

# Graft Versus Host Disease of the Brain Following Allogeneic Stem Cell Transplant for Myelodysplastic Syndrome

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## ABSTRACT

Graft-versus-host disease (GVHD) is a frequent cause of morbidity and mortality following bone marrow transplantation (BMT). GVHD, which can present either acutely or chronically, typically involves the skin, gastrointestinal tract, and liver. In contrast, GVHD involving other organs such as the heart and kidney is highly uncommon and involvement of the central nervous system has only rarely been described in the literature. We report an unusual case of GVHD that involved the heart, kidney, adrenals, and the brain of a recipient of a dual haploidentical stem cell transplant for myelodysplastic syndrome. Pre-mortem, the patient developed GVHD of the skin and liver. The clinical course was also complicated by fungal infection (Rhizopus). GVHD of the CNS was characterized by a lymphocytic leptomeningitis with few perivascular multinucleated giant cells. Immunohistochemical studies demonstrated both CD8+ and CD4+ lymphocytes in the leptomeninges and the brain parenchyma with a marked predominance of CD8+ lymphocytes. CD20 and VZV immunohistochemistry was negative. Post-mortem PCR analysis of short tandem repeat (STR) polymorphisms demonstrated a range of ~20-50% of both donors' lymphocytes in multiple organs. However, due to prolonged formalin fixation, no PCR signal could be detected in the brain. GVHD of the CNS is rare and likely underreported due to the declining autopsy rate and a lack of recognition of the salient histologic features.

## CLINICAL HISTORY, AUTOPSY FINDINGS

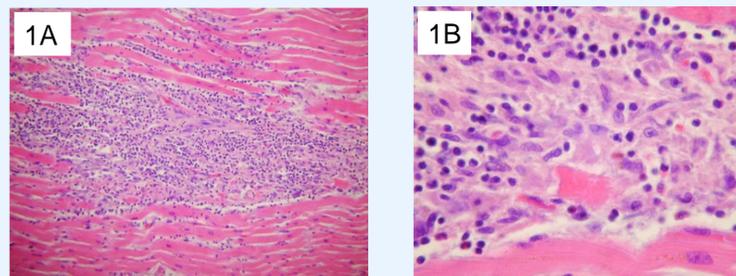
The patient was a 55 year old male who presented to Thomas Jefferson University Hospital for autologous stem cell transplant for treatment of myelodysplastic syndrome. He received a 2-donor haploidentical stem cell transplant in August 2011. Bone marrow analysis demonstrated 20% donor 1 and 80% donor 2 engraftment. The hospital course was complicated by cardiac arrhythmias, renal failure, respiratory failure, an esophagopulmonary fistula and GVHD of the skin and liver. He was also noted to have episodes of altered mental status with lethargy and somnolence. CT scans showed no acute infarcts. No brain MRIs were performed. Premortem testing for BK virus and CMV was negative.

The significant findings at autopsy included an esophogastric stent perforation of the stomach and pericardium with rare Rhizopus hyphae and GVHD of the heart, kidneys, bladder, adrenal glands, and brain. GVHD was most prominent in the heart (Figure 1). In other organs, GVHD manifested as variable (moderate to severe) perivascular and intraparenchymal lymphocytic infiltrates along with a variable number of histiocytes.

