Continued Disease Activity in a Patient With Multiple Sclerosis After Allogeneic Hematopoietic Cell Transplantation

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Objective: To examine the effect of allogeneic hematopoietic cell transplantation (HCT) on disease activity in a patient with multiple sclerosis (MS).

Design: Case report, prospective study, and autopsy.

Setting: Departments of Clinical Neurosciences, Internal Medicine, and Pathology at the University of Calgary, Alberta, Canada.

Patient: A 39-year-old woman with chronic myelogenous leukemia and concurrent mild MS.

Interventions: Hematopoietic cell transplantation from a healthy unrelated donor.

Results: After HCT the patient developed graft-vs-host disease and experienced worsening, but not new, neurological symptoms. Her circulating leukocytes were 100% of donor origin. Magnetic resonance imaging showed increased lesion burden. She died of adenovirus hepatitis 20 weeks after HCT. An autopsy revealed demyelinating-inflammatory activity in active lesions and chronic active lesions.

Conclusion: Despite high-dose, cytotoxic, immunosuppressive therapy and exchange of a presumed autoreactive immune system with a healthy immune system, MS in this patient continued to be active.

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THE HALLMARK OF MULTIPLE sclerosis (MS) is inflammatory demyelination associated with neurodegeneration. The demyelination is thought to be caused by autoreactive lymphocytes because experimental allergic encephalomyelitis, a mouse model of MS, can be transferred by infusing lymphocytes from a diseased animal to a healthy animal or cured by bone marrow transplantation from a healthy to a diseased animal. The evidence for the immunopathogenesis of human MS includes the infiltration of lymphocytes in MS lesions, increased concentration of antemyelin antibodies in the sera of some MS patients, presence of oligoclonal immunoglobulins in the cerebrospinal fluid of most MS patients, and a modest response to immunosuppressive-immunomodulatory drugs. Here we present a case of continued MS activity after allogeneic hematopoietic cell transplantation (HCT) in spite of complete chimerism of circulating leukocytes.

REPORT OF A CASE

A 39-year-old woman had MS for 19 years at the time of HCT. She first presented with numbness of both buttocks, which resolved spontaneously. In her sixth year of MS, she developed recurrent paresthesias of both buttocks and her lower extremities. She was diagnosed with MS based on clinical and magnetic resonance imaging (MRI) findings. In her 16th year of MS, she had another relapse manifested by unsteadiness and paresthesias in multiple body regions, and later that year she experienced unilateral optic neuritis. Her Extended Disability Status Scale (EDSS) score at the end of that period was 1.5. The following year she experienced 2 relapses. Both were treated with high-dose corticosteroids and resolved. Her only residual symptom was paresthesias of fluctuating intensity in her feet. Treatment with glatiramer acetate was started after 17 years with MS. No further MS relapses occurred for the next 2 years. When HCT conditioning started, glatiramer acetate was discontinued.

Chronic myelogenous leukemia presented 2 years before HCT, shortly after initiation of glatiramer acetate, with thrombocytosis. Translocation t(9;22) and bcr-abl transcripts were detected. Treatment with imatinib and dasatinib resulted in tolerable neutropenia. Transplantation of filgrastim-mobilized blood mononuclear cells from an unrelated, HLA antigen-matched,
male donor was then performed using conditioning with busulfan, fludarabine, and antithymocyte globulin and graft-vers-host disease (GVHD) prophylaxis with cyclosporine and methotrexate. The donor was a healthy individual who passed the screening tests required for donation of a hematopoietic cell graft. The HLA antigen type of both the donor and the recipient was A0301/2301, B4402/4403, C0501/0409N, DRB1 0701/1501, and DQB1 0202/0602.

Figure 1. Fluid-attenuated inversion recovery magnetic resonance images showing an increase in lesion burden (B, arrows) 8 weeks after allogeneic hematopoietic cell transplantation compared with 4 weeks before transplantation (A).

