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CASE REPORT

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Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy

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Abstract Nonmyeloablative allogeneic stem cell transplantation (NMASCT) can be used to exploit the graft-versus-tumor (GVT) potential of allogeneic donor cells in the setting of reduced conditioning regimen toxicity. This approach is particularly attractive for patients who have received extensive prior therapy and are poor candidates for traditional allogeneic stem cell transplantation. However, toxicity in heavily pretreated patients remains uncertain. Additional immunosuppression in already immunocompromised patients may result in unexpected toxicity. We report a case of probable progressive multifocal leukoencephalopathy (PML) responsive to interleukin-2 (IL-2) following a NMASCT in a 29-year-old woman with relapsed Hodgkin's lymphoma. The patient developed severe neurological symptoms approximately 6 weeks following NMASCT associated with low CD4+ cell counts and magnetic resonance imaging (MRI) was consistent with PML. IL-2 therapy resulted in increasing CD4+ counts and progressive resolution of neurological symptoms. Disruption of IL-2 therapy led to neurological deterioration, which responded to reinstitution of IL-2 therapy. The patient's lymphoma initially progressed following NMASCT, but has responded to donor leukocyte infusions (DLI). This case reiterates the potent GVT potential of NMASCT in patients with Hodgkin's disease. However, it demonstrates the potential for severe complications related to immunosuppression, especially in heavily pretreated patients. The toxicity after NMASCT should not be understated and will need to be explored further.

Keywords Nonmyeloablative allogeneic stem cell transplant · Progressive multifocal leukoencephalopathy · Graft-versus-lymphoma

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Introduction

Mounting evidence for a potent immune mediated graft-versus-tumor (GVT) effect of hematopoietic allografting has led to increasing interest in nonmyeloablative (NMA) allogeneic stem cell transplantation (SCT) [1, 2]. Nonmyeloablative SCT offers reduced conditioning regimen toxicity and is therefore particularly attractive for patients who have received extensive prior therapy and who are poor candidates for traditional allogeneic SCT. However, the potential complications of NMASCT are not fully understood, and toxicity related to immunosuppression in heavily pretreated patients may be significant [3, 4]. We report a case of interleukin-2 (IL-2) responsive clinical progressive multifocal leukoencephalopathy (PML) following NMASCT in a 29-year-old woman with Hodgkin's disease (HD) in relapse after autologous SCT. This case highlights the potential complications that may arise with the use of intensive immunosuppressive therapy, especially in heavily pretreated patients.

Case report

This patient was treated with NMASCT in her third relapse for HD. She had received prior X-ray therapy, mechlorethamine, vincristine, procarbazine (MOPP)/doxorubicin, bleomycin, vinblastine (ABV) chemotherapy, and finally high-dose chemotherapy and autologous SCT. The NMA conditioning included cyclophosphamide and fludarabine [4]. Her donor was her HLA-identical sister who received granulocyte colony-stimulating factor (G-CSF) prior to leukapheresis of a peripheral blood stem cell graft that contained 4.7×10^8 mononuclear cells/kg and 1.1×10^8 CD3+ cells/kg. Graft-versus-host disease (GVHD) prophylaxis included

