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Reversible Leukoencephalopathy Associated with Graft-versus-Host Disease: MR Findings

James M. Provenzale and Michael L. Graham

Summary: Ten weeks after undergoing bone marrow transplantation for metastatic lymphoma of the parotid gland, a 9-year-old girl became disoriented and had tremor and myoclonus in the context of graft-versus-host disease (GVHD). MR images showed abnormal signal primarily within the brain stem and deep white matter, which resolved almost completely after treatment. The findings are consistent with brain involvement by GVHD.

Index terms: Bone marrow transplantation; Brain, diseases

Graft-versus-host disease (GVHD) is a complication of bone marrow transplantation caused, at least in part, by the reaction of immunocompetent donor T cells against host histocompatibility antigens. The most common sites of GVHD involvement are the skin, gastrointestinal tract, liver, and hematopoietic system. Neurologic complications associated with bone marrow transplantation are common but are most frequently the result of opportunistic infections and drug toxicity. The existence of central nervous system (CNS) involvement by GVHD has been suggested but not established. Recently, the occurrence of post-transplantation leukoencephalopathy associated with confusion, tremor, myoclonus, and evidence of demyelination has been reported, primarily in patients in whom allogeneic bone marrow transplantation was complicated by GVHD (1). We report the magnetic resonance (MR) imaging findings in a patient with severe acute GVHD and leukoencephalopathy following allogeneic bone marrow transplantation that responded to high-dose corticosteroid therapy, consistent with CNS involvement by GVHD.

Case Report

A 9-year-old girl had a B-lineage lymphoblastic lymphoma of the right parotid gland. No other sites of disease were found, and she underwent a 7-month course of che-

motherapy. At age 14, a pelvic mass developed that had cellular markers identical to the previous tumor, compatible with recurrence. She received therapy with vincristine, prednisone, cyclophosphamide, cytarabine, methotrexate, and asparaginase, which resulted in a second remission that was followed by allogeneic bone marrow transplantation from her HLA-identical 21-year-old brother. She received preparative therapy with total body irradiation (150 cGy \times 9 fractions over 5 days), melphalan, and cyclophosphamide; cyclosporine and methotrexate were given as GVHD prophylaxis. By day 20, fever and diffuse skin erythema developed, compatible with GVHD, for which she received intravenous methylprednisolone and an increased dose of cyclosporine. As the corticosteroid dose was tapered, massive diarrhea developed on day 33. She was treated with a murine monoclonal antibody H65 conjugated to a ricin A chain, with little improvement. A biopsy of colonic mucosa revealed persistent GVHD. Immunostaining of the colonic mucosa for cytomegalovirus was negative, but a polymerase chain reaction assay was positive. Although the significance of this test result was unclear, she was treated with gancyclovir and intravenous immunoglobulin, which produced modest improvement in the diarrhea.

On day 71, disorientation, tremor, and myoclonus were noted. MR imaging showed multiple foci of hyperintense signal on T2-weighted images within the brain stem and deep white matter (Fig 1A-E). These regions did not enhance after contrast administration. Lumbar puncture revealed an elevated protein (90 mg/dL), no pleiocytosis, and elevated cerebrospinal fluid IgG and albumin levels. An electroencephalogram revealed diffuse slowing. She was treated with 1 g methylprednisone daily for presumed transplantation-related leukoencephalopathy. She regained orientation and returned to her earlier mental status, with significant decrease in tremor within a few days. Despite improvement in the patient's neurologic status, progressive gastrointestinal GVHD developed with the onset of a functional ileus.