Figure 2. Photomicrograph of an active lesion in the frontal juxtacortical region. Inflammatory/demyelinating activity throughout the lesion with decreased intensity of Luxol fast blue staining for myelin (A; original magnification ×100); CD68-immunoreactive macrophages (B; original magnification ×200); CD3- (C; original magnification ×200); CD6- (D; original magnification ×400), and CD4-immunoreactive (E; original magnification ×400) T cells; and scattered damaged axons immunoreactive for amyloid precursor protein (F; original magnification ×200). In B, C, and F, the insets show higher magnification.
Five weeks after HCT, owing to increased paresthesias in her lower extremities, cyclosporine was replaced with mycophenolate mofetil. Graft-vs-host disease primarily involving the skin and digestive system developed 8 weeks after HCT. It was refractory to methylprednisolone but responded partially to antithymocyte globulin given 11 to 12 weeks after HCT or experimental therapy (either mesenchymal stromal cells [Prochymal; Osiris Therapeutics, Baltimore, Maryland] or placebo) given from 11 to 19 weeks after HCT. Fulminant hepatitis due to adenovirus developed 20 weeks after HCT. Fourteen weeks after HCT, the marrow was in remission, without detectable bcr-abl transcripts. Complete chimerism of circulating leukocytes was documented by X- and Y-chromosome fluorescent in situ hybridization 10 weeks after HCT and reconfirmed 14 weeks after HCT.

Immediately before HCT, the only MS symptom was paresthesias of both lower extremities, while neurological examination revealed sensory changes in her legs, generalized hyperreflexia with extensor plantar responses. Five weeks after HCT she noted worsening paresthesias with neuropathic pain that involved both her lower and upper extremities. This prompted cyclosporine discontinuation, as it can also cause these symptoms. Worsening paresthesias and pain persisted until treatment with methylprednisolone began 8 weeks after HCT. Ten weeks after HCT she again developed worsening of paresthesias with new, sustained, bilateral ankle clonus. This manifestation continued until her death 20 weeks after HCT.

Her EDSS was 2.0 before HCT, 3.0 ten weeks after HCT, and 2.5 seventeen weeks after HCT.

Four weeks before HCT, cranial MRI showed more than 20 T2-hyperintense lesions involving the periventricular white matter and juxtacortical regions (Figure 1A), but none convincingly in the infratentorial regions. None enhanced with gadolinium on T1-weighted images. Eight weeks after HCT, cranial MRI revealed several new and enlarging T2-hyperintense lesions in the cerebrum (Figure 1B) without enhancement on T1-weighted images.

The general autopsy confirmed the presence of massive liver necrosis and numerous adenovirus inclusions in the liver and lungs. Examination of the spinal cord was precluded because of infectious precautions. The brain

Figure 3. Photomicrograph of a chronic active lesion in the lateral pons. The lesion exhibiting a hypocellular center (A, left lower zone; Luxol fast blue; original magnification ×100) and inflammatory/demyelinating edge containing CD68-immunoreactive macrophages (B; original magnification ×400) and CD3-immunoreactive T cells (C; original magnification ×400). Colocalization of myelin with CD68-immunoreactive macrophages is indicative of ongoing demyelination (D; myelin basic protein [green], CD68 [red], original magnification ×400, with the insert showing a CD68-immunoreactive cell stripping away the myelin).
was examined after fixation in 10% neutral formalin. A total of 22 MS plaques were found. Inflammatory demyelinating activity was microscopically identified in 2 active lesions and 7 chronic active lesions. Both active lesions, located in the frontal juxtacortical regions, exhibited active inflammation/demyelination throughout their entire extent (Figure 2A) and contained frequent CD68-immunoreactive macrophages (Figure 2B), perivascular and rarely intraparenchymal CD3- and CD8-immunoreactive T cells (Figure 2C and D), scattered perivascular CD4-immunoreactive T cells (Figure 2E), and scattered damaged axons immunoreactive for amyloid precursor protein (Figure 2F). The chronic active lesions were distributed within the cerebral hemispheres and brainstem. Their ongoing inflammatory demyelination was confined to the edges (Figure 3A) containing frequent CD68-immunoreactive macrophages (Figure 3B) and scattered CD3-immunoreactive T cells (Figure 3C), some of which exhibited remyelination. Active demyelination in active and chronic active lesions was confirmed by colocalization of myelin basic protein with the CD68-immunoreactive macrophages (Figure 3D). Lesions had rare CD138-immunoreactive plasma cells and CD34-immunoreactive endothelial cells, but no CD20-immunoreactive B cells. Markers for professional antigen presenting cells CD1a and CD21 were negative. Extensive examination revealed no other pathology; no leukemic infiltration or infection, including adenovirus inclusions, was identified.

