Angiitis of the Central Nervous System After Allogeneic Bone Marrow Transplantation?

Claudio S. Padovan, MD; Karl Bise, MD; Joachim Hahn, MD; Petra Sostak, PhD, MD; Ernst Holler, MD; Hans-Jochem Kolb, MD; Andreas Straube, MD

Background and Purpose—There is only limited information about late neurological complications after bone marrow transplantation (BMT). The purpose of this study is to describe a cerebral angiitis-like syndrome after allogeneic BMT.

Methods—Clinical and diagnostic findings of 5 BMT patients with chronic graft versus host disease and neuropathological data of 1 patient were reported.

Results—In the described patients, focal neurological signs and neuropsychological abnormalities occurred years after BMT. MRI revealed periventricular white matter lesions, lacunar or territorial infarctions, leukoencephalopathy, and hemorrhages. Angiitis of the central nervous system was confirmed in 1 patient at autopsy, and an angiitis-like syndrome was suspected in the other patients because of the clinical course and response to treatment. Three patients received cyclophosphamide and steroids (2 improved, 1 died), 1 patient improved after steroids alone, and 1 patient without immunosuppressive therapy deteriorated further.

Conclusions—We propose that an angiitis-like syndrome of the central nervous system can be a neurological manifestation of graft versus host disease, which should be considered a possible cause of cerebral ischemic episodes and pathological MRI scans in BMT patients with graft versus host disease. (Stroke. 1999;30:1651-1656.)

Key Words: angiitis ■ bone marrow transplantation ■ cerebral infarction ■ cerebrovascular disorders ■ complications ■ graft vs host disease ■ white matter

Bone marrow transplantation (BMT) and hematopoietic stem cell transplantation are important treatments for a variety of malignant diseases and nonmalignant disorders. Frequent neurological sequelae in the early period after allogeneic BMT include encephalopathy, cerebrovascular accidents, central nervous system (CNS) infections, and recurrence of the malignant disease. Despite the large and growing number of long-term survivors of BMT, there is only limited information about late neurological complications. Neurological involvement in chronic graft versus host (GVH) disease has until now been restricted to myasthenia gravis, polymyositis, and polyneuropathy. We describe a patient with chronic GVH disease who had neuropathologically confirmed cerebral angiitis. In addition, we describe 4 other BMT patients with chronic GVH disease and suspected cerebral angiitis-like syndrome.

Subjects and Methods
From June 1993 through January 1998, 5 BMT patients with active chronic GVH disease and suspected cerebral angiitis-like syndrome were included in this study. All patients (4 men, 1 woman; age range, 19 to 53 years) had had allogeneic BMT from HLA-matched family or nonrelated donors for treatment of chronic myelogenous leukemia (n=1), acute myelogenous leukemia (n=1), and acute lymphoblastic leukemia (n=1). They were prepared for marrow transplantation with fractionated total body irradiation (3×4 Gy) and cyclophosphamide (2×60 mg/kg). Two patients received intrathecal methotrexate prophylaxis. After BMT, patients were monitored for infections by microbiological cultures (blood, sputum, urine), antibody response, and polymerase chain reaction (PCR). At the time of neurological disease, bacterial or fungal infections were excluded by routine monitoring and cerebrospinal fluid (CSF) examinations. Infection with herpes simplex virus, varicella-zoster virus, human herpesvirus 6, adenovirus, cytomegalovirus, coxsackievirus (B1 to B6), parvovirus B19, Epstein-Barr virus, or JC virus was unlikely because of negative serum and CSF antibody response or negative PCR, as appropriate. Standard parameters for systemic vasculitis (eg, erythrocyte sedimentation rate), underlying collagen vascular disease (eg, antinuclear antibodies), or coagulopathy (lupus anticoagulant, cardiolidipin antibodies) were either absent or normal. Diagnostic parameters included CT, MRI, transcranial Doppler sonography (TCD), CSF analysis, and cerebral angiography (summarized in the Table). Neuropathological findings from 1 patient were reported. Patients were followed up from 1 month to 3 years.

