Neuroinflammation and Demyelination in Multiple Sclerosis After Allogeneic Hematopoietic Stem Cell Transplantation

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Objective: To evaluate the effects of allogeneic hematopoietic stem cell transplantation (allo-HSCT) on the brains of persons with and without multiple sclerosis (MS) by means of postmortem histopathological examination.

Design: Postmortem histopathology, case studies, and case-control studies.

Patients: Four patients with MS who died at a median of 4.5 months (range, 3-9 months) after allo-HSCT for a concomitant hematologic malignant neoplasm; 5 patients without MS who died at a median of 10.0 months (1-29 months) after allo-HSCT; and 5 control subjects without MS who did not undergo allo-HSCT.

Setting: Referral centers.

Intervention: Allogeneic hematopoietic stem cell transplantation.

Main Outcome Measures: Morphological features and immunohistochemical features, including the quantitative measures of chronic inflammatory cells.

Results: Demyelinating and inflammatory activities of MS persisted after allo-HSCT in all of the patients with MS. Active and chronic active MS lesions exhibited significantly higher numbers of CD3+ T cells and CD8+ cytotoxic T cells and significantly higher scores of CD68+ microglia/macrophages than did chronic inactive lesions or normal-appearing white matter. The normal-appearing brains of allo-HSCT recipients who did not have MS were found to have significantly higher numbers of CD3+ T cells and CD8+ cytotoxic T cells and higher scores of CD68+ microglia/macrophages compared with the controls; however, no demyelination was identified in these non-MS samples.

Conclusion: Allo-HSCT fails to halt the demyelination and inflammation of MS.

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The pathologic processes of multiple sclerosis (MS) are thought to be contributed to by T and B cells that invade the central nervous system (CNS) to cause oligodendrocyte damage, demyelination, and axonal loss.1-3 Current therapies for MS consist of immunomodulating agents such as interferon beta and glatiramer acetate and anti-inflammatory and immunosuppressive drugs such as glucocorticoids and mitoxantrone hydrochloride. Hematopoietic stem cell transplantation (HSCT) is a form of therapy in which immune suppression is maximized to the point of immune ablation.4 Selected patients with MS, after preparation for the transplant by means of a potent immunosuppressive regimen, undergo autologous HSCT to restore the host immune system.5 An increasing number of studies have assessed autologous HSCT as a potential new therapeutic strategy in severe forms of MS. Based on the published studies, autologous HSCT produces a broad range of patients with survival free of MS progression (36%-95%) and MS activity (33%-64%).1,6 The only published histopathological study of autologous HSCT in MS indicated a failure to arrest demyelination and neurodegeneration in 5 patients who died within 1.5 years after the transplantation.7

Allo-HSCT is inspired by case reports of MS patients who have undergone allo-HSCT for a concomitant hematologic malignant neoplasm and subsequently has been supported by animal models of MS. Because allo-HSCT is designed to furnish a new immune system in primary lymphoid tissues, it represents an approach different from autologous HSCT for the eradication of autoimmune disease.5,8 This has not been explored in prospective studies, however, because treatment-related morbidity in allo-HSCT is substantially higher than that in autologous HSCT, mostly ow-
body irradiation.

GVH, graft-vs-host; MS, multiple sclerosis; NA, not applicable; PPMS, primary progressive multiple sclerosis; RRMS, relapse-remitting multiple sclerosis; TBI, total body irradiation.

Of these reports, 3 patients showed clinical improvement or stabilization.11-13 Two patients exhibited clinical and radiological evidence of persistent MS activities with follow-up times of 24 and 4 months after allo-HSCT.14,15 To our knowledge, our recent case report15 was extended in the present study as the only study with postmortem histopathological examination that demonstrated persistent inflammatory and demyelinating activities of MS 4 months after allo-HSCT.

The present study examined the histopathological findings of MS in 4 patients who received allo-HSCT. Our recently reported case15 was extended in the present study (case 1 in Table 1) for the purpose of quantitative analyses. To assess whether allo-HSCT in the absence of MS could be associated with CNS inflammation, we further examined a group of non-MS allo-HSCT recipients and a group of non-MS, non-allo-HSCT control subjects.