On day 90, a blood culture was positive for *Candida albicans*. Despite therapy with amphotericin, aphasia developed on day 108. MR imaging revealed a mass in the

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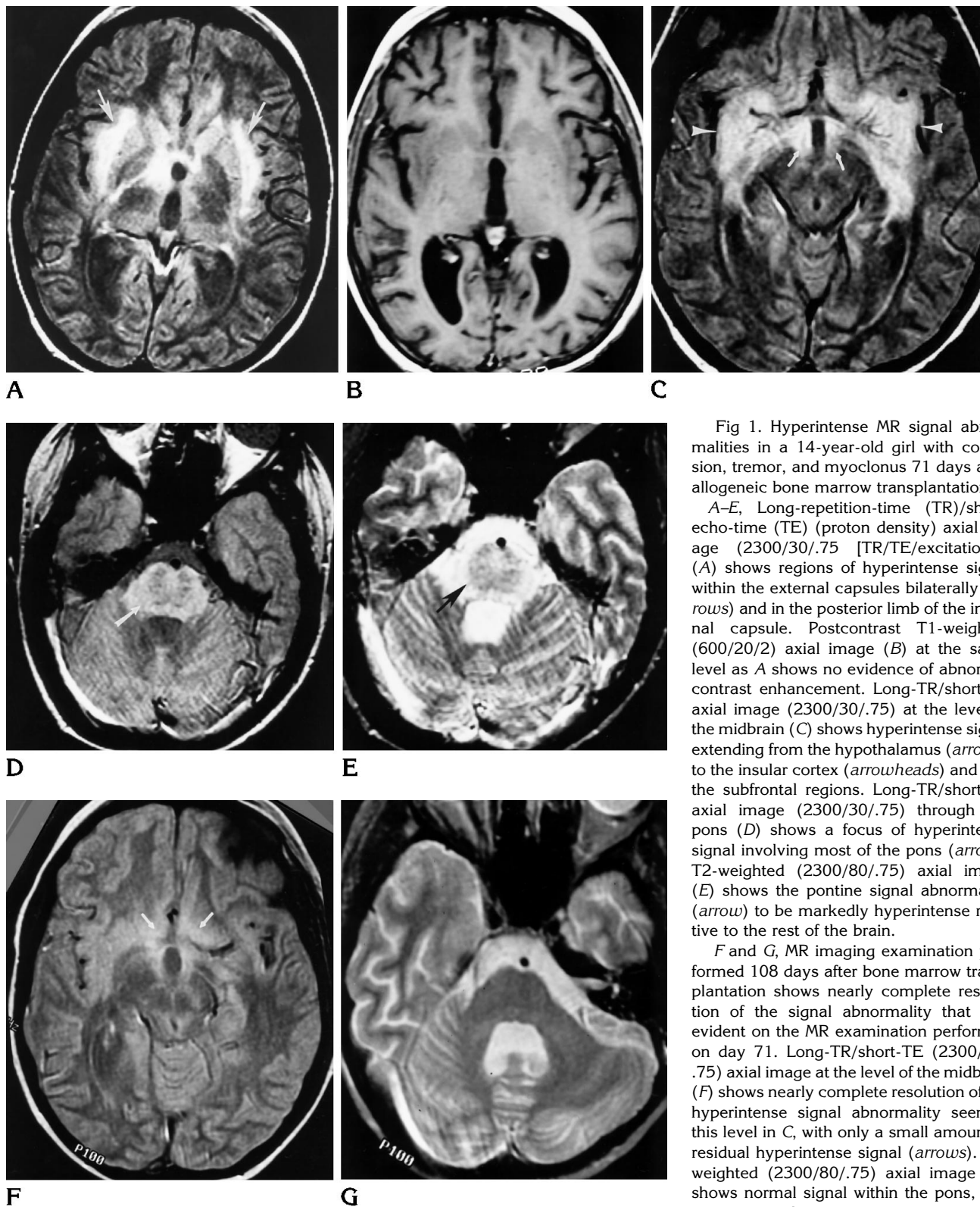


Fig 1. Hyperintense MR signal abnormalities in a 14-year-old girl with confusion, tremor, and myoclonus 71 days after allogeneic bone marrow transplantation.

A–E, Long-repetition-time (TR)/short-echo-time (TE) (proton density) axial image (2300/30/.75 [TR/TE/excitations]) (A) shows regions of hyperintense signal within the external capsules bilaterally (arrows) and in the posterior limb of the internal capsule. Postcontrast T1-weighted (600/20/2) axial image (B) at the same level as A shows no evidence of abnormal contrast enhancement. Long-TR/short-TE axial image (2300/30/.75) at the level of the midbrain (C) shows hyperintense signal extending from the hypothalamus (arrows) to the insular cortex (arrowheads) and into the subfrontal regions. Long-TR/short-TE axial image (2300/30/.75) through the pons (D) shows a focus of hyperintense signal involving most of the pons (arrow). T2-weighted (2300/80/.75) axial image (E) shows the pontine signal abnormality (arrow) to be markedly hyperintense relative to the rest of the brain.

