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Progressive Multifocal Leukoencephalopathy Following Heightened Immunosuppression after Lung Transplant: A Case Report

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system caused by the JC virus that occurs in the setting of immune suppression. A 38-year-old lung transplant recipient at this institution received treatment for episodes of acute rejection with steroids, anti-thymocyte globulin, and alemtuzumab, in addition to her maintenance immunosuppression. She was diagnosed with PML thirteen months after the last episode of rejection, for which she had received alemtuzumab. Despite attempted treatment with cidofovir followed by mirtazapine, her PML progressed, and she ultimately died of an acute pulmonary infection and respiratory failure. We provide a detailed clinical and radiographic description of PML in a lung transplant patient and highlight its potential relationship to intensive immunosuppression, as the infection developed in the setting of markedly reduced CD4 counts.

Introduction

Progressive multifocal leukoencephalopathy (PML) was first described in 1958 as a complication in patients with chronic lymphocytic leukemia (CLL) and Hodgkin's lymphoma.¹ Patients present with focal neurological symptoms, most commonly hemiparesis, cognitive disturbances, or visual field deficits. A typical course involves the steady deterioration of neurological function, leading to death within 6 months to a year.² The disease results from infection of oligodendrocytes by a polyoma virus, the JC virus, which causes demyelination of CNS axons.³ Serologic evidence shows that 60-80% of adults in the United States have been exposed to JC virus, but PML typically develops in the setting of reduced cellular immunity, possibly related to viral reactivation.^{2,4} Since its original description, PML has been reported in patients with AIDS and recipients of both solid organ and bone marrow transplants (BMT).^{2, 5-7} Most recently, it has been reported in three patients following administration of a humanized, monoclonal antibody, natalizumab, used in the treatment of multiple sclerosis and Crohn's disease.⁸

Only two cases of PML following lung transplant have been reported.⁵⁻⁷ The first patient developed PML after treatment of multiple episodes of allograft rejection with steroids and anti-thymocyte globulin. This case resulted in death despite the reduction of immunosuppression to only prednisone.⁶ The second patient presented with symptoms seven months post-transplant while taking a tacrolimus-based maintenance regimen. The patient's neurological function eventually stabilized after a reduction in immunosuppression and the initiation of cidofovir, and he survived.⁷ In this paper, we present the third case of PML in a lung transplant recipient. The disease developed in the setting of a profoundly

reduced CD4 count after augmented immunosuppression with rabbit anti-thymocyte globulin (RATG) and alemtuzumab for the treatment of allograft rejection.

Case Presentation

A 38 year old woman underwent bilateral lung transplantation in December 2003 for pulmonary fibrosis. Intraoperatively, she was treated with methylprednisolone. Initial maintenance immune suppression consisted of prednisone, azathioprine, and tacrolimus. Her hospital course was unremarkable, and she was discharged on post-op day 14 with a prophylaxis regimen of trimethoprim-sulfamethoxazole (TMP-SMX) and one month of ganciclovir (donor and recipient were cytomegalovirus (CMV) positive). Over the next two and a half years, she received multiple treatments for episodes of acute rejection, four times with intravenous (IV) pulses of methylprednisolone (500 mg daily for three days) and twice with RATG (1.5 mg/kg/day for three days). In May 2006, six weeks after her second RATG treatment, she received a single, 30 mg dose of alemtuzumab for recurrent acute cellular rejection and was subsequently maintained on two-drug immune suppression with tacrolimus and prednisone (5 mg daily). Her post-alemtuzumab prophylaxis included voriconazole, TMP-SMX, IV ganciclovir, and inhaled Abelcet. One month later, her CD4 count reached its nadir at 1 cell/ μ L (2%). This increased only to 41 cells/ μ L one year after treatment (Figure 1; a CD4 count prior to alemtuzumab treatment was not measured).

Thirteen months after alemtuzumab therapy, the patient presented to a scheduled followup appointment complaining of gait instability and non-specific visual changes that worsened with sun exposure. Her neurological exam revealed no focal deficits in motor, sensory, or cerebellar function, and her symptoms were attributed to side-effects from medications. Voriconazole was discontinued; her tacrolimus was maintained at a therapeutic level. Five weeks later, she was admitted with worsening ataxia, visual changes and confusion. Her neurological exam revealed dysarthria with word-finding difficulties, poor fine motor skills using her right hand, and an ataxic gait. Her strength and sensory exams were normal. MRI of the brain showed white matter signal abnormalities involving the bilateral cerebellar hemispheres, right external capsule and to a lesser extent the left pons and bilateral corona radiata, consistent with viral or autoimmune encephalitis (Figure 2). Lumbar puncture was performed. CSF studies revealed zero nucleated cells, normal glucose, and a mildly elevated protein at 84 mg/dl (upper limit of normal: 50). Bacterial and fungal cultures were negative, as were assays for neurosyphilis, CMV, herpes simplex virus, human herpes virus 6, and Epstein-Barr virus. JC virus PCR from the CSF was positive.

She began treatment with cidofovir, which was discontinued after three doses due to line related sepsis. The patient and her healthcare power of attorney declined further treatment with cidofovir. Therefore, her immune suppression was decreased, and she was started on mirtazapine 15 mg daily as alternative treatment for PML. Three weeks later, she had her peak CD4 count of 162 but her gait had worsened, and she had limited movement of her right hand. The dose of mirtazapine was increased to 30 mg daily.

