

Mirtazapine in Progressive Multifocal Leukoencephalopathy Associated with Polycythemia Vera

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Progressive multifocal leukoencephalopathy (PML) is a usually fatal cerebral white matter disease found in patients with human immunodeficiency virus infection and other immunocompromised states. We present the case of a 63-year-old woman with polycythemia vera who developed a progressive focal neurological deficit with white matter abnormalities on magnetic resonance images of the brain that was proved on biopsy to be PML. She was treated with the serotonin reuptake inhibitor mirtazapine and remains neurologically stable, with resolution of cerebral lesions, >2 years after diagnosis. We propose that mirtazapine should be investigated further for use in PML.

Progressive multifocal leukoencephalopathy (PML) is a severe neurological disease that predominantly affects the subcortical white matter of the central nervous system (CNS), resulting in demyelination. It is caused by the human JC polyomavirus (JCV), which infects both oligodendrocytes and astrocytes. PML occurs almost exclusively in severely immunosuppressed patients and typically manifests with focal neurologic deficits. Treatment of PML is unsatisfactory, and there is no therapeutic agent that affects its progressive, usually fatal course. In the context of HIV infection, highly active antiretroviral therapy

(HAART) improves outcome in patients with PML [1, 2]. However, this treatment is not indicated in patients without HIV infection, who have other causes of immunosuppression. In vitro studies have suggested that JCV may infect cells via the serotonin receptor 5HT_{2a}, which indicates a putative role for serotonin reuptake inhibitors in the treatment of PML [3].

Subject and methods. A 63-year-old right-handed woman was admitted with confusion and progressive left-sided weakness. Fifteen years before admission she had received a diagnosis of polycythemia vera. Bone marrow biopsy in 2002 revealed hypocellular bone marrow with extensive fibrosis. She was treated with interferon (IFN)- α 2B and thalidomide until she first developed neurological symptoms in November 2004. These included memory impairment, difficulty with spatial orientation, and weakness of the left side of the face and left arm. On general examination, she had multiple echymoses, splenomegaly, and mild lower extremity edema. Neurologic examination revealed fluent speech, impaired attention, and reduced short-term memory. There were marked left-sided deficits, including hemineglect, homonymous hemianopsia, central facial weakness, and hemiparesis. Laboratory results indicated a white blood cell (WBC) count of 26.1 cells/ $10^3 \mu\text{L}$, a hemoglobin level of 12.1 g/L, and a platelet count of 28.0 cells/ $10^3 \mu\text{L}$. An HIV antibody test was negative. Magnetic resonance imaging (MRI) of the brain showed multiple lesions in the right parietal white matter (figure 1).

Stereotactic brain biopsy of the large lesion in the right parietal lobe was performed after platelet transfusion. Histologic analysis revealed a demyelinating lesion with relative preservation of axons. Enlarged oligodendrocytes with hazy intranuclear inclusions positive for JCV T antigen were identified by immunohistochemical analysis, establishing the diagnosis of PML. Immunostaining for HIV p24 antigen was negative.

During the next month, the patient had marked progression in neurological deficits, including increased left-sided weakness and an inability to stand without assistance. IFN was restarted, and corticosteroids were added. She was then transferred to our institution. Neurological exam demonstrated moderate dysarthria, difficulty following 2-step commands, homonymous hemianopsia, left central facial weakness, and left hemiparesis with neglect.

At admission, CD3⁺, CD4⁺, and CD8⁺ T cell counts were normal: the CD3⁺ T cell count was 1416 cells/mm³ (normal range, 750–2500 cells/mm³), the CD4⁺ T cell count was 614 cells/mm³ (normal range, 480–1700 cells/mm³), and the CD8⁺ T cell count was 706 cells/mm³ (normal range, 180–1000 cells/

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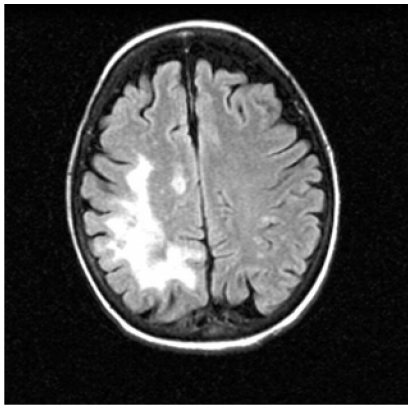


Figure 1. Magnetic resonance image dated 13 November 2004 (initial scan). The single axial fluid-attenuated inversion recovery image through the superior right parietal region demonstrates a large lesion of abnormally high signal in the white matter. There is no significant mass effect and no contrast enhancement. There are smaller lesions in the right and left parietal regions.

mm³). The ratio of CD4⁺:CD8⁺ T cells was 0.9 (normal range, 1.0–3.0). At that time, lymphocyte function studies showed only mildly blunted T cell responses to the mitogens phytohemagglutinin, concanavalin A, and pokeweed.

Magnetic resonance spectroscopy of the confluent abnormal fluid-attenuated inversion recovery–hyperintense (FLAIR) image in the white matter of the right cerebral hemisphere (figure 1) revealed decreased N-acetylaspartate levels, elevation of the lactate peak, and a prominent increase in the choline to creatine ratio. These findings, although nonspecific, have been reported in PML [4]. Lumbar puncture revealed a glucose level of 40 mg/dL, a protein level of 57 mg/dL, and a WBC count of 2 cells/ μ L. Polymerase chain reaction (PCR) assay of the cerebrospinal fluid for JCV was positive, with 16,300 JCV DNA copies/mL. A ⁵¹Cr release assay aimed at detecting JCV-specific CD8⁺ cytotoxic T lymphocytes (CTLs) in the patient’s blood was negative [5]. The JCV load, measured using quantitative PCR as described by Ryschkeiwitsch et al. [6], was 5.8×10^4 copies/mL of plasma.