F and G, MR imaging examination performed 108 days after bone marrow transplantation shows nearly complete resolution of the signal abnormality that was evident on the MR examination performed on day 71. Long-TR/short-TE (2300/30/.75) axial image at the level of the midbrain (F) shows nearly complete resolution of the hyperintense signal abnormality seen at this level in C, with only a small amount of residual hyperintense signal (arrows). T2-weighted (2300/80/.75) axial image (G) shows normal signal within the pons, and pontine atrophy.

left frontal lobe, thought most consistent with a fungal abscess. There was nearly complete resolution of the hyperintense signal seen on the previous MR study (Fig 1F and G). The patient became progressively unresponsive and died 123 days after the transplantation. Permission for an autopsy was not granted.

Discussion

Acute GVHD is usually manifested initially by dermatitis, which is often followed by enteritis (diarrhea, abdominal pain, and ileus) and hepatitis. The process is frequently accompanied by severe immunologic deficiency and, as in this patient, fatal infection. A number of agents have been used to prevent acute GVHD, including methotrexate, corticosteroids, and cyclosporine. Once established, acute GVHD can be treated with high-dose methylprednisolone, cyclosporine, anti-T cell monoclonal antibodies, or animal antithymocyte globulin.

The most common neuropathologic findings in patients who have undergone bone marrow transplantation are cerebrovascular lesions (mainly infarcts or intraaxial or extraaxial hemorrhage), CNS infection, and recurrence of malignant lesions (2-4). Leukoencephalopathy is not uncommon, but is seen primarily in patients who have had high doses of cranial radiation or intrathecal chemotherapy (2). Our patient had clinical and MR imaging evidence of a leukoencephalopathy, which was acute in onset and responsive to corticosteroid treatment. Because many of the therapeutic agents (eg, methotrexate, acyclovir, and cyclosporine) used in preparation for, and following, bone marrow transplantation are associated with neurotoxicity (2), it is important to consider that some of these drugs may have been responsible for the clinical and imaging findings in our patient. Cyclosporine toxicity has been associated with neurologic complications (visual disturbance, headache, ataxia, and seizures) and white matter signal abnormalities on MR imaging, which reverse after the drug is withheld (5). MR findings in cyclosporine toxicity have been reported to predominate within the occipital white matter, but reversible foci of hyperintense signal on T2-weighted images within the brain stem, hippocampus, and brain cortex have also occasionally been reported (5-7). Cyclosporine toxicity is unlikely to have been the cause of the findings in our patient because she improved without a lowering of the cyclosporine dose and

in response to high-dose corticosteroids. A CNS infection is also unlikely to have been the cause, given the relatively normal cerebrospinal fluid findings; the negative viral, bacterial, and fungal cultures; and the resolution following corticosteroid administration. Evidence of cytomegalovirus encephalitis following bone marrow transplantation has been intensively sought, but not clearly documented even in patients with disseminated cytomegalovirus infection (3). The clinical course of patients with cytomegalovirus encephalitis is usually rapidly progressive encephalopathy leading to death (8), whereas our patient recovered from the leukoencephalopathy before succumbing to infection. The MR imaging findings in cytomegalovirus encephalitis, moreover, usually consist of periventricular regions of hyperintense signal on T2-weighted images, often accompanied by leptomeningeal contrast enhancement on T1-weighted images (8), rather than the distribution of signal abnormalities seen in our patient. The fact that our patient had neither culture nor histologic evidence of cytomegalovirus infection also argues against this entity as a cause of neurologic compromise. Finally, it is unlikely that the findings represent CNS lymphoma, because the spinal fluid was negative for malignancy and the non-enhancing MR findings were not typical of CNS lymphoma. The clinical and imaging findings in this patient are most consistent, therefore, with direct CNS effects of acute GVHD.