### Table 1. Demographic and Clinical Characteristics of Allo-HSCT

<table>
<thead>
<tr>
<th>Case No./Sex/Age at Allo-HSCT, y</th>
<th>Conditioning/GVH Disease Prophylaxisa</th>
<th>Time From MS Dx to Allo-HSCT, y</th>
<th>Clinical Disease Course</th>
<th>EDSS Before Allo-HSCT</th>
<th>EDSS After Allo-HSCT</th>
<th>Time of Death After Allo-HSCT, mo</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/63</td>
<td>Busulfan, fludarabine phosphate, ATG/methotrexate sodium, cyclosporine</td>
<td>19</td>
<td>RRMS</td>
<td>2.0</td>
<td>3.0</td>
<td>4</td>
<td>Multiple organ failure</td>
</tr>
<tr>
<td>2/F/38</td>
<td>Cyclophosphamide, thiota, TBI, ATG/corticosteroids, cyclosporine</td>
<td>9</td>
<td>RRMS</td>
<td>Unknown</td>
<td>Unknown</td>
<td>5</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>3/M/42</td>
<td>Busulfan, cyclophosphamide/methotrexate, cyclosporine</td>
<td>5</td>
<td>PPMS</td>
<td>Unknown</td>
<td>Unknown</td>
<td>9</td>
<td>Myocardial infarction/pneumonia</td>
</tr>
<tr>
<td>4/F/59</td>
<td>Busulfan, fludarabine, ATG/methotrexate, cyclosporine</td>
<td>Incidentalb</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>Pneumonia</td>
</tr>
</tbody>
</table>

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; Dx, diagnosis; EDSS, Expanded Disability Status Scale; GVH, graft-vs-host; MS, multiple sclerosis; NA, not applicable; PPMS, primary progressive multiple sclerosis; RRMS, relapse-remitting multiple sclerosis; TBI, total body irradiation.

aMedications designated for conditioning were administered before HSCT; medications for GVH disease prophylaxis were administered after HSCT.

bIndicates no documentation of MS in the clinical medical record.

### Table 2. Demographic and Clinical Characteristics of non-MS Patients

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Hematological Disease</th>
<th>Conditioning/GVH Disease Prophylaxis</th>
<th>Time of Death After Allo-HSCT, mo</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/63</td>
<td>Idiopathic myelofibrosis</td>
<td>Busulfan, fludarabine phosphate, ATG/methotrexate sodium, cyclosporine</td>
<td>1</td>
<td>Multiple organ failure</td>
</tr>
<tr>
<td>2/F/58</td>
<td>Cutaneous T-cell lymphoma</td>
<td>CHOP/alemtuzumab (Campath), corticosteroids</td>
<td>12</td>
<td>Multiple organ failure</td>
</tr>
<tr>
<td>3/F/56</td>
<td>Acute lymphoblastic leukemia</td>
<td>Busulfan, fludarabine, ATG/methotrexate, cyclosporine, corticosteroids</td>
<td>3</td>
<td>Multiple organ failure</td>
</tr>
<tr>
<td>4/M/54</td>
<td>Acute myelogenous leukemia</td>
<td>Idarubicin hydrochloride, cytarabine/methotrexate, cyclosporine, corticosteroids</td>
<td>10</td>
<td>Diffuse alveolar damage</td>
</tr>
<tr>
<td>5/M/33</td>
<td>Chronic myelogenous leukemia</td>
<td>Hydroxyurea/corticosteroids, cyclosporine</td>
<td>29</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>6-10/3 M, 2 F/26-65a</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; CHOP, cyclophosphamide, doxorubicin, vincristine sulfate, and prednisone; GVH, graft-vs-host; MS, multiple sclerosis; NA, not applicable.

a Indicates a group of age-matched controls.

The present study examined the histopathological findings of MS in 4 patients who received allo-HSCT. Our recently reported case15 was extended in the present study (case 1 in Table 1) for the purpose of quantitative analyses. To assess whether allo-HSCT in the absence of MS could be associated with CNS inflammation, we further examined a group of non-MS allo-HSCT recipients and a group of non-MS, non-allo-HSCT control subjects.

