

Anthony Amoroso and Ajit P. Limaye, Section Editor

Progressive Behavior Changes and Brain Lesions in a Lung Transplant Recipient

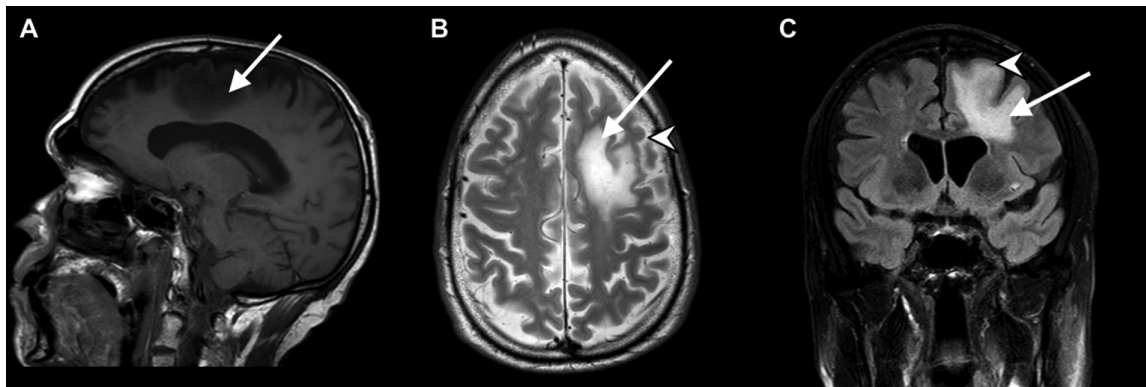


Figure 1. Magnetic resonance images. *A*, Sagittal-T1-weighted image demonstrating hypointensity (arrow) with lack of enhancement in the frontal lobe white matter. *B*, *C*, Axial T2-weighted (*B*) and coronal fluid-attenuated inversion-recovery (*C*) images demonstrating hyperintensity (arrows) within the frontal lobe white matter, with involvement of the subcortical U fibers (arrowheads), as well as absence of mass effect.

A 68-year-old man with a history of familial idiopathic pulmonary fibrosis after bilateral lung transplant 2 years earlier presented with 4 weeks of progressive behavioral changes, short-term memory loss, word-finding difficulties, and gait instability. His initial transplant course included basiliximab induction, and he had no history of transplant rejection. His posttransplant course included severe pancytopenia, requiring cessation of mycophenolate mofetil 16 months earlier and a reduced immunosuppression regimen of tacrolimus (target level, 4–6 ng/mL) with prednisone (5 mg/d), as well as frequent doses of granulocyte colony-stimulating factor. The patient had experienced cytomegalovirus (CMV) viremia (without end-organ disease) 15 months earlier with low-grade persistence (50–200 IU/mL) despite ongoing therapeutic-dose valganciclovir. His infectious prophylaxis regimen included dapsone, after discontinuation trimethoprim-sulfamethoxazole 12 months earlier owing to bone marrow suppression. Pretransplant infectious testing demonstrated the patient to be seropositive for Epstein-Barr virus (EBV) immunoglobulin G (IgG), herpes simplex virus 1/2 IgG, and varicella-zoster virus IgG, seronegative for *Toxoplasma* IgG, negative for *Mycobacterium tuberculosis* by interferon γ release assay, and a CMV IgG-seronegative recipient of lungs from a CMV IgG-positive donor. He lived in the Northwestern United States, did not travel internationally, had no sick contacts or animal exposures, and was sexually monogamous with his wife.

Examination revealed an afebrile, well-appearing man with expressive aphasia and 4/5 strength in right-sided motor groups.

Brain magnetic resonance imaging demonstrated hypointensity in the frontal lobe white matter on T1-weighted images, and T2-weighted and fluid-attenuated inversion-recovery images demonstrated a 4.9 × 4.8 × 3.3-cm nonenhancing, confluent hyperintensity in the frontal lobe white matter and subcortical U fibers, and patchy subcortical white matter T2 hyperintensity (Figure 1).

Laboratory results showed a white blood cell count of 1950/ μ L, an absolute neutrophil count of 661/ μ L, an absolute lymphocyte count of 1189/ μ L, negative plasma EBV polymerase chain reaction (PCR) results, and stable CMV PCR results, at 60 IU/mL. Results of antibody testing for human immunodeficiency virus, toxoplasmosis, and *Coccidioides* were negative, as were urine *Histoplasma* antigen results. The chest, abdomen, and pelvis appeared unremarkable at computed tomography. Cerebrospinal fluid findings included an opening pressure of 28 cm H₂O (normal, 10–25 cm H₂O), white blood cell count of 2/ μ L (100% lymphocytes; normal, 0–5/ μ L), a protein level 56 mg/dL (normal, <50 mg/dL), and a glucose level 68 mg/dL (normal, >60% of serum glucose). The cerebrospinal fluid was negative for bacterial and fungal cultures, viral testing with PCR (for CMV, EBV, varicella-zoster virus, herpes simplex virus, and JC virus), and cryptococcal antigen. Bone marrow biopsy revealed <5% cellularity with trilineage hypoplasia. Fluorescent in situ hybridization (FISH) and immunostaining results was negative for EBV, CMV, and parvovirus.

What is your diagnosis?