Results
Patient 1
A 43-year-old right-handed male patient underwent BMT for chronic myelogenous leukemia. He developed acute and chronic extensive GVH disease, which was treated with...
Clinical Presentation, Diagnostic Findings, and Outcome

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Clinical Presentation</th>
<th>MTX</th>
<th>CsA</th>
<th>G VH Disease</th>
<th>CSF</th>
<th>TCD</th>
<th>Angiography</th>
<th>MRI</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vertigo, hemianopia, aphasia, hemiparesis</td>
<td>No</td>
<td>No*</td>
<td>+ + +</td>
<td>↑ Protein</td>
<td>Abnormal</td>
<td>Normal</td>
<td>WML, ischemic areas, hemorrhages</td>
<td>Cy/steroids</td>
<td>Hemianopsia, MRI regressive, deceased (non-CNS cause)</td>
</tr>
<tr>
<td>2</td>
<td>Aphasia, hemiparesis, seizures</td>
<td>No</td>
<td>No</td>
<td>+</td>
<td>Normal</td>
<td>Abnormal</td>
<td>ND</td>
<td>Ischemic areas, WML</td>
<td>Cy/steroids</td>
<td>Bilateral MCA/ACA infarctions, deceased (tentorial herniation)</td>
</tr>
<tr>
<td>3</td>
<td>Confusion, spastic hemiparesis</td>
<td>Yes</td>
<td>Yes</td>
<td>+ + +</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Leukoencephalopathy</td>
<td>Steroids</td>
<td>Normal, MRI regressive</td>
</tr>
<tr>
<td>4</td>
<td>Aphasia, apraxia, dementia, tetraparesis</td>
<td>Yes</td>
<td>Yes</td>
<td>+ +</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Leukoencephalopathy, hemorrhages</td>
<td>Cy/steroids</td>
<td>Clinically stable, MRI unchanged</td>
</tr>
<tr>
<td>5</td>
<td>Cognitive deficit, aphasia</td>
<td>No</td>
<td>Yes</td>
<td>+ + +</td>
<td>↑ Cells</td>
<td>Normal</td>
<td>MCA branch occlusion</td>
<td>Periventricular WML, frontoparietal ischemia</td>
<td>...</td>
<td>Clinically worsened, MRI progressive (confluent WML)</td>
</tr>
</tbody>
</table>

*Pt indicates patient; MTX, intrathecal methotrexate; CsA, cyclosporine A; +, mild; + + , moderate; + + + , severe; ND, not performed; WML, white matter lesions; and Cy, cyclophosphamide.

Cyclosporine (during the first 5 months), mycophenolate mofetil (given instead of cyclosporine), prednisolone, and azathioprine. Other complications were cytomegalovirus pneumonia (cytomegalovirus PCR and antibody titer in CSF were always negative) and reactivated hepatitis B virus infection in the early period after BMT. Six months after BMT, the patient complained of transient mild nonrotational vertigo for 2 weeks, but clinical examination and cranial MRI were normal.

Eighteen months after BMT, rotational vertigo and dysarthria occurred. At this time, active GVH disease involving the skin and liver was present. CT scans showed bilateral caudate nuclei and deep white matter hypodensities. One month later, the patient suddenly developed a hemianopsia on the left. Two days later, an additional mixed aphasic syndrome (progressive for several days) and a moderate paresis of the right arm occurred. MRI revealed an occipital hematoma and an older small pontine hematoma (Figure 1A and 1B) as well as multiple periventricular, caudate nuclei, thalamic, and brain stem T2-weighted hyperintense lesions (Figure 1A, 1B, and 1E). Some of the lesions were hyperintense in T1-weighted scans and had additional weak gadolinium enhancement (Figure 1C and 1D). TCD examination showed bilateral pathological increased mean velocities (140 to 150 cm/s in both middle cerebral arteries [MCAs]). CSF analysis revealed an elevated total protein (1.12 g/L); cell count and glucose concentration were normal. Cerebral angiography and transesophageal echocardiography were normal. Treatment with cyclophosphamide (500 mg IV every 2 weeks) was started, and steroid medication was increased (1.5 mg/kg IV prednisolone QID, tapered to <1 mg/kg after 4 weeks). Despite normal angiography, nimodipine was given to possibly increase cerebral ischemic tolerance because of assumed vasculitis. During the next 10 days, the patient markedly improved, and TCD velocities normalized. After 3 weeks, the patient’s neurological status had returned to normal except for a residual incomplete hemianopsia. MRI 2 months later showed that thalamic and brain stem signal abnormalities had resolved (Figure 1F), whereas periventricular and caudate nuclei lesions remained unchanged. No further bleeding or enlargement of ischemic areas was seen. The patient died of pneumonia 5 months after developing initial neurological symptoms.