### METHODS

**SUBJECTS**

This study was approved by local research ethics boards and performed on archival autopsy tissues from 4 MS (Table 1) and 10 non-MS (Table 2) cases that were obtained from the departments of pathology of the University of Calgary and the University of Alberta. A prior diagnosis of MS was made clinically in 3 of these MS patients, but a diagnosis of MS was not noted in the hospital records of the fourth patient. Postmortem neuropathological examination in all the MS patients revealed multiple lesions diagnostic of MS. The MS patients received allo-HSCT for treatment of their concurrent hematological diseases, including chronic myelogenous leukemia in case 1 and acute myelogenous leukemia in cases 2 through 4 (Table 1). Their lengths of time to death after allo-HSCT ranged from 3 to 9 months (median, 4.5 months).

Five non-MS patients from the Calgary archives (cases 1-5 in Table 2) who were described as having a normal brain and spinal cord on macroscopic and routine histopathological examination were included to investigate the effect of allo-HSCT on normal-appearing brains. Their lengths of time to death after allo-HSCT ranged from 1 to 29 months (median, 10.0...
months). Five neuropathologically normal subjects who did not undergo allo-HSCT (cases 6-10 in Table 2) served as the controls in the present study. All the non-MS patients who did or did not undergo allo-HSCT were free of neurological symptoms and abnormal radiologic findings of the CNS.

Although complete chimerism of circulating leukocytes were achieved by allo-HSCT in all the cases (data not shown), the protocols for allo-HSCT differed by individual in the present study (Tables 1 and 2).

HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMISTRY STUDIES

The postmortem delay was less than 24 hours in all cases. All brain tissue was fixed in 10% formalin for at least 1 week. Neuropathological examination was performed on sections of the cerebral hemispheres, brainstem, and cerebrum ranging from 0.5 to 1.0 cm in thickness. The tissue blocks containing MS lesions and control areas were sampled from various brain regions. In the non-MS cases, 3 sampling blocks were taken from the frontal lobe, brainstem, and temporal lobe (or basal ganglia, depending on the availability) in the present study. The tissue samples were embedded in paraffin, cut into 6-µm-thick tissue sections, deparaffinized, and stained with hematoxylin-eosin and Luxol fast blue to locate the lesions.

The primary antibodies used were mouse antihuman CD68 (macrophages/microglia; DAKO Denmark A/S, Glostrup, Denmark), anti-CD3 (T cells; Thermo Scientific, Rockford, Illinois), anti-CD4 (helper T cells; Cell Marque Corporation, Rocklin, California), anti-CD8 (cytotoxic T cells; DAKO Denmark A/S), anti-CD20 (B cells; DAKO Denmark A/S), anti-CD138 (plasma cells; Thermo Scientific), anti-CD21 (professional antigen-presenting cells; DAKO Denmark A/S), anti-CD1a (professional antigen-presenting cells; Immunotech, Marseilles, France), anti-myelin basic protein (a myelin marker; Millipore, Billerica, Massachusetts). Double immunofluorescence staining was performed with primary antibodies against myelin basic protein and CD68 to detect myelin degradation products in macrophages.

The MS lesions were histopathologically classified using a modification of the Bö-Trapp staging system into active, chronic active, and chronic inactive lesions.

QUANTITATIVE AND SEMIQUANTITATIVE ANALYSES OF INFLAMMATORY ACTIVITY

To assess inflammatory activity, the numbers of CD3⁺ and CD8⁺ T cells were counted in a high-power field (original magnification ×400) in a high-power field (original magnification ×100). Other features of inflammatory activity in this patient were described in our previously published study.25
cantly × 200, defined as 0.79 mm²), with separate counting in the perivascular and parenchymal areas. The frequency of CD68⁺ macrophages was scored as follows: 0 indicates none; 1, rare; 2, scattered; and 3, frequent per high-power field. For counting or scoring in the perivascular areas, the fields containing the vessels larger than 300 µm were excluded. The values represent sums of 10 consecutive high-power microscopic fields.

