Progressive Multifocal Leukoencephalopathy
After Allogeneic Bone Marrow Transplantation for Acute Myeloid Leukemia

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Abstract
Progressive multifocal leukoencephalopathy (PML) is a rare fatal complication of allogeneic bone marrow transplantation (BMT) resulting from chronic immunosuppression and impaired cellular immunity. This report discusses 2 cases of PML in patients with acute myeloid leukemia after allogeneic BMT. Diagnosis was made based on characteristic brain MRI findings and positive PCR results for John Cunningham virus in the cerebrospinal fluid. Unfortunately, therapeutic options are limited and nearly always result in terminal outcomes. Although immunosuppression is an unavoidable risk of allogeneic BMT, these cases highlight a rare, yet fatal, consequence of prolonged T-cell lymphopenia and impaired cellular immunity after allogeneic BMT in this patient population. (J Natl Compr Canc Netw 2014;12:1660–1664)

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Progressive multifocal leukoencephalopathy (PML) represents a rare central nervous system (CNS) demyelinating disorder caused by the reactivation of the neurotropic John Cunningham virus (JCV) that leads to the destruction of CNS oligodendrocytes. First described in 1958, PML is invariably associated with impaired cellular immunity because most cases are seen in the AIDS population. However, PML has gained newfound significance in the past decade with the advent and use of novel monoclonal antibodies and other chemotherapeutics that alter normal immune function. With the number of solid organ and allogeneic bone marrow transplantation (BMT) recipients increasing, these patients also represent an important at-risk population for developing PML because of chronic immunosuppression. This report presents 2 patients diagnosed with PML after receiving allogeneic BMTs for acute myeloid leukemia (AML) in the setting of significant T-cell lymphopenia.

Case 1

A 69-year-old man was diagnosed with acute myelomonocytic leukemia with complex cytogenetics and an FLT3-ITD mutation. His disease failed to respond to initial induction therapy with idarubicin and high-dose cytarabine, and the patient instead received salvage therapy that included AC220 and experienced a morphologic complete remission. He was subsequently treated with decitabine until undergoing a 10/10 HLA-matched unrelated donor allogeneic BMT. Donor and recipient were both cytomegalovirus-negative. His conditioning regimen consisted of fludarabine, 40 mg/m² for 4 days and pharmacokinetic dose-adjusted busulfan targeting a daily area under the curve of 4000 µMol/min⁻¹. Posttransplant, the patient received cyclophosphamide, 50 mg/kg on posttransplant day 3 and 4 and tacrolimus for immunosuppression. On posttransplant day 26, results of a bone marrow biopsy showed full donor chimerism and no evidence of AML. He then developed steroid-refractory grade III acute skin and colon graft-versus-host disease (GVHD) on posttransplant day 55, which was initially treated by methylprednisolone, 2 mg/kg, and mirtazapine, 30 mg/d. He also received 1 dose of intravenous immunoglobulin at 0.5 g/kg. After day 25 of melfoquine and mirtazapine therapy, the patient showed continued rapid neurologic decline and therapy was discontinued. A donor lymphocyte infusion was considered to facilitate immune reconstitution, but because of the patient’s severe irreversible and progressive neurologic damage, the decision was made to transition the patient to hospice care. He expired shortly afterwards on posttransplant day 361.

Case 2

A 77-year-old man was diagnosed with AML with diploid cytogenetics. He received standard induction therapy with idarubicin and cytarabine, experienced (posttransplant day 63–65) with good response. On continued improvement of the patient’s GVHD, tacrolimus and prednisone were completely tapered by posttransplant day 140.