General autopsy revealed pneumonia, aortic valve endocarditis, renal infarctions, and hepatosplenomegaly. Microscopic examination showed hepatic lymphocytic infiltrations corresponding to GVH disease. Brain edema, the right occipital hematoma (2 × 1.7 cm), and the pontine hematoma (1 × 1 cm) were seen at gross neuropathological examination. Histological and immunohistological examinations revealed multifocal distribution of inflammatory infiltrations of blood vessel walls and perivascular areas (Figure 2). Subendothelial lymphocytic infiltrations, sectorial vessel wall infiltrations, and perivascular infiltrations were found (Figure 2A). Cellular infiltrations consisted of T cells, B cells, and mononuclear cells (Figure 2C and 2D). Affected vessels had hyalin changes and partial lumen occlusions with organized thrombotic material. Typical angiitis was found in small arterioles, precapillary, and capillary vessels (Figure 2). Leptomeningeal vessels showed fibrosis without lymphocytic infiltration, whereas large arteries were normal. The basal ganglia had several lacunar ischemic areas. The cerebral white matter additionally showed sporadic focal demyelination and microglia reaction. No signs of viral CNS infection were detected.

**Patient 2**

A 32-year-old female patient with acute myelogenous leukemia had had chronic skin GVH disease after BMT, which did not require immunosuppressive therapy. Twenty-eight months after BMT, she developed nonrotational vertigo, and
2 weeks later she experienced a progressive aphasic syndrome with a right-sided hemiparesis. CT scans showed several hypodensities in the left frontoparietal region. CSF analysis and transesophageal echocardiography were normal. TCD examination revealed elevated mean flow velocities in the MCA (180 cm/s), anterior cerebral artery (ACA) (120 cm/s), and basilar artery (80 cm/s). MRI scans showed bilateral ischemic lesions in cortical-subcortical areas, basal ganglia, and periventricular and deep white matter. Treatment with cyclophosphamide (500 mg IV every 2 weeks), prednisolone (1.5 mg/kg IV QID), and nimodipine was started. The patient improved during the following 3 weeks and only had residual mild aphasia. However, TCD mean velocities did not normalize. One month after admission, the patient developed a left hemiparesis and seizures. CT scans showed a right anterior MCA territory infarction. Again, no cardiac embolic source was seen on transesophageal echocardiography. The next day bilateral ACA and MCA infarctions occurred, and the patient subsequently died of tentorial herniation. Permission for autopsy was refused.

**Patient 3**

A 19-year-old male patient had had BMT, including prophylactic intrathecal methotrexate, because of acute lymphoblastic leukemia. He received cyclosporine for extended acute and chronic GVH disease involving skin, bowel, and liver. Thirty-one months after BMT, he developed subacute confusion and a right hemiparesis. MRI showed bilateral, confluent white matter lesions in the frontal and parieto-occipital region and a leptomeningeal contrast enhancement. CSF analysis, TCD examination, and cerebral angiography were normal. $^{99m}$Tc-hexamethylpropyleneamine oxime single-photon emission CT (SPECT) showed disseminated areas of lowered perfusion. Cyclosporine medication was stopped, and treatment with prednisolone 1.5 mg/kg QID was started. The right hemiparesis and the cognitive status improved markedly; steroids were tapered and were stopped after 1 year. Follow-up examination 3 years later revealed normal clinical status. MRI again showed meningeal enhancement, but leukoencephalopathy had markedly regressed.