In addition to the MR findings of cyclosporine toxicity noted above, MR white matter abnormalities have also been noted in patients undergoing other components of our patient's therapy, including methotrexate administration and radiation. Large confluent regions of hyperintense signal on T2-weighted MR images, similar to those in our patient, have been reported in patients with methotrexate neurotoxicity (9). However, clinical features of methotrexate-related leukoencephalopathy, when present, usually developed within 10 days of methotrexate administration (9). In our patient, leukoencephalopathy began more than 7 weeks after methotrexate administration. Leukoencephalopathy associated with extensive supratentorial hyperintense white matter signal abnormalities has also been reported 1 month after cessation of intrathecal methotrexate administration in combination with craniospinal axis irradiation, which suggested to the authors a possible synergistic effect of methotrexate and

irradiation (10). However, this occurred almost exclusively in patients receiving far more radiation therapy (1350 cGy in nine fractions over 5 days) and methotrexate than our patient received 4 months before the syndrome developed. Hyperintense supratentorial white matter signal abnormalities on T2-weighted images, similar to those seen in our patient, are a well-described phenomenon in patients undergoing high-dose cranial irradiation for CNS tumors (11, 12). These lesions are variable in onset (ranging from a few weeks to many months), often have no clinical correlate, are frequently bilateral and symmetric, involve the periventricular regions, and often extend to the gray-white junction (11, 12). Unlike our patient, in whom abnormal brain stem signal was a prominent feature, the brain stem is usually unaffected or relatively spared after cranial irradiation (11). Our patient also differed from these patients in that the dose of cranial radiation, which was given as a component of the preparatory regimen for bone marrow transplantation, was much lower than that given for treatment of CNS tumors.

A syndrome of demyelinating leukoencephalopathy, which could not be explained by drug toxicity, CNS infection, or tumor recurrence, has been described in recipients of bone marrow transplants (1). Like our patient, most of the patients in that series underwent allogeneic bone marrow transplantation and became disoriented and had tremor and myoclonus. Some of the patients in that series also exhibited bradykinesia and rigidity, which were not present in our patient. MR findings in these patients included hyperintense signal abnormalities on T2-weighted images predominantly in the supratentorial white matter, but also in the basal ganglia in one patient and the calcarine cortex in another patient. The authors postulated that the syndrome was related to engraftment of the donor marrow, although they did not directly implicate GVHD as a cause of the syndrome. Until recently, the CNS was considered to be unaffected by GVHD (3, 4), but the possibility of CNS involvement has recently been suggested (13–15). In one report, in which no other cause could be implicated, brain stem dysfunction led to death in a patient with chronic GVHD (13). Findings at autopsy showed perivascular lymphoid infiltration and microglial activation, consistent with the presence of major histocompatibility complex gene products not found in the

normal CNS. Focal mononuclear aggregates consistent with GVHD have been found within the brain stem, hippocampus, and Virchow-Robin spaces in another patient with chronic GVHD in whom the role of radiation and chemotherapy could be excluded (14). Diffuse degeneration of both axons and myelin sheaths with infiltration of mononuclear cells have been reported in another patient with chronic GVHD, encephalopathy, and seizures (15). In one autopsy series of bone marrow transplant recipients, cerebellar Purkinje or granular cell degeneration was found in a minority (11%) of patients with GVHD, but in no patients without GVHD, although the clinical complications in the GVHD cohort could not be directly attributed to GVHD (2). The authors noted that Purkinje cells and hematopoietic cells have some common antigenic surface markers, and that immune processes directed against hematopoietic precursors might also react with cerebellar neurons (2).

In the absence of histologic proof, the diagnosis of brain involvement by acute GVHD in our patient is a presumptive one, made on the basis of clinical and MR imaging evidence. This entity, although rare, is important to recognize because of the obvious treatment implications. Brain involvement by GVHD should be suspected in bone marrow transplantation patients in whom encephalopathy and hyperintense white matter MR signal changes on T2-weighted images are seen in the presence of systemic GVHD and in the absence of other causes of CNS dysfunction.

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