One month after admission, the patient’s CD4⁺ T cell count was 231 cells/mm³. Her IFN- α dose of 4×10^6 U every other day was modified to 180 μ g of IFN- α 2A/week. Because she continued to deteriorate clinically, 15 mg of mirtazapine/day was initiated.

The patient was transferred to a subacute rehabilitation facility. During the next month, her left hemiparesis improved. Repeat lymphocyte subset determinations revealed a CD4⁺ T cell count of 619 cells/mm³ and a CD8⁺ T cell count of 299 cells/mm³. She was then discharged home and has remained neurologically stable for >2 years since the diagnosis of PML. A subsequent MRI scan demonstrated significant improvement

(figure 2), and a repeat ⁵¹Cr release assay revealed that she now had detectable CTLs against JCV. Her plasma JCV load decreased to 3×10^3 copies/mL.

Discussion. PML is a subacute demyelinating disease of the CNS that is caused by human JCV. This virus infects and destroys oligodendrocytes, resulting in multiple areas of demyelination, and causes a restrictive infection of astrocytes. The initial infection is subclinical and usually occurs during late childhood. JCV establishes lifelong, persistent infection. PML generally becomes clinically manifested in profoundly immunosuppressed individuals, including those with AIDS or leukemia, and in organ transplant recipients. There have been cases of PML reported recently that were associated with natalizumab treatment in patients with multiple sclerosis and Crohn disease [7].

There is no specific therapy for PML. Clinical trials of cytosine arabinoside [8] and cidofovir [9] in AIDS-associated PML have been generally unsuccessful. The role of IFN in PML and in our patient’s clinical course is unclear. Coincident with initiation of mirtazapine therapy, she had a modification of the IFN- α regimen. There has been a report of an HIV-negative patient with hepatitis C who developed PML after therapy with pegylated IFN- α 2A and ribavirin [10]. However, in HIV-infected patients, a retrospective review of 97 cases suggested longer survival for those patients who received a combination of IFN- α and HAART [11]. Although it is difficult to be certain whether IFN contributed to the increase in CD4⁺ T cell count and clinical improvement in our patient, she had been receiving long-term IFN- α treatment, and her disease initially deteriorated rapidly despite the cessation of IFN for a month.

5HT₂ receptors are expressed in brain microvasculature and

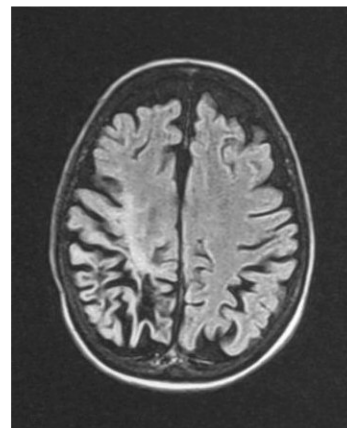


Figure 2. Magnetic resonance image dated 7 December 2005 (1 year after the diagnosis of progressive multifocal leukoencephalopathy). The axial fluid-attenuated inversion recovery image through the superior right parietal region demonstrates significant interval changes. The previously noted high-signal-intensity lesion in the right parietal white matter is markedly decreased in size and intensity. There is encephalomalacia and prominent atrophy of the right parietal lobe.

on astrocytes at the blood-brain barrier. JCV may spread to the CNS via hematogenous spread. In vitro data have indicated that the serotonin receptor 5HT2a acts as the receptor for JCV in glial cells [3]. The cultured glial cells in the present study were predominantly composed of astrocytes, which develop a restricted infection in PML. Oligodendrocytes, which are the primary cell type affected in the disease, have not been established as a cell line in culture. However, the 5HT2a receptor also appears to be an important receptor on diverse cell types for JCV. Receptor-negative HeLa cells regain their susceptibility to infection by JCV when expressing the 5HT2a receptor [3]. These data suggest that serotonin receptor antagonists may be useful in the treatment of PML and possibly in its prophylaxis through their ability to block virus entry into glial cells via 5HT2a serotonin receptors. This provided the rationale for mirtazapine therapy in our patient. Because JCV infection was already established in the CNS, the putative role of mirtazapine in this case was to prevent the spread of JCV to other glial cells, rather than to avoid the passage of JC virions present in the bloodstream across the blood-brain barrier.

Our patient had a favorable clinical evolution of PML, despite an undetectable cellular immune response against JCV initially. The lack of such a cellular immune response is usually associated with progressive disease and a rapidly fatal outcome [12]. Her improvement was temporally associated with the onset of mirtazapine treatment at a time when there was no evidence of a contribution of a specific immune response against JCV. It was only 2 years later that repeated evaluation showed detectable CD8⁺ CTLs against JCV, as well as a 1-log decrease in the plasma JCV load.

In summary, the putative therapeutic effect of mirtazapine in PML occurs via the down-regulation of 5HT2a receptors, which are used by JCV to enter glial cells. Preliminary experiments have suggested that this compound decreases JCV replication in infected glial cells in vitro [13]. Further studies are necessary to determine whether mirtazapine or other serotonin receptor antagonists may be useful in the prophylaxis or treatment of PML.

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