Progressive Multifocal Leukoencephalopathy in a Lung Transplant Recipient: Isolation of John Cunningham (JC) Virus from Bronchoalveolar Lavage

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by polyomavirus John Cunningham (JC) virus. We report the case of a 60-year-old woman who presented 16 months after right single lung transplant with worsening memory, behavioral problems, emotional lability, and progressive left upper extremity weakness. Magnetic resonance imaging revealed white matter changes suggestive of PML. JC virus infection was confirmed with polymerase chain reaction (PCR) from both the bronchoalveolar lavage (BAL) fluid and cerebrospinal fluid. To our knowledge, this is the first report of PCR isolation of JC virus from a BAL specimen. We also review the two additional cases in the literature that describe PML after lung transplantation. JC virus infection should be considered in the differential diagnosis of lung transplant recipients who develop neurological symptoms. BAL may have a role in the etiologic diagnosis of PML after lung transplantation.

Key words: Acquired immunodeficiency syndrome, John Cunningham virus, lung transplant, progressive multifocal leukoencephalopathy

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) has been reported just twice in lung transplant recipients, in men of ages 43 and 60 years, respectively.¹,² These patients' neurological symptoms included visual disturbances, confusion, aphasia, memory loss, and mono- or hemiparesis. One patient was diagnosed after polymerase chain reaction (PCR) for polyomavirus John Cunningham (JC) virus in his cerebrospinal fluid (CSF); the other patient’s PCR studies for JC virus were negative in CSF, but the definitive diagnosis was made after stereotactic brain biopsy. Here we report a case of isolation of JC virus from bronchoalveolar lavage (BAL) performed during bronchoscopy and confirmed after PCR was done on CSF. To our knowledge, this is the first report of JC virus causing PML that was diagnosed on BAL.

CASE REPORT

A 60-year-old woman with severe chronic obstructive pulmonary disease (COPD) underwent right single lung transplantation. Sixteen months later, she presented with progressive weakness of the left arm of 2 months' duration, cognitive decline, memory and visual deficits,
crying spells, and emotional lability. She was admitted to the hospital and was found to have appropriate levels of immunosuppression with tacrolimus (FK-506) and prednisone. Upon neurological examination, she was alert and oriented to person and place had a labile pseudobulbar affect, and was tearful. Her mini-mental status examination score had declined dramatically from 28/30 2 months before admission to 14/30 at the time of admission. Visual field testing revealed a right hemianopia. She also had left facial weakness and left upper extremity weakness, with a positive snout reflex suggestive of frontal release signs. T2-weighted, fluid-attenuated inversion recovery magnetic resonance imaging (MRI) of the brain showed circumscribed areas of hyperintensity in the dorsal right frontal lobe and right frontal operculum [Figures 1 and 2]. Lesions similar in appearance were also noted in the lateral left frontal and inferior left occipitotemporal region. Initially, these findings were thought to be side effects of the tacrolimus; she was therefore switched to rapamycin.

CSF analysis revealed that her glucose, protein, and cell count were within normal limits. However, PCR for JC virus was positive, confirming the diagnosis of PML. She also underwent a bronchoscopy with BAL, which was also positive for JC virus by PCR. Her immunosuppression was switched from tacrolimus to rapamycin, and her steroid dose was lowered. When the diagnosis and prognosis were explained to the patient's family, they requested comfort measures and declined further intervention or immunosuppression. The patient received hospice care and died 3 weeks later from progressive respiratory failure. She had ceased taking her antirejection medications, a behavior that highlights the tremendous social and psychological effects of PML.

**DISCUSSION**

Astrom et al. first described PML in 1958, and in 1971 Padgett et al. cultured JC virus in fetal brain cells after inoculation with PML material. The virus takes its name from the initials of the patient from whom the material was recovered. JC virus of the polyoma group is the causative agent in almost all cases of PML. In some rare instances, polyomavirus simian vacuolating virus 40 (SV-40) has also been implicated as a cause of PML. Furthermore, some viruses that share many antigens with SV-40 have been isolated from a few patients with PML and may represent another causative agent.

The prevalence of JC virus infection in the general population is ubiquitous, with seropositivity ranging from 50% in children to 90% in adults who have anti-JC virus antibodies. Currently, human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) are the most common diseases associated with PML, and PML is one of the AIDS-defining illnesses described by the Centers for Disease Control and Prevention surveillance case definition. Prior to the AIDS epidemic, several conditions (all characterized by immunosuppression) were associated with PML, including lymphoproliferative and myeloproliferative diseases, chronic infections or granulomatous diseases, organ transplantation, and corticosteroid-induced immunosuppression.