STATISTICAL ANALYSIS

We used the Mann-Whitney test to assess the difference in various measures of inflammation between groups. P < .05 was regarded as significant.

RESULTS

The clinical features of the MS patients who underwent allo-HSCT are summarized in Table 1. After allo-HSCT, MS in 1 patient progressed clinically (represented by a change in the Expanded Disability Status Scale score from 2.0 to 3.0); 2 MS patients did not have information of assessments specifically for MS in their medical records; and the last patient had no clinical documentation of MS as a concurrent condition (MS was an incidental neuropathological finding). Besides the MS lesions, histopathological examinations revealed no other abnormality in case 1, disclosed multiple acute and chronic infarcts in cases 2 and 3, and found a focus of leukoencephalopathy in case 4. The non-MS patients who underwent allo-HSCT and the controls died of various causes (Table 2), but the routine neuropathological examination exhibited normal brain and spinal cord.

DEMYELINATING ACTIVITY IN MS PATIENTS WHO UNDERWENT ALLO-HSCT

All 4 MS patients showed varying degrees of demyelinat-
ing activity, that is, with active lesions (case 1 in Table 1) and/or chronic active lesions (cases 1-4 in Table 1). Active lesions exhibited demyelinating activity throughout the lesions, containing abundant macrophages/microglia (Figure 1A and B) and frequent T cells. Chronic active lesions were hypocellular in their cores but inflammatory and demyelinating at their edges, with frequent macrophages/microglia and T cells (Figure 1D and Figure 2). The demyelinating activity was demonstrated by diminishing intensity of Luxol fast blue staining (Figures 1A and 2A) and macrophages phagocytosing myelin debris (Figure 1A) and was confirmed by colocalization of myelin basic protein with the CD68⁺-immunoreactive macrophages on double immunofluorescence staining (Figures 1B and 2F). Focal remyelination was suggested in some of the chronic active lesions (Figure 1D). Relatively mild axonal injury was associated with the demye-
linating activity and shown by immunoreactivity for amyloid precursor protein (Figures 1C and 2E).

INFLAMMATORY ACTIVITY IN MS PATIENTS WITH ALLO-HSCT

Inflammatory activity was identified in the active lesions (Figure 1A and B) and in chronic active le-
sions predominantly at their edges (Figures 1D and 2). Inflammatory cells were mainly macrophages/microglia immunoreactive for CD68 (Figures 1A and B and 2B and F); T cells (lymphocytes) were variably immunoreactive for CD3, CD4, and CD8 (Figure 2C and D). These lesions had rare CD138⁺ plasma cells but no CD20⁺ B cells. The markers for professional antigen-presenting cells, CD1a and CD21, yielded negative results.

The analysis of 13 lesions (active or chronic active) with inflammatory/demyelinating activities disclosed that the lesions with the activities had significantly higher numbers of CD3⁺ T cells and CD8⁺ cytotoxic T cells, as well as significantly higher scores of CD68⁺ microglia/macro-
phages than chronic inactive lesions (n = 13) or normal-appearing white matter (n = 14) from the same patients (P < .001; Table 3).

One MS patient (case 4 in Table 1) had focal leukoen-
cephalopathy mainly in the posterior cerebral hemi-
spheres, which was presumably owing to immuno-
suppressant treatment with methotrexate sodium and/or cyclosporine. This additional leukoencephalopathy was
characteristically necrotic and distinct from the MS lesions. In this case, 4 MS lesions (1 chronic active lesion and 3 chronic inactive lesions) apart from the foci of leukoencephalopathy were included in the present analysis; the other lesions abutting the focus of leukoencephalopathy were excluded.