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The differential diagnosis for neurologic symptoms and focal brain lesions in a solid organ transplant (SOT) recipient is broad. Diagnostic categories include (1) central nervous system (CNS) infections, (2) cancer (CNS lymphoma/posttransplant lymphoproliferative disorder, metastatic solid tumors), and (3) anatomic complications (ischemic stroke, hemorrhage, vasculitis, immunosuppression-related posterior reversible leukoencephalopathy syndrome [PRES]) [1, 2]. Infectious considerations that may cause focal CNS lesions include bacterial abscesses, *Nocardia*, *Mycobacterium tuberculosis*, endemic fungi, *Cryptococcus*, invasive molds (commonly *Aspergillus*), toxoplasmosis, herpesviruses, including cytomegalovirus, and progressive multifocal leukoencephalopathy (PML).

In this patient, because of a suspicion of PML despite the negative cerebrospinal fluid (CSF) JC virus polymerase chain reaction (PCR) findings, a brain biopsy was performed, which showed atypical astrocytes, extensive macrophage infiltration, and nuclear inclusions involving oligodendrocytes (Figure 2). Cells with nuclear inclusions were positive for SV40 antigen. The commercial anti-SV40 large T antigen monoclonal antibody used for immunohistochemistry cross-reacts with JC virus T antigen, confirming the diagnosis of JC virus–associated PML.

PML is a rare CNS disorder caused by the polyoma JC virus. Primary infection is acquired in childhood, with most adults having had previous exposure. After primary infection, the virus commonly enters a latent phase in lymphoid organs, with other sites including renal tubular cells and bone marrow. Clinical disease occurs owing to reactivation and

frequently involves the CNS, where it infects and destroys myelin-producing oligodendrocytes. Presenting symptoms are variable. CSF is typically bland, including a white blood cell count $<20/\mu\text{L}$ and normal or mildly elevated protein levels [3]. Importantly, the absence of JC virus by PCR in the CSF does not rule out PML. Although sensitivities $>95\%$ have been reported for ultrasensitive CSF PCR assays for JC virus DNA, traditional PCR techniques are only 75% sensitive [3, 4]. Blood JC virus PCR may provide additional diagnostic yield in patients with suspected PML and negative findings at CSF JC virus PCR, particularly in the human immunodeficiency virus (HIV)–negative population [5].

In our patient, the indolent but progressive presentation was less consistent with bacterial infection or cerebrovascular complications, and the negative CSF findings excluded many other infectious considerations. Magnetic resonance neuroimaging findings (Figure 1 in Photo Quiz) were consistent with demyelination, including patchy T1 hypointensity, T2 hyperintensity, involvement of the subcortical U fibers, and lack of contrast enhancement or mass effect, all supportive of PML [6]. These features are in contrast to those seen with posttransplant lymphoproliferative disorder, which commonly demonstrates hemorrhage, necrosis, and intra-axial contrast-enhancing lesions. PRES may be difficult to differentiate from PML by neuroimaging alone but is more likely to be present in the posterior subcortical white matter and less likely to present with a subacute time course [1].

Most cases of PML have been associated with profound immunosuppression, classically in patients with advanced

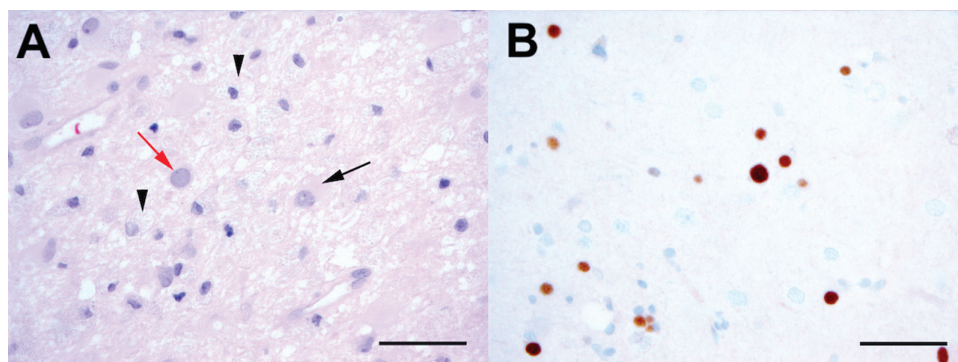


Figure 2. A, Hematoxylin-eosin–stained section showing a rarefied background with many macrophages (arrowheads), atypical astrocytes (black arrow) and oligodendrocytes with enlarged nucleus containing viral inclusions (red arrow). B, Immunohistochemistry for SV40 antigen showing many cells with intranuclear inclusions (brown). (Scale bars represent 50 μm .)

HIV/AIDS. However, reports have emerged in patients with connective tissue disease receiving immunomodulating agents and in hematopoietic stem cell transplant and SOT recipients [7]. In 6 prior reports of PML in lung transplant recipients, all but 1 case occurred in the first year after transplantation and/or after augmented immunosuppression [7–13]. The case we report occurred despite relatively low doses of immunosuppressives. Protracted posttransplant pancytopenia and development of a severely hypocellular bone marrow with genetic features of myelodysplasia may have contributed to our patient's immunodeficiency.

Treatment options are limited and prognosis poor in SOT-associated PML, with a median survival of 6.4 months after symptom onset [7]. Therapy in the non-HIV population involves reduction in immunosuppression, which is often difficult in SOT recipients. Other therapies have been reported, including interleukin 7, Toll-like receptor agonists, and vaccination with JC virus capsid protein, but they remain experimental and were not used in our patient [14–16]. We substituted tacrolimus with everolimus, and mirtazapine was added for its potential effect on JC virus cell entry via the serotonin 5HT2a receptor. Despite this, our patient's neurologic symptoms progressed, leading to his death 4 months after diagnosis.

Notes

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