On posttransplant day 315, the patient experienced new-onset expressive aphasia and right upper extremity dyspraxia. A brain MRI showed a 1.7 x 2.0-cm periventricular lesion in the left centrum semiovale involving the white matter with peripheral T2 enhancement (Figure 1A). Results of cerebrospinal fluid (CSF) cellular, biochemical, and routine microbiology studies were within normal limits, but qualitative CSF PCR was positive for JCV, consistent with a diagnosis of PML, and serum PCR showed 1724 copies/mL of JCV DNA. The absolute CD4+ T-cell count was low at 178 cells/µL and the CD8+ T-cell count was 372 cells/µL. The patient was started on therapy with melfoquine, 250 mg/d for 3 days followed by 250 mg weekly, and mirtazapine, 30 mg/d. He also received 1 dose of intravenous immunoglobulin at 0.5 g/kg. After day 25 of melfoquine and mirtazapine therapy, the patient showed continued rapid neurologic decline and therapy was discontinued. A donor lymphocyte infusion was considered to facilitate immune reconstitution, but because of the patient’s severe irreversible and progressive neurologic damage, the decision was made to transition the patient to hospice care. He expired shortly afterwards on posttransplant day 361.

Figure 1 T2-weighted MRI brain images at diagnosis of progressive multifocal leukoencephalopathy depicting abnormal T2 white matter lesions. (A) Case 1 and (B) Case 2 with arrows indicating areas of abnormal enhancement.
a complete remission, and then received 2 additional cycles as consolidation therapy. The patient then experienced disease relapse and achieved a second remission after treatment with high-dose cytarabine and vosaroxin followed by decitabine. He then proceeded with an allogeneic BMT from a 10/10 HLA-matched matched unrelated donor. Both the patient and the donor were cytomegalovirus-negative. His conditioning regimen consisted of fludarabine, 25 mg/m² for 5 days; melphalan, 70 mg/m² for 2 days; and antithymocyte globulin (ATG) for 3 days. After BMT, the patient received methotrexate, 5 mg/m² on posttransplant days 1, 3, 6, and 11 and tacrolimus, MMF, and steroids, MMF, and ATG for GVHD prophylaxis. On posttransplant day 30, results of a bone marrow biopsy showed full donor chimerism and no evidence of leukemia. His posttransplant period was complicated by deconditioning and pneumonia that resolved with antibiotics, although he did not develop any evidence of GVHD.

On posttransplant day 153, the patient developed symptoms of lethargy and right lower extremity weakness. Brain MRI showed a 5.4 x 2.3-cm enhancing lesion in the left centrum semiovale white matter (Figure 1B). Results of CSF cellular, biochemical, and routine microbiology tests were within normal range. However, qualitative CSF PCR was positive for JCV, and serum viral load was 6376 copies/mL, consistent with a diagnosis of PML. The absolute CD4+ T-cell count was decreased at 99 cells/µL, and the CD8+ T-cell count was 195 cells/µL. Because of the lack of a proven effective treatment for PML, the patient was discharged to a skilled nursing facility without further therapy and died on posttransplant day 202.

Discussion

This report presents 2 cases of PML diagnosed after allogeneic BMT in the setting of marked T-cell lymphopenia. To the authors’ knowledge, these are also the first reported cases of PML in adult patients who received pentostatin (Case 1) and ATG (Case 2). PML is a fatal CNS demyelinating disease caused by reactivation of the neurotropic JCV, a double-stranded circular DNA virus belonging to the Polyomaviridae family. JCV is ubiquitous in the human adult population, and primary infection is believed to occur in early childhood through the fecal–oral route, suggested by detection of JCV in gastrointestinal epithelial cells. It has specific tropism to cells such as oligodendrocytes, peripheral blood cells, and kidney epithelial cells that contain the α(2,6)- and α(2,3)-linked sialic acid residues of N-linked glycoproteins, which act as a receptor for JCV entry. The virus remains latent, yet in the context of T-cell mediated immunosuppression, it can reactivate and consequently lead to widespread lysis of oligodendrocytes and subsequent CNS demyelination.