**INFLAMMATION IN NON-MS PATIENTS WHO UNDERWENT ALLO-HSCT**

Because persistent inflammatory/demyelinating activities of MS were present after allo-HSCT, further investigation was focused on whether inflammation/demyelination can result from allo-HSCT in the absence of MS. Five neuropathologically normal non-MS allo-HSCT recipients were examined (Figure 3A-C, E, and G) and compared with 5 neuropathologically normal subjects who did not receive allo-HSCT (Figure 3D, F, and H). The analysis of 3 brain regions in each subject demonstrated that the patients who underwent allo-HSCT had significantly higher numbers of CD3⁺/H11001 T cells (Figure 3C) and CD8⁺/H11001 T cells (Figure 3E) cytotoxic T cells and higher scores of CD68⁺/H11001 microglia/macrophages (Figure 3G) compared with the controls (Figure 3D, F, and H, respectively; \( P < .05 \)) in both the parenchyma and perivascular areas (except for CD8⁺ cytotoxic T cells in perivascular areas; Table 4). However, no obvious demyelination was identified by the Luxol fast blue stain (Figure 3B) or by double immunostains of myelin basic protein/CD68 in these non-MS brains that did not undergo allo-HSCT (not shown).

**COMMENT**

The present study is, to our knowledge, the first to examine CNS histopathological findings in MS patients after allo-HSCT. Despite the procedure, active demyelination and inflammation persisted, indicating the failure of allo-HSCT to halt the MS disease activity, at least during the follow-up period in these patients. This failure may be attributed to several possibilities.

First, the persistence of recipient immune cells in the brain may fuel the MS activities. This possibility is supported by our previous finding in which fluorescent in situ hybridization analysis of sex chromosomes of cells in a female MS patient who received allo-HSCT from a male donor (case 1 in Table 1) revealed that, although only donor blood cells were present in the peripheral circulation,
Fourth, although the CNS showed no evidence of infection, a systemic viral infection after allo-HSCT in some of the patients could trigger the relapse of MS and contribute to the progression of MS. This possibility cannot be excluded in the present study, although at least 1 of the patients (case 1 in Table 1) exhibited increased lesion burden in magnetic resonance images and clinical progression of MS several weeks before the occurrence of viral infection. Finally, the beneficial effect of allo-HSCT may take a longer time to manifest in the CNS. Studies on the mitotic life span of lymphocytes have yielded widely disparate results. The reason for the discrepancy in these estimates is unclear. Most of the studies have demonstrated an average life span of months or years for T cells and of several weeks or months for B cells. In the present study, the longest survival after allo-HSCT was 9 months (with a median survival of 4.5 months). It is possible that allo-HSCT may not yet exhibit optimal effects on the brains by the time of histopathological examination. Nevertheless, the fatal outcome after allo-HSCT in these MS patients implies that the complications of allo-HSCT (along with its conditioning regimen) and potential progression of MS dominate the prognosis of allo-HSCT.

In comparison with autologous HSCT, which has been reported to suppress the inflammatory activity of MS, allo-HSCT in our patients failed to halt the demyelinating and inflammatory activities of MS. Because the conditioning treatment of allo-HSCT is similar to that of autologous HSCT, the difference in the effect on MS inflammatory activity between the 2 kinds of transplantation presumably lies in the nature (autologous vs allogeneic) of the cells transplanted into the patients. This presumption is compatible with the possibility (discussed in the preceding paragraphs) that the persistence of inflammation after allo-HSCT is likely to result from complications of allo-HSCT, especially of GVH reaction. We cannot completely exclude other possibilities, however, such as the difference in the selection of MS patients between the present study and the only histopathological study on autologous HSCT. 

Although the non-MS brains that underwent allo-HSCT contained diffuse but mild inflammation, no obvious demyelination was identified in the present study. The hypotheses for the preservation of myelin sheaths in these brains are the following: (1) possible dissociation of inflammation with demyelination after HSCT, 

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Table 4. Inflammation in Normal-Appearing Brains After Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT)

<table>
<thead>
<tr>
<th>Group</th>
<th>CD3+ T Cells Paranohya</th>
<th>CD3+ T Cells Perivascular</th>
<th>CD8+ T Cells Paranohya</th>
<th>CD8+ T Cells Perivascular</th>
<th>CD68+ Microglia/Macrophages Paranohya</th>
<th>CD68+ Microglia/Macrophages Perivascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo-HSCT</td>
<td>35 (3-72)</td>
<td>35 (2-96)</td>
<td>11 (1-93)</td>
<td>18 (2-90)</td>
<td>19 (11-21)</td>
<td>11 (5-18)</td>
</tr>
<tr>
<td>Control†</td>
<td>4 (0-14)</td>
<td>18 (4-27)</td>
<td>3 (0-16)</td>
<td>16 (2-38)</td>
<td>11 (0-10)</td>
<td>5 (3-14)</td>
</tr>
</tbody>
</table>