All currently known polyomaviruses such as JC virus, BK virus, and SV-40 are known to establish chronic latent infection in the human host and undergo reactivation

**Figure 1:** Axial T2-weighted magnetic resonance image shows progressive multifocal leukoencephalopathy with a large confluent hyperintense lesion in the left occipitotemporal region

**Figure 2:** Axial T2-weighted, fluid-attenuated inversion recovery magnetic resonance image shows progressive multifocal leukoencephalopathy with a high signal intensity lesion involving the white matter of the dorsal right frontal lobe and right frontal operculum, as well as lateral left frontal and inferior left occipitotemporal region with no mass effect
when immunosuppression occurs. The latent infection has been described in the kidney, brain, and spleen. More recently, DNA sequences of three viruses have been identified in peripheral blood B lymphocytes, hematopoietic progenitor cells, and tonsillar stromal cells. This has significant implications for the latency theory of polyomaviruses. In our case, the isolation of JC virus from BAL further supports the theory of reactivation of the disease when early infection occurs during childhood. Whether the lungs are the site of latency for PML or are subsequently seeded by circulating B-lymphocytes carrying the virus remains unknown.

PML by JC virus has been described previously in two patients after lung transplantation; however, to our knowledge this is the first case of PML in a female COPD patient after lung transplantation. It is the first report of JC virus isolation from BAL fluid in a suspected case of PML. The neurological manifestations most commonly associated with PML in patients after solid organ transplantation are apathy, confusion, mono- or hemiparesis, visual symptoms, confusion, seizure activity, and frontal release signs. These symptoms are similar to those described in AIDS patients and in patients with other immunodeficiencies and are generally progressive with new or worsening neurological manifestations as the disease progresses. Computed tomography (CT) studies of patients with PML reveal hypodense, nonenhancing white matter changes. MRI, which appears to be more sensitive than CT for detecting PML lesions, is characterized by increased signal intensity on proton-density and T2-weighted images [Figures 1 and 2].

Neurological manifestations and white matter changes seen on neuroimaging studies of heart or lung transplant recipients mimic those caused by immunosuppression with cyclosporine or tacrolimus. However, leukoencephalopathy associated with immunosuppression tends to occur earlier in the postoperative course, although late-onset neurotoxicity has also been reported. The clinical and neuroimaging findings are usually reversible after cessation or reduction of cyclosporine or tacrolimus. Diagnosis can be made by brain tissue biopsy or by PCR of the CSF. On light microscopy, PML is characterized by white matter interspersed with foci of demyelination at different stages of evolution, which is caused by the cytopathic effects of JC virus on the oligodendrocytes. Light microscopy will also reveal nuclear enlargement, intranuclear basophilic accumulations, and loss of normal chromatin pattern. Notably, these lesions have minimal or no inflammation. Whitman et al found that in HIV-seropositive patients, PCR of the CSF for JC virus had a sensitivity of 72-93% and a specificity of 92-100%. PCR of the CSF is therefore accepted as a diagnostic test for PML when characteristic clinical and radiological evidence are also present. A positive PCR for JC virus in BAL fluid has not been previously reported, but it may be another diagnostic method for JC virus in lung transplant recipients who have neurological symptoms, helping avoid a brain biopsy. Whether the presence of JC virus reflects primary infection, reactivation after latent infection in the lung, or reactivation from another reservoir (e.g., the kidney) with seeding of the bloodstream and subsequent isolation in BAL remains to be determined.

Various reports have been published regarding therapeutic regimens for PML. These include modulation of the immunosuppressive regimen to minimal blood levels; discontinuation of steroids, cytarabine, and cidofovir; and highly active antiretroviral therapy with cidofovir and cytarabine in combination with interleukin-2. However, most of the evidence for these treatments is anecdotal or based only on a few case reports. To date, the only published randomized controlled trial has shown no significant benefit to cytosine arabinoside (ARA-C). An open-label study of 24 HIV patients with PML showed that cidofovir, a nucleoside analog, had minimal effect. Reversing the patient's immunosuppressive state is the best treatment strategy at this time, and initiation of highly active antiretroviral therapy is critical for patients with HIV or AIDS.

We treated our patient by reducing her steroid dose and switching her prescribed immunosuppressive agent from tacrolimus to rapamycin in an effort to reach whole blood trough levels of 6-8 ng/mL. She was also treated with mirtazapine, a 5HT2A receptor antagonist with antidepressant effects that efficiently cross the blood brain barrier. Vulliemoz et al demonstrated that combined treatment of ARA-C and mirtazapine may be beneficial for HIV-negative patients with PML. We decided against using cidofovir or ARA-C in our patient, however, because their efficacy is limited and their associated side effect profiles are too severe. In summary, PML should be considered in the differential diagnosis of patients presenting with neurological symptoms after heart or lung transplantation. Presently, PML is diagnosed by a positive PCR for JC virus from the CSF or by a brain biopsy. As our case shows, isolation of JC virus from the BAL fluid may also serve as a valuable diagnostic tool. Unfortunately, the outcome of PML is invariably fatal, although in some patients it has stabilized over the course of several months with immune status improvement. PML is a rare complication of lung transplantation, but with the worldwide evolution of lung
and heart-lung transplantation and increasing allograft survival, clinicians should be familiar with the clinical presentation of this entity.

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Conflicts of interest

There are no conflicts of interest.

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