With the escalation of the HIV epidemic, PML-related deaths increased 4-fold from 1979 to 1987 in the United States, and is still seen most often as a late complication of HIV infection. However, the increasing use of immunomodulating agents, such as monoclonal antibodies, in the treatment of oncologic and autoimmune diseases has led to the emergence and identification of new at-risk patient populations. Carson et al observed 57 cases of PML in a large case series of patients treated with rituximab, although the true incidence of PML with rituximab therapy remains unclear. Other novel agents, such as brentuximab and ruxolitinib, have also been associated with PML, highlighting the importance of both physician and patient awareness of the risks of immunosuppression and possibility of JCV reactivation with the continued development and regulatory approval of similar drugs in the future.

As demonstrated in these cases, PML is also becoming increasingly recognized as a serious complication of allogeneic stem cell transplantation. To date, PML has been reported in 22 patients who received allogeneic hematopoietic stem cell transplantations, of which 3 were matched unrelated donor BMTs, such as those seen in the patients discussed herein. The necessity of posttransplant immunosuppression to prevent GVHD provides a fertile environment for opportunistic infections, such as JCV, to flourish. Along with conventional immunosuppression with tacrolimus, the patient in Case 1 received additional immunosuppression with posttransplant cyclophosphamide to mitigate alloreactive T-cell proliferation and steroids, MMF, and pentostatin to treat the grade III acute skin and colon GVHD. Prolonged CD4+ lymphopenia has been observed after fludarabine-based regimens for chronic lymphocytic leukemia. Therefore, the use of a purine analogue (pentostatin) for the treatment of steroid-refractory GVHD may have contributed to the sustained depression of CD4+ T cells, even after all immunosuppression had been completely tapered.
off for almost 6 months. In Case 2, it is probable that ATG was a significant contributor to the patient's prolonged T-cell lymphopenia, a well-described phenomenon in the solid organ transplant literature.\textsuperscript{35,36} However, it is generally difficult to implicate a single immunosuppressive agent as the inciting reason for the development of PML, because most patients who develop PML after allogeneic BMT are exposed to more than one immunosuppressive drug.\textsuperscript{37} Although immunosuppression is an unavoidable risk in patients undergoing allogeneic BMT, the present cases highlight the potential fatal complications of the resultant impaired cellular immunity and T-cell lymphopenia that occurs with time.

No effective treatment is available for PML, and the clinical course usually results in progressive neurologic decline and death. In a recent cohort study by Mateen et al.,\textsuperscript{17} the average time of PML onset in 25 patients who received autologous or allogeneic stem cell transplantations was 11 months, with a median survival after symptom onset of 19.5 months. Immunosomodulatory agents such as interleukin-2 and interferon-alpha, and antivirals such as cytarabine and cidofovir have shown efficacy in isolated cases but failed to show benefit in larger studies.\textsuperscript{38–40} Because JCV entry into human glial cells may be mediated by the serotonergic 5-HT\textsubscript{2A} receptor, interest has been shown in using 5-HT\textsubscript{2A} receptor antagonists, such as melfloquine and mirtazapine, to treat PML.\textsuperscript{41} However, a phase I/II clinical trial (ClinicalTrials.gov identifier: NCT00746941) that studied the effects of melfloquine in patients with PML was terminated early because it failed to reduce the titer of JCV in the CSF after treatment, a finding consistent with the outcome of the patient described in Case 1.\textsuperscript{42}

PML should be considered in the differential diagnosis of any immunocompromised patient who presents with progressive neurologic decline. Although pathologic confirmation through brain biopsy is deemed the gold standard for diagnosis of PML, a positive CSF PCR result for JCV is also considered confirmatory and circumvents the risks associated with brain biopsy.\textsuperscript{37} Unfortunately, overall prognosis is dismal with limited therapeutic options.

### References


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Posttest Questions

1. True or False: Brain biopsy is mandatory to confirm a diagnosis of PML.
2. Exposure to which of the following drugs has been reported to be associated with the development of PML?
   a. Brentuximab
   b. Rituximab
   c. Natalizumab
   d. Ruxolitinib
   e. All of the above
3. Which of the following therapies has been shown to be effective in the treatment of PML in phase II clinical trials?
   a. Cidofovir
   b. Interleukin-2
   c. Mefloquine
   d. Mirtazapine
   e. None of the above