**Patient 4**

A 32-year-old male patient had received BMT with prophylactic intrathecal methotrexate treatment because of chronic myelogenous leukemia. Because of extended acute and chronic skin GVH disease, he was treated with cyclosporine. Nine months after BMT, the patient developed a right hemiparesis. MRI showed left parietal hemorrhage and mild leukoencephalopathy. Cyclosporine was stopped, but in the following 2 years additional parenchymal hemorrhages occurred in the left frontal and right parietal lobes. Cerebral angiography, TCD examination, and CSF analysis were normal. Clinical examination 5 years after BMT revealed mild aphasia, apraxia, spastic tetraparesis, and cognitive impairment. MRI showed leukoencephalopathy, residual signs from the hemorrhages, and bilateral gadolinium enhancement in the trigones. $^{99m}$Tc-ethyl cysteinate dimer SPECT revealed multifocal cortical and white matter hypoperfusion. The patient was treated with cyclophosphamide (500 mg IV every 3 weeks) and steroids (prednisolone 1.5 mg/kg QID). One year later, the patient’s neurological condition was stable, and MRI remained unchanged.

**Patient 5**

A 53-year-old male patient had had BMT for chronic myelogenous leukemia. Cyclosporine, prednisolone, and thalidomide were given for extensive acute and chronic GVH disease involving bowel and liver. The patient developed cognitive deficits 30 months after BMT and an aphasic syndrome 8 months later. MRI scans showed left frontoparietal infarction and periventricular hypertensive lesions. CSF analysis showed a mild pleocytosis (7 white blood cells/mm$^3$)
90% lymphocytes). TCD examination was normal. Cerebral angiography revealed a left MCA branch occlusion. Treatment with cyclosporine and thalidomide was stopped, but no immunosuppressive treatment was started. The patient's condition slowly deteriorated, and he developed 2 additional episodes of cerebral ischemia. The clinical examination 6 years after BMT showed a spastic tetraparesis, tremor, and an aphasic syndrome. MRI showed confluent white matter lesions in the parieto-occipital region and bilateral frontoparietal subcortical infarctions.

Discussion

The patients described here developed acute to subacute focal neurological deficits, encephalopathy, or neuropsychological impairment approximately 2 years after allogeneic BMT. MRI in all cases showed multifocal or confluent white matter signal changes; in addition, 2 patients had lacunar ischemic lesions (cortical-subcortical, basal ganglia, thalamic, or brain stem), 2 patients had territorial infarctions, and 2 patients developed parenchymal hemorrhages. As a result of the clinical course and the radiological findings, a cerebral angiitis-like syndrome must be discussed. Since biopsy was not performed because of higher complication rates in BMT patients (thrombocytopenia, immunosuppression), histological confirmation of cerebral vasculitis was available only for the 1 autopsied patient. This patient had severe chronic GVH disease and developed progressive neurological symptoms because of subacute gray and white matter ischiasms as well as cerebral hemorrhages. After treatment, he recovered from neurological disease but died of septic pneumonia 5 months later. Autopsy showed lymphocytic infiltrations corresponding to GVH disease in the patient's liver parenchyma. In addition, multiorgan failure, including aortic valve endocarditis, was found, but these terminal changes
were most likely not responsible for the neurological symptoms, which occurred 5 months earlier. At this time, systemic inflammatory signs or bacteremia was absent, and transesophageal echocardiography was repeatedly normal. Furthermore, histological examination did not show brain abscess or embolic vessel occlusion, and no predominance of lesions in the MCA territory, which would be expected in an embolic disease, was found. Neuropathological examination revealed multifocal cerebral angiitis of arteriolar, precapillary, and capillary vessels. Subendothelial and sectorial vessel wall infiltrations as well as perivascular infiltrations with lymphocytes and monohistiocytes were found (Figure 2A through 2D). No histological signs of CNS infection such as glial mesenchymal nodules or inclusion bodies were detected.