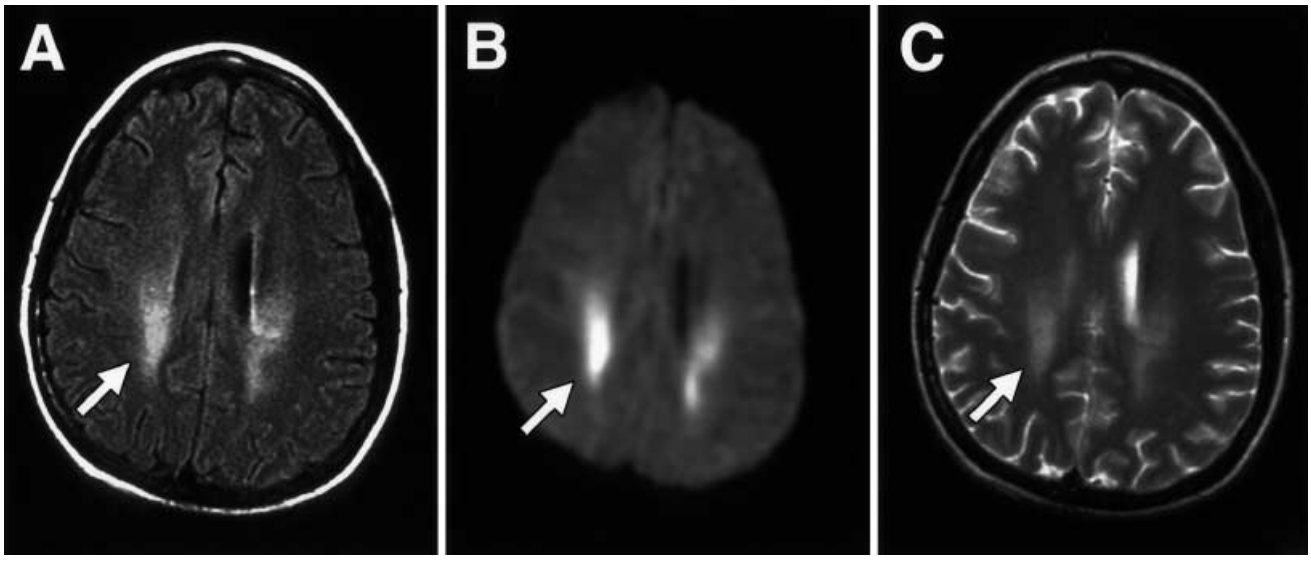

Fig. 1A–C MRI scan of brain showing changes consistent with PML. Long TR (**A**), diffusion-weighted (**B**), and T1-weighted post gadolinium (**C**) magnetic resonance axial images through the brain. Each image is an approximately similar level of the brain, with *arrows* indicating regions of abnormal increased signal intensity in the periventricular white matter of the parietal lobes. No enhancement of the abnormality after administration of contrast (**C**)

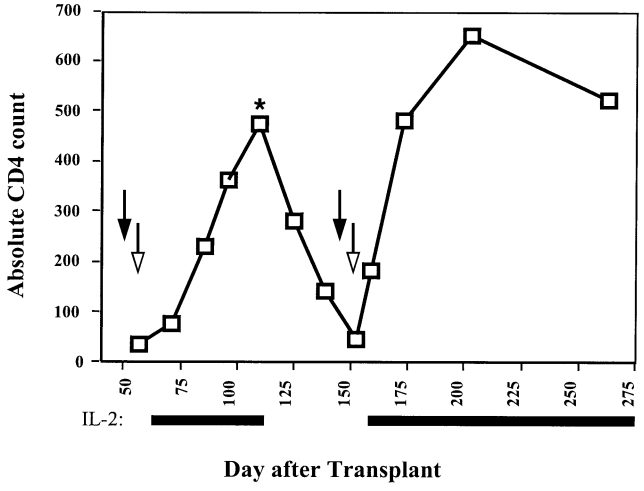

Fig. 2 Graphic display of patient's CD4+ counts over time correlating low CD4+ cell counts with neurological symptoms and increasing CD4+ cell counts with IL-2 therapy. *Solid arrows* indicate onset of neurological symptoms. *Open arrows* indicate initiation of IL-2 therapy. *Asterisk* indicates termination of IL-2 therapy

4 weeks of cyclosporine (CSA) followed by a rapid taper. By 21 days after SCT, 98% donor chimerism was achieved and by day 75 there was 100% donor chimerism. Subsequent analyses have shown stable complete donor chimerism for the entire duration of follow-up (determined by polymerase chain reaction (PCR) using primers to heterogeneous short tandem repeat loci as previously described [4]. Six weeks after transplant the patient complained of imbalance and visual disturbances. CSF fluid was unremarkable (1 WBC/mm^3, 0 RBCs/mm^3), and an initial magnetic resonance imaging (MRI) revealed minimal nonspecific changes of the posterior white matter. However, MRI 14 days later showed progressive diffuse periventricular white matter abnormalities without regions of enhancement consistent with PML (Fig. 1). Notably, both PCR testing of CSF viral infections [Jamestown Canyon (JC), cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV)] and CSF viral cultures (including HSV, VZV, CMV, respiratory, and enteroviruses) were negative.

