated to be 10:1 in these patients, but for reasons that are unclear, brainstem involvement is more common in AIDS patients, whose ratio of cerebral to brainstem involvement is approximately 4:1.[13] Symptoms include motor weakness, progressive decline in cognition, and visual disturbances. Thus, the diagnosis of PML should be suspected in immunosuppressed patients who present with subacute, focal, progressive neurologic symptoms. Although PML has been regarded as a "slow virus" infection, it is really a subacute illness with focal neurologic symptoms evolving over days to weeks.

MRI scanning is far superior to CT in visualizing abnormalities of PML in the brain.[14] Unifocal abnormalities on MRI scan

Figure 1. Magnetic Resonance Image (MRI)



MRI T2 fluid attenuated inversion recovery (FLAIR) image at time of presentation (A), and MRI T2 FLAIR image at 12 months post-treatment (B).

Figure 2. Histopathologic Evaluation of Tissue Biopsy

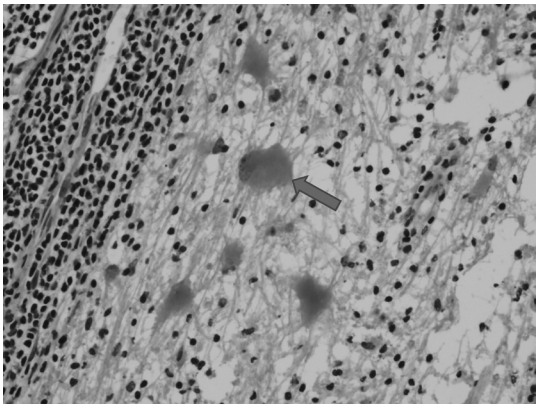
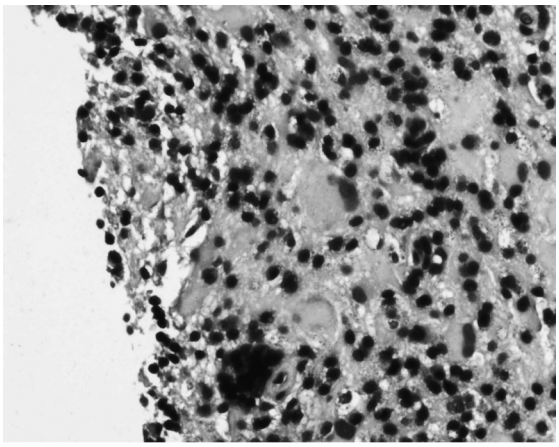


Image shows bizarre astrocytes with large atypical and eccentric nuclei (arrow). Hematoxylin and eosin stain, 40x magnification.

Table 2. Mortality Rates in AIDS-related Progressive Multifocal Leukoencephalopathy (PML) and Natalizumab-associated PML

Category	Mortality	Comments
AIDS-related PML	1-year mortality ranges from 30.5%[18] to 37.6%[19]	The improvement in 1-year mortality associated with HAART was independent of HIV RNA load and the total CD4+ T cell count at diagnosis however JC virus-specific cytotoxic CD8+ T cell responses are important.[20]
Natalizumab-associated PML	66% mortality within 2 years of initiating natalizumab	Of the 3 case reports of natalizumab-associated PML, 1 PML patient survived, indicating that withdrawal of natalizumab, possibly in combination with antiviral therapy, may permit survival.[21]
Non-AIDS/non–natalizumab-associated PML	High	Heterogeneous category and hence the exact mortality rates unknown.

Figure 3. Positive Chromogenic In Situ Hybridization (CISH) for JC Virus (JCV) under 40x Magnification



with little mass effect and contrast enhancement in the brainstem suggest PML. Polymerase chain reaction (PCR) analysis of cerebral spinal fluid (CSF) is used for confirming the diagnosis by detecting the viral particles.[15] Brain biopsy at the advancing edges of suspected PML lesions is confirmatory in patients with PCR-negative CSF. In situ hybridization or immunohistochemistry are the confirmatory techniques for identifying JCV in an affected brain.[11,16]

To date, there is no satisfactory treatment for PML. The disease is almost always progressive, barring very rare cases where spontaneous partial recovery and prolonged survival have been reported.[12] Mortality rates for PML in both AIDS-associated and non-AIDS associated patients remain high (Table 2). Reduction or withdrawal of immunosuppressants in patients with non-AIDS PML, and the use of highly active antiretroviral therapy (HAART) in AIDS-related PML, are the only known previous interventions that allowed immune reconstitution and control of pathological viral activity.

Since the 5-HT2A serotonin receptor has been found to act as a receptor for JCV in glial cells,[21] the use of medications selective for these receptors, such as the antidepressant mirtazapine and antipsychotic risperidone, appears warranted.[13] These classes of medications have been shown to inhibit viral entry into unaffected glial cells. The antimalarial drug mefloquine recently has been recognized to have anti-JCV activity at nontoxic concentrations with in vitro culture and passes the blood-brain barrier to achieve concentrations in the brain above the level inhibiting JCV replications in vitro.[22] Mefloquine works through a different mechanism, inhibiting JCV replication in cells after viral entry.[22] Experience with these medications has come from case reports and case series. The use of either of these agents has not been shown to improve outcomes in large prospective studies.

There have been several case reports on the successful use of mefloquine alone or in combination with mirtazapine in treatment of non-HIV PML.[9,23-25] Schroder et al[9] described a 41-year-old woman in whom JCV (1387 copies/mL) was recovered from CSF samples during the treatment for multiple sclerosis with natalizumab. She was placed on mirtazapine 60 mg daily and mefloquine 250 mg daily for 3 days followed by 250 mg weekly. The patient began to improve, and 1 month after initiation of the combination therapy, her CSF JCV load decreased to 169 copies/mL.[9] In our case, mirtazapine (30 mg daily) was selected to block infection of oligodendrocytes with JCV, preventing further demyelination, and mefloquine (250 mg daily for 3 days followed by 250 mg once weekly) was added to prevent viral replication. The patient responded well with both clinical and radiological improvement and is into his 24th month of treatment.