Four months after the diagnosis of PML, the patient was admitted with fever and new pulmonary infiltrates. Broad spectrum antibiotics were started, and she required intubation for hypercarbic respiratory failure. Trans-bronchial biopsies showed acute and organizing pneumonitis without evidence of rejection or specific infectious agents. After five weeks of ventilator dependence with progressive worsening of her respiratory status, support was withdrawn, given the irreversible nature of her underlying problems. The family declined a postmortem examination.

Discussion

This case demonstrates a typical presentation for PML in the post-transplant setting, and it represents the third reported case in a lung transplant recipient. Of the two previous lung transplant patients who developed PML, one received multiple treatments for allograft rejection with steroids and anti-thymocyte globulin, and the second had only received standard triple-drug immunosuppression. While our patient received maintenance immunosuppression, IV steroids and RATG, she also received treatment with alemtuzumab, a humanized, monoclonal antibody directed against the CD52 antigen. Alemtuzumab, which is increasingly used in the treatment or prevention of heart and lung allograft rejection, causes suppression of CD4 lymphocytes beyond a year, in contrast to other immunosuppressants such as RATG, which allow a more rapid recovery of CD4 counts.⁹⁻¹³ The combined effects of our patient's immunosuppression likely contributed to her risk for PML.

The initial differential diagnosis for the neurological complaints that our patient presented with included medication toxicity, CNS involvement of post-transplant lymphoproliferative disorder, or opportunistic CNS infections.⁶ The initial complaints in this case included ataxia and visual changes, prompting consideration of voriconazole toxicity.¹⁴ However, symptoms persisted after this was discontinued. The MRI findings were not typical for reversible posterior leukoencephalopathy syndrome, which is a known complication of calcineurin inhibitor therapy, but were consistent with viral or autoimmune encephalitis.¹⁵ A positive JC virus PCR from the CSF is 95.8% specific for PML, and in the setting of the other negative viral and autoimmune CSF studies, confirmed the diagnosis.¹⁶

Management of patients with PML is difficult and often disappointing. One option in transplant patients is to reduce maintenance immune suppression, as was done in this case. In addition, cidofovir and mirtazapine have been employed in the treatment of PML. Much of the data supporting the use of cidofovir comes from the study of HIV-positive patients along with anti-retroviral therapy; whether this can be generalized to the transplant setting is unknown.¹⁷ At trial doses of cidofovir up to 50% of patients will require dose reduction or discontinuation due to renal tubular necrosis.¹⁸ The use of mirtazapine is appealing as a 5-HT_{2A} antagonist (the cellular receptor used by the JC virus) with fewer side effects, and its use in PML is supported by a few case reports in the literature.¹⁹ Its efficacy in this case cannot be determined, as the patient died shortly after the initiation of this agent.

In the only review of PML cases following transplantation (solid organ or BMT), nine of 17 cases died from the disease, and the median time to death was 2.5 months.⁵ Two cases of PML have been documented following the use of alemtuzumab, but these patients had CLL and received cumulative doses over 12 times those used in this case. Both cases resulted in death.^{20,21} Three patients developed PML following treatment with natalizumab, another humanized, monoclonal antibody, which binds α 4 integrins and hinders T-cell transmigration across the blood-brain barrier.⁸ Given the poor outcomes of these and other patients with PML, efforts have been made to find a non-CSF based screening test. In two of the patients treated with natalizumab, stored serum samples were screened, but no evidence of JC viremia preceding the diagnosis of PML was found.⁸ In one trial of patients with Crohn's disease (none of whom had PML), the incidence of JC viruria did not differ between immunosuppressed and immunocompetent patients, but immunosuppressed patients had higher viral loads in the urine compared to controls.²² Thus the relationship between JC virus, its reactivation leading to PML, and CD4 cell immunity warrants further study.

In summary, we present the third documented case of PML in a lung transplant recipient. While it is a rare complication, PML should remain in the differential diagnosis of lung and

other solid-organ transplant recipients presenting with CNS complaints. The intense immunosuppression employed after lung transplant, including RATG and alemtuzumab, profoundly deplete host defenses and should heighten suspicion for opportunistic infections in appropriate clinical settings.

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Figure 1.

CD4 cell count versus days after alemtuzumab treatment. Our patient's CD4 count rose slowly and eventually peaked at 162 cells/ μ L. Arrow marks the date of her first presentation with neurological complaints; immune suppression was reduced at that time to low dose tacrolimus (levels of 3-5 ng/ml) and prednisone 5 mg daily. The CD4 count improved but later fell in the setting of a blood stream infection.

Figure 2.

Brain MRI. The study was performed fourteen months after alemtuzumab treatment, five weeks after symptom onset, and showed nonspecific white matter signal abnormality involving bilateral cerebellar hemispheres, right external capsule, and to a lesser extent left pons and bilateral corona radiata. The radiological differential included viral or autoimmune encephalitis or, less likely, osmotic demyelination. This figure demonstrates (A) confluent increased T2-FLAIR signal involving the bilateral cerebellar hemispheres entering the middle peduncles bilaterally (arrows); (B) absence of restricted diffusion on ADC map reconstruction images, making ischemia unlikely; (C) low signal on T1-weighted images in the corresponding distribution; and (D) no evidence of enhancement on T1-weighted images post-contrast administration.