The patient's neurological condition rapidly deteriorated requiring hospitalization. She became bed-bound, markedly ataxic, and had a dramatic decrease of visual acuity with bilateral inferior visual field deficits. Repeat CSF chemistries and viral cultures were negative. Paraneoplastic antineuronal antibodies were all negative. The CD4+ count was 57/mm^3 despite 98% donor chimerism. The patient's presentation was felt to be most consistent with PML. Given the low CD4+ counts and anecdotal reports of the successful treatment of PML with IL-2 [5], continuous infusion of IL-2 (0.5 million units/m^2 per day) was initiated. Within 5 days the patient began to have a slow resolution of her neurological symptoms that continued over the next 6 weeks, with CD4 counts rising from 57 to 279 cells/mm^3 (Fig. 2). MRI of the brain remained unchanged. Repeat computed tomography (CT) scans of the abdomen, approximately 16 weeks after NMASCT and 6 weeks after starting IL-2 therapy, revealed progression of the her HD. IL-2 therapy was discontinued on day 116, and on day 136 systemic chemotherapy (mitoxantrone, ifosfamide, and etoposide) was administered. This was complicated by neutropenic fevers and a fungal pneumonia requiring hospitalization. While hospitalized the patient's neurological status again deteriorated, with worsening ataxia and visual disturbances associated with an extremely low CD4 count (34/mm^3). The patient was restarted on IL-2 therapy with a recovery of neurological symptoms within several days. The CD4 count rose to 480/mm^3 over the next several weeks. On day 175, donor leukocyte infusion (DLI) was performed and tolerated without complication. Follow-up scans of the abdomen after DLI have revealed a slow decrease in the patient's hepatic mass and abdominal adenopathy (Fig. 3). Furthermore, the patient's neurological symptoms have almost completely resolved; she is currently completely independent and performing all activities of daily living. She has been placed on subcutaneous IL-2 and has maintained CD4 counts between 500 and 850 cells/mm^3.