We also suspected a cerebral angiitis-like syndrome in the other 4 BMT patients with chronic GVH disease because of their clinical course and diagnostic findings. In these patients, systemic inflammatory disease (except for GVH disease) was absent, and no CNS infection was found. Elevated flow velocities in the Doppler examination, pathological perfusion SPECT, and CSF pleocytosis or elevated protein (Table) are common findings in patients with cerebral vasculitis. In contrast, angiography, which is reported to have a sensitivity of 60% to 80% in detecting angiitis, was pathological in only 1 of the 4 patients studied. However, patient 1 had a neuropathological confirmed angiitis and highly elevated TCD velocities despite normal angiography. This apparent discrepancy might be explained by vasculitic narrowing of arteriolar and precapillary vessels only, which are not visible at angiography. In addition, confluent white matter lesions or leukoencephalopathy was present in patients 3 and 4 at the time of angiography, indicating small-vessel disease that cannot be detected by angiography. Nevertheless, the suspected angiitis seems to affect vessels of different size. In our series, manifestation in larger to medium-sized vessels occurred, leading to ischemia and strokes, as well as small-vessel and microvascular involvement, producing cognitive impairment and MRI leukoencephalopathy. The differential diagnoses in the reported patients mainly consisted of (1) cerebral angiopathy of other etiologies, (2) cyclosporine neurotoxicity, (3) leukoencephalopathy due to intrathecal methotrexate administration or irradiation, and (4) CNS infection. (1) Cerebrovascular accidents due to thrombotic nonbacterial endocarditis normally occur in the early period after BMT and classic systemic angiitis syndromes were ruled out. Until now, CNS mononuclear cell or perivascular infiltrations have been reported in 4 patients with GVH disease. Marosi et al found interstitial and perivascular lymphoid cell infiltrations in brain and meninges in a patient with progressive brain stem dysfunction. Iwasaki et al described perivascular and focal parenchymal lymphocytic infiltration in 2 children with cognitive impairment, seizures, and tetrapasticity. Finally, Rouah et al reported focal meningeal and parenchymal lymphohistiocytic aggregates in an asymptomatic child. In addition, experimental BMT studies have detected cerebral perivascular cellular infiltrations and increased endothelial expression of adhesion molecules. Such neuropathological and experimental findings are similar to the mononuclear perivascular infiltrates found in skin, liver, and kidney biopsy specimens of chronic GVH disease patients. Therefore, cerebral manifestation of GVH disease seems to be a likely explanation for the neuropathologically confirmed CNS angiitis of patient 1. When the CNS findings of the other described patients with classic GVH disease are compared, both seem to be heterogeneous diseases. Because of inflammatory vascular or parenchymal infiltrates, GVH disease occurs with a variety of clinical symptoms ranging from skin rash, bowel inflammation, liver abnormalities, and pulmonary involvement. The patients with suspected angiitis-like syndrome described in this study also showed a heterogeneous clinical presentation because of small-vessel disease as well as involvement of larger arteries. However, cerebral involvement during chronic GVH disease has not been shown in larger autopsy studies. In contrast to these studies with a short mean survival time after BMT, in a previous study we found an association of clinical and MRI abnormalities with chronic GVH disease in long-term BMT.
survivors. Until now, the apparent rarity of confirmed brain GVHD has remained unclear, possibly because brain involvement during GVH disease might take longer to develop and mild CNS GVH disease might not be diagnosed properly or is clinically asymptomatic.

In this report, we present 1 case of confirmed cerebral angiitis and 4 cases with suspected angiitis-like syndrome in association with chronic GVH disease. These findings support our previous hypothesis that cerebral involvement occurs during GVH disease. Cerebral angiitis, which may be a particular neurological manifestation of GVH disease, should be considered as a cause of cerebral ischemic or hemorrhagic episodes and pathological MRI scans in BMT patients with chronic GVH disease. Important differential diagnoses are CNS infection, multiple emboli, or cyclosporine neurotoxicity. The course, incidence, and typical vessel size at which the angiitis manifests as well as the optimal treatment must be established in further studies.

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References

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