Encephalomyelitis Mimicking Multiple Sclerosis Associated with Chronic Graft-Versus-Host Disease after Allogeneic Bone Marrow Transplantation

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Abstract

We describe a case of encephalomyelitis mimicking multiple sclerosis associated with chronic graft-versus-host disease (GVHD) occurring after allogeneic bone marrow transplantation (BMT) for myelodysplastic syndrome. Immunosuppressive therapy, consisting of a therapeutic dose of cyclosporine A and a maintenance dose of methylprednisolone, was effective in treating symptoms. Although central nervous system GVHD is very rare and remains controversial, presentation of neurological symptoms after allogeneic BMT warrants consideration of GVHD in the differential diagnosis.

Key words: allogeneic bone marrow transplantation, graft-versus-host disease, multiple sclerosis

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Introduction

Bone marrow transplantation (BMT) recipients are at high risk for neurological complications, including infection, metabolic abnormalities, drug toxicity, cerebrovascular events, posterior reversible encephalopathy syndrome (PRES), Epstein-Barr virus-associated lymphoproliferative disease (EBV-LPD), and relapse of malignant disease in the central nervous system (CNS) (1). Graft-versus-host disease (GVHD) is a systemic complication after BMT mediated by donor T cells targeting the skin, gastrointestinal tract, and liver. Involvement of other organ systems has been observed, but effects on the CNS are rare and controversial (2). Here, we describe a case of immune-mediated encephalomyelopathy mimicking MS associated with chronic GVHD after allogeneic BMT.

Case Report

In 1995, a 22-year-old woman was diagnosed with myelodysplastic syndrome (MDS). In 2006, she became transfusion-dependent and underwent allogeneic BMT using donor cells from her HLA-identical brother in May 2006. Transplant conditioning and GVHD prophylaxis consisted of busulfan (4 mg/kg per day for 4 days) plus cyclophosphamide (60 mg/kg per day for 2 days) and cyclosporin A (CyA) plus short methotrexate, respectively. Rapid engraftment and sustained complete donor chimerism was achieved. Her transplant course was uneventful and no acute GVHD was observed until two months after transplantation. CyA was tapered off and discontinued five months after transplantation.

Six months after transplantation, the patient developed pancytopenia, liver dysfunction, and oral lichen planus (Fig. 1). Her bone marrow cells showed no dysplasia of tri-lineage blood cells, and complete donor chimerism of bone

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Figure 1. Clinical course of the patient. BM: bone marrow, MRI: magnetic resonance imaging, CSF: cerebrospinal fluid, CyA: cyclosporine A, Tx: therapy, mPSL: methylprednisolone

Figure 2. T2-weighted MRI of the brain reveals multiple white matter lesions.

Figure 3. Spinal MRI reveals a high intensity lesion of the thoracic spinal cord.

marrow cells was maintained, as determined by variable number of tandem repeat analysis. At this time, she was diagnosed with chronic GVHD.

Seven months after transplantation, the patient developed blurred vision in the right eye and was diagnosed with optic neuritis after fundus examination revealed optic nerve head edema (Fig. 1). However, brain magnetic resonance imaging (MRI) did not reveal white matter lesions or optic nerve abnormalities at that time. She received methylprednisolone pulse therapy (1 g/day for 3 days), but her visual acuity gradually worsened. In addition, she gradually developed weakness and numbness of the lower limbs, urinary retention, and blurred vision in both eyes. Her visual acuity declined rapidly, finally becoming only able to observe counting fingers. Brain and spinal MRI revealed multiple high intensity lesions of white matter mainly in the right posterior limb of the internal capsule and thalamus (Fig. 2) and in the thoracic spine (Fig. 3). These lesions were enhanced with gadolinium. Cerebrospinal fluid (CSF) was clear, with normal pressure, cell counts (3 cells/μL), and myelin basic protein levels, glucose at 64 mg/dL, total protein at 20.0 mg/dL, IgG at 1.32 mg/dL, and an IgG index of 0.50. Oligoclonal bands were not detected in the CSF sample. Cytology of CSF revealed no evidence of malignancy and cultures of CSF were negative for bacteria and fungus. CSF for CMV, HHV-6, EBV, JC virus, and toxoplasma were negative for polymerase chain reaction (PCR).

The patient was subsequently treated with CyA and methylprednisolone pulse therapy. Neurological symptoms and white matter lesions visible by MRI improved (Fig. 4). Other manifestations of chronic GVHD also achieved remission. However, she developed weakness and numbness of
the upper and lower limbs again after methylprednisolone was tapered off, even though a therapeutic dose of CyA was administered at that time. Spinal MRI revealed new lesions of the cervical spine. The patient was again treated with methylprednisolone pulse therapy, and her neurological symptoms and radiological lesions of the cervical spine improved (Fig. 1). Improved neurological symptoms remained stable two years after transplantation, despite tapering of the methylprednisolone dose to 0.5 mg/kg.

Discussion

Although GVHD commonly affects the skin, gastrointestinal tract, liver, and hematopoietic system, recent reports have described patients with neurologic manifestations associated with GVHD (2-14). Animal studies support the possibility of the brain being a target organ for GVHD (15), however, CNS-GVHD remains controversial. CNS-GVHD may be properly diagnosed only if there is no evidence of other diseases with overlapping features and if radiographic characteristics of CNS involvement, response to immunosuppressive therapy, and T cell infiltration according to histological evaluation are observed (2). In the present case, negative evaluation for infection, multiple radiological lesions of the brain and spinal white matter, the development of systemic GVHD after discontinuation of CyA, and a response to CyA plus methylprednisolone immunosuppressive therapy support a diagnosis of CNS-GVHD, even though we do not have histological data.

Our patient developed optic neuritis and myelitis in separate time courses. MRI imaging revealed multiple white matter lesions of the brain and spinal cord. Acute disseminated encephalomyelitis (ADEM) also shows such multiple white matter lesions and typically follows an acute monophasic clinical course (16). These separate episodes of neurologic symptoms and radiologic findings are characteristic of MS, which is thought to be caused by immune-mediated demyelination. Immune-mediated myelitis after BMT is very rare, with only three other reported cases in the English literature (8, 11, 13).

There is no consensus on treatment options for CNS-GVHD. In most cases previously reported in the literature, treatment consisted of high-dose methylprednisolone or calcineurin-inhibitor (2). The present patient was first treated with methylprednisolone alone for optic neuritis, but her visual acuity worsened and neurological symptoms caused by myelitis emerged. After treatment with CyA plus methylprednisolone as a second line therapy for chronic GVHD (17), the neurological deficits improved. The patient developed myelitis again after methylprednisolone was discontinued. Finally, after treatment with CyA plus a maintenance dose of methylprednisolone, the neurological symptoms stabilized. This clinical course may indicate that as with systemic GVHD in other organs, a therapeutic dose of calcineurin inhibitor and a maintenance dose of corticosteroid for second line therapy are necessary for the treatment of CNS-GVHD.

Clinically significant CNS-GVHD is rare, but the consequences can be serious. A diagnosis of CNS-GVHD should be considered in cases of neurologic symptoms after allogeneic BMT if there is no evidence of other diseases with overlapping features and if radiographic characteristics of CNS involvement and response to immunosuppressive therapy are observed.

References

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Figure 4. MRI of the brain after immunosuppressive therapy shows improvement of white matter lesions.


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