*Frequency of CD68+ microglia/macrophages was scored from 0 to 3 by summing 10 consecutive high-power (>200) microscopic fields.*

*P<.001 by Mann-Whitney test vs controls.*

*P<.01 by Mann-Whitney test vs controls.*

*P<.05 by Mann-Whitney test vs controls.*

*P<.05 by Mann-Whitney test vs controls.*

*Indicates neuropathologically normal subjects who did not undergo allo-HSCT.*

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most CD45+ and CD68+ cells within the brain were still of the female recipient’s origin. Although complete chimerism of circulating leukocytes can be optimally achieved by allo-HSCT, the conditioning immunosuppressive treatment may have much less effect on the cells trapped or resident within the CNS. In support, Mondria et al examined 2 markers indicative of lymphocyte activation in the cerebrospinal fluid, sCD27, and oligoclonal IgG bands, and found that these were still evident 6 to 9 months after whole-body immune ablation in MS subjects. The authors concluded that complete eradication of activated lymphocytes from the CNS had not been achieved despite intense immunoablation.

Second, GVH reaction could theoretically induce allo-immune damage to the brain and may complicate the pathologic processes of MS after allo-HSCT. In the present study, all the patients (including the MS patients and non-MS patients with normal-appearing brains) developed histopathologically confirmed GVH disease after allo-HSCT, involving the skin, gut, or liver. Graft-versus-host disease is associated with a cytokine storm and T-cell activation, which induces the complex immune reactions that interact with the pathological processes of MS. The present study demonstrated increased diffuse infiltration of T cells and macrophages/microglia within the normal-appearing brains of non-MS patients after allo-HSCT, which would be consistent with the GVH reaction after allo-HSCT. Nevertheless, the contribution of GVH disease to the demyelinating activity of MS may be minor in the present study because (1) at least 1 patient (case 1 in Table 1) showed clinical evidence of MS progression before the development of GVH disease; (2) there was no obvious demyelination in the non-MS allo-HSCT recipients, although their brains showed mild and diffuse inflammation; and (3) demyelination and neurodegeneration were active even with marked suppression of the inflammatory activity in MS patients who received autologous HSCT.

Third, the failure to arrest MS progression has been often attributed to studying patients in whom MS has progressed into advanced stages. This possibility is unlikely in the present study because one of our patients (case 1 in Table 1) had a pretransplantation Expanded Disability Status Scale score of 2.0 and another patient (case 4 in Table 1) was asymptomatic before allo-HSCT. Therefore, the failure of allo-HSCT may occur even in less advanced MS.
(2) insufficient severity of inflammatory activity to produce demyelination, (3) individual vulnerabilities including genetic predisposition,27,38 or (4) different antigen specificities of the T cells in the MS vs non-MS cohorts. As well, the CNS milieu of non-MS subjects is likely different from that of MS subjects, as evident by increase in the levels of chemokines, cytokines, free radicals, proteases, and other molecules in the MS brains, and may not be able to promote the activation and pathogenic potential of infiltrating T cells. Finally, although we did not look for this, the increased cell content in the normal brain after transplant without evidence of damage to histological structures may be related to increased regulatory T-cell content, which could prevent autoactivity to brain tissues. In transplant models, protection of organs from allogeneic immune cells is associated with an increased regulatory T-cell content in that organ.39,40

In conclusion, the demyelinating and inflammatory activities of MS persist after allo-HSCT. The demyelinating activity is presumably due to the persistence of recipient immune cells in the MS brain, whereas the inflammatory activity is more likely the result of GVH reaction after allo-HSCT. The findings of the present small series of MS patients indicate that allo-HSCT fails to stop the demyelination and inflammation of MS.

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