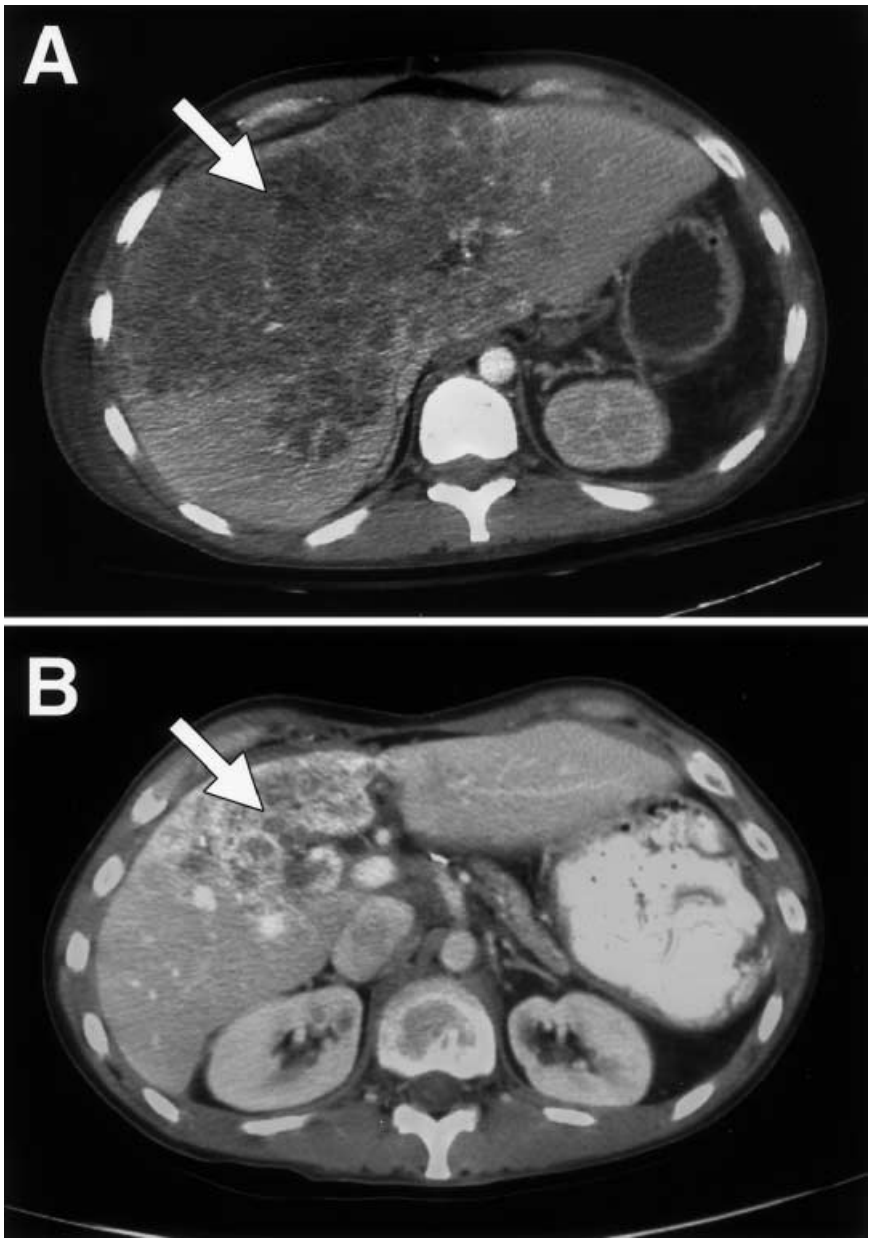

Fig. 3A, B CT scans of the liver 10 months apart demonstrating improvement in the large hepatic mass resulting from nonmyeloablative allogeneic SCT that occurred despite neurologic deterioration. **A** Axial image through the liver after intravenous contrast from 1/28/00. *Large arrow* indicates heterogeneously enhancing mass lesion involving the anterior segment of the right lobe of the liver and medial segment of the left lobe of the liver measuring approximately 18×12 cm. Numerous small hypoattenuation lesions are noted throughout the liver. **B** Axial image through the liver following administration of oral and intravenous contrast from 11/12/00 following DLI. Image is from a similar thoracic level as in image **A**. *Large arrow* indicates mass lesion still present within the liver, but significantly reduced in size, now measuring approximately 9×7 cm. In addition, a reduction of number and size of hypoattenuating lesions throughout the liver was noted as well as a decrease in lymphadenopathy seen at other levels (data not shown). Note that these images are at the same vertebral level, but that the massive size of the liver in image **A** distorts liver anatomy and creates caudal displacement of the right kidney

Discussion

We believe this patient's progressive neurologic decline and radiographic changes are consistent with PML after NMASCT. As PCR testing of the cerebral spinal fluid for JC virus was negative, several other diagnoses were considered, but felt to be unlikely. Posterior leukoencephalopathy (PLE) is a rare but well-documented complication of CSA therapy associated with hypertension [6]. However, our patient's symptoms occurred after CSA had been discontinued, she had never had a documented elevated CSA level, was never hypertensive, and her symptoms resolved over a period of 6–8 weeks while the radiological findings were unchanged, making this diagnosis unlikely. The time course of the neurological disease was also consistent with fludarabine toxicity, which often occurs many weeks after administration. However, severe neurological symptoms are rare at the dose of fludarabine administered and in patients her age [7]; fludarabine-induced MRI changes are also uncommon [8]. The response of symptoms to IL-2 also makes drug toxicity unlikely. We also considered the possibility that the symptoms could be a direct or paraneoplastic result of her lymphoma. However, her lymphoma was progressing while her neurological symptoms were initially improving, and then her neurological symptoms recurred when her HD appeared to be improving, arguing against the possibility that her symptoms were related to lymphoma. In addition, laboratory studies for the traditional and novel antineuronal paraneoplastic antibodies were negative (J. Posner lab, personal communication). Finally, infection by CMV or VZV was considered unlikely

since all CSF studies for these viruses were negative and radiological images were not typical for either CMV or VZV, and were consistent with PML.

The time course and progressive nature of this patient's symptoms and combination of visual, behavioral, and motor symptoms is typical of PML. PML is a virally induced, typically progressively fatal disease, most often seen in AIDS patients with low CD4 counts, but has also been reported after autologous and allogeneic bone marrow transplantation (BMT). In HIV-infected patients with PML, increasing the CD4 counts with antiretroviral therapy can lead to prolonged survival [9]. Resolution of PML with IL-2 therapy has been reported in at least two patients. One patient had JC virus demonstrated in the CSF after autologous BMT [5]. The second patient, similar to our patient, had a negative CSF JC virus PCR [10] (interestingly, both of these patients had underlying lymphomas). Both at the time of initial neurological deterioration and secondary deterioration after discontinuation of IL-2 therapy, this patient had very low CD4 counts (57 and 34 cells/mm^3, respectively). IL-2 therapy led to a concomitant increase in CD4 counts and resolution of the neurological symptoms, showing that the symptoms and CD4 counts ran a parallel course (Fig. 2). Thus, the response of our patient's neurological symptoms to IL-2 therapy is consistent with PML.

Interestingly, IL-2 therapy has been reported to enhance the GVT effects of DLI and allogeneic SCT [11], but there is a theoretical concern that it may increase the risk of serious GVHD. In our patient, IL-2 did not seem to contribute to the antilymphatic effect (in fact, there was evidence of progressive disease after IL-2 therapy), and at no time did IL-2 therapy appear to induce GVHD.

This case demonstrates the potent graft-versus-Hodgkin's disease potential of allogeneic cell therapy [4, 12, 13]. However, our patient developed both PML, a disease believed to be due to human papovavirus, and a fungal pneumonia in conjunction with very low CD4 counts. These observations demonstrate that deficiencies of T-cell function and regulation may prove to be critical in patients receiving NMASCT and highlight the potential risks of this approach, especially in heavily pretreated patients who may already be immunosuppressed. As NMASCT is now applied for an increasing number of patients with malignant and nonmalignant diseases, caution and further study of the complications of NMASCT is warranted.

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