As the patient received HCT from an opposite-sex donor, fluorescence in situ hybridization analysis was performed for X and Y chromosomes to distinguish donor from recipient cells. Male donor cells with Y chromosomes constituted 3% to 17% of CD45-immunoreactive leukocytes (varying from region to region) and less than 10% of CD68-immunoreactive macrophages in the brain parenchyma. Rare CD3-immunoreactive T cells with Y chromosomes were noted in the brain parenchyma (Figure 4).

**COMMENT**

New MS disease activity is evident on clinical, MRI, and postmortem histopathological examination in this patient whose immune system was exchanged for a healthy immune system. Jeffery3 reported a similar case; a 43-year-old man with concurrent chronic myelogenous leukemia and MS underwent allogeneic HCT from an HLA-matched sibling and became a complete chimera 4 weeks after HCT. Relapse of MS necessitating methylprednisolone therapy occurred 6 weeks after HCT. Magnetic reso-
nance imaging scans 6 weeks and 2 years after HCT suggested ongoing MS disease activity. In contrast to that case report, our patient was studied prospectively and had histologically and immunohistochemically confirmed active inflammation/demyelination with axonal injury.

Our case study has a few limitations. First, the patient survived only 20 weeks after HCT, and examination of autopsy materials provided only a single time point for assessments of disease activity. Second, the patient died of fulminant liver failure secondary to adenovirus hepatitis. One could argue that the post-HCT neurologically progression represented an injection-triggered relapse of MS. However, the post-HCT infection in our patient occurred in the week prior to her death, only after the clinical worsening of her MS and corresponding MRI showed an increase in lesion burden. Third, the post-HCT course of MS was complicated by occurrence of GVHD. In this case, the worsening of MS appeared to occur before the development of GVHD. Moreover, GVHD-induced demyelination has not been reported after allogeneic HCT in patients without MS. Nevertheless, a GVHD reaction in the MS brain cannot be completely excluded.

Recent studies, including one on 5 autopsy cases, in patients treated for MS with autologous HCT showed that high-dose cytotoxic/immunosuppressive therapy did not halt inflammatory demyelination and axonal degeneration. Our case suggests that even high-dose cytotoxic/immunosuppressive therapy coupled with the exchange of the immune system for a healthy immune system may not halt the progression. Given the minority of donor immune cells identified in this brain, the recipient/patient immune cells seem to still be dominating the immunopathogenesis of MS after allogeneic HCT. Thus, the efficacy of HCT, particularly of its penetration into the brain, is uncertain.

It has been hypothesized that HCT might be an effective therapy for MS. Several patients have been reported to improve after allogeneic HCT, whereas others did not improve after allogeneic or autologous HCT. Studies suggest that the failure to arrest MS progression after HCT is because these patients had progressed into advanced stages of MS. Our patient with the pre-HCT EDSS score of 2.0 and continued disease activity suggests that the failure of HCT may occur in less advanced MS.

In conclusion, allogenic HCT may not be effective, even in patients with less advanced MS, as demonstrated in the present case showing clinical, MRI, and histopathological evidence of MS disease activity after allogeneic HCT.

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REFERENCES