CONCLUSIONS

In the recent trial involving PML patients, the antimalarial drug mefloquine was investigated to determine its efficacy in reducing JCV DNA levels in the CSF. It was noted that mefloquine failed to reduce JCV DNA levels in the CSF.[26] However, of the 24 patients who were analyzed, 21 patients were HIV-positive (all of them were on HAART) and 3 patients were HIV negative. The sample size for non–AIDS-related PML (secondary to either cancer or rheumatoid arthritis) patients was small and therefore difficult to draw definitive conclusions. Additionally, this clinical trial used monotherapy, unlike our case where combination therapy with mefloquine and mirtazapine was administered. The clinical

response (functional and cognitive) seen in our patient after the initiation of combination therapy (mirtazapine and mefloquine) suggests additional studies in the form of randomized controlled trials in non–AIDS-related PML are needed to validate this therapeutic approach.

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REFERENCES

1. Albrecht H, Hoffmann C, Degen O, et al. Highly active antiretroviral therapy significantly improves the prognosis of patients with HIV-associated progressive multifocal leukoencephalopathy. *AIDS* 1998;12(10):1149-1154.

2. Aksamit AJ. Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. *J Neurovirol* 2001;7(4):386-390.

3. Vulliemoz S, Lurati-Ruiz F, Borruat FX, et al. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. *J Neurol Neurosurg Psychiatry.* 2006;77(9):1079-1082.

4. Verma S, Cikurel K, Koralnik IJ, et al. Mirtazapine in progressive multifocal leukoencephalopathy associated with polycythemia vera. *J Infect Dis.* 2007;196(5):709-711.

5. Owczarczyk K, Hilker R, Brunn A, Hallek M, Rubbert A. Progressive multifocal leucoencephalopathy in a patient with sarcoidosis--successful treatment with cidofovir and mirtazapine. *Rheumatology* (Oxford). 2007;46(5):888-890.

6. Terrier B, Hummel A, Fakhouri F, et al. [Progressive multifocal leukoencephalopathy in a non-AIDS patient: high efficiency of combined cytarabine and cidofovir]. [Article in French] *Rev Med Interne.* 2007;28(7):488-491.

7. De Raedt S, Lacor P, Michotte A, Flamez A, Ebinger G. Progressive multifocal leukoencephalopathy as first manifestation of sarcoidosis. *Clin Neurol Neurosurg.* 2008;110(2):186-189.

8. Yagi T, Hattori H, Ohira M, et al. Progressive multifocal leukoencephalopathy developed in incomplete Heerfordt syndrome, a rare manifestation of sarcoidosis, without steroid therapy responding to cidofovir. *Clin Neurol Neurosurg.* 2010;112(2):153-156.

9. Schröder A, Lee DH, Hellwig K, Lukas C, Linker RA, Gold R. Successful management of natalizumab-associated progressive multifocal leukoencephalopathy and immune reconstitution syndrome in a patient with multiple sclerosis. *Arch Neurol.* 2010;67(11):1391-1394.

10. Berger JR, Pall L, Lanska D, Witeman M: Progressive multifocal leukoencephalopathy in patients with HIV infection. *J Neuroviro/1998*,4:S9-68.

11. Aksamit AJ: Nonradioactive in situ hybridization in progressive multifocal leukoencephalopathy. *Mayo Clin Proc.* 1993, 68:899-910.

12. Brooks BR, Walker DL. Progressive multifocal leukoencephalopathy. *Neurol Clin* 1984;2(2):299–313.

13. Aksamit AJ. Progressive multifocal leukoencephalopathy. *Curr Treat Options Neurol.* 2008,10(3):178-185.

14. Whiteman ML, Post MJ, Berger JR, Tate LG, Bell MD, Limonte LP. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. *Radiology.* 1993;187(1):233-240.

15. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis.* 2005;40(5):738-744.

16. Aksamit AJ. Progressive multifocal leukoencephalopathy: a review of pathology and pathogenesis. *Microsc Res Tech.* 1995;32(4):302-311.

17. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis.* 2003;36(8):1047-1052.

18. Khanna N, Elzi L, Mueller NJ, et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. *Clin Infect Dis.* 2009;48(10):1459-1466.

19. Khanna N, Wolbers M, Mueller NJ, et al. JCV-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal leukoencephalopathy. *J Virol.* 2009;83(9):4404-4411.

20. Aksamit AJ. Review of progressive multifocal leukoencephalopathy and natalizumab. *Neurologist.* 2006;12(6):293-298.

21. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science.* 2004;306(5700):1380-1383.

22. Brickelmaier M, Lugovskoy A, Kartikeyan R, et al. Identification and characterization of mefloquine efficacy against JC virus in vitro. *Antimicrob Agents Chemother.* 2009;53(5):1840-1849.

23. Kishida S, Tanaka K. Mefloquine treatment in a patient suffering from progressive multifocal leukoencephalopathy after umbilical cord blood transplant. *Intern Med.* 2010;49(22):2509-2513.

24. Gofton TE, Al-Khotani A, O'Farrell B, Ang LC, McLachlan RS. Mefloquine in the treatment of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry.* 2011;82(4):452-455.

25. Beppu M, Kawamoto M, Nukuzuma S, Kohara N. Mefloquine improved progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus. *Intern Med.* 2012;51(10):1245-1247.

26. Friedman R. News from the AAN Annual Meeting: malaria drug fails to fulfill promise in PML. *Neurology Today.* 2011;11:8.

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