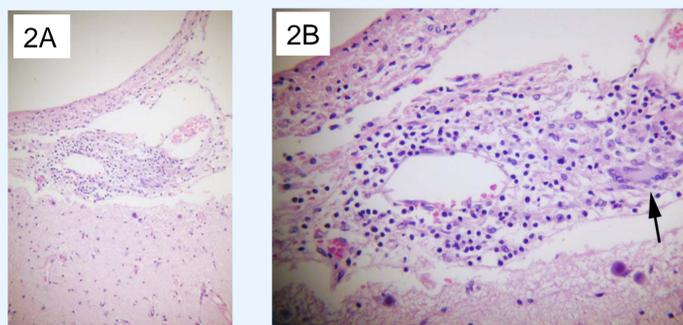
## REFERENCES

Padovan C, Bise K, Hahn J et al. Angiitis of the Central Nervous System After Allogeneic Bone Marrow Transplantation? *Stroke*. 1999; 30: 1651-1656  
 Kamble, R. T., C. C. Chang, S. Sanchez, and G. Carrum. 2007. Central nervous system graft-versus-host disease: report of two cases and literature review. *Bone Marrow Transplant* 39:49-52.  
 Saad, A. G., E. P. Alyea, 3rd, P. Y. Wen, U. Degirolami, and S. Kesari. 2009. Graft-versus-host disease of the CNS after allogeneic bone marrow transplantation. *J Clin Oncol* 27:e147-9.

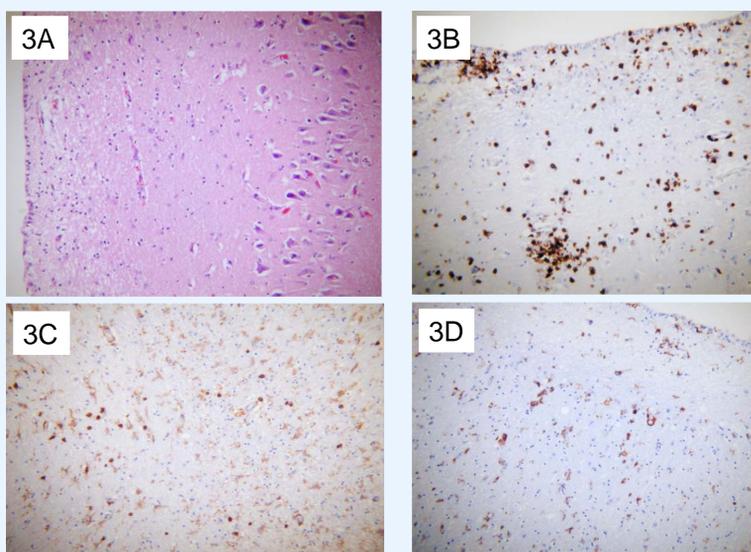
## RESULTS



**Figure 1: Myocardium:** A) Focus of intense inflammation consisting of eosinophils, macrophages and lymphocytes consistent with GVHD (H&E, 100X). B) Higher magnification demonstrating myocyte necrosis with associated lymphocytes, eosinophils and macrophages ((H&E, 400X)



**Figure 2:** A) Brain, Temporal Lobe (H&E 100X): Perivascular lymphocytes and macrophages with giant cells. B) Higher magnification (H&E 400X): Multinucleated giant cell arrowed.



**Figure 3: Brain, Hippocampus with Lymphohistiocytic Parenchymal Inflammation.** A) Few lymphocytes can be discerned in the subependymal zone (H&E). B) CD 8+ lymphocytes. C) CD 4+ lymphocytes (small dark cells) and microglia (extended cells). D) CD 68+ microglia. All images 100X.

Tissue	Donor 1 %	Donor 2 %
Brain, Left Hippocampus	ND	ND
Left Kidney	26	25
Right Kidney	24	21
Left Adrenal, Testis	18	18
Bladder and Prostate	14	12
Right Adrenal, Testis	10	12
Heart, Right Ventricle	7	11

**Table 1: Percentages of Donor cells in Tissues with GVHD:** PCR of short tandem repeat (STR) markers was used to assess cell populations from donor 1 or donor 2 in 10 µm thick post-mortem paraffin embedded tissues (Powerplex STR system (Promega, USA)). In some cases, more than one tissue was present per block. ND (not detected) due to prolonged formalin fixation.

## DISCUSSION

GVHD occurs when transplanted immune cells from a non-identical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune response. GVHD involving organs other than skin, gastrointestinal tract and the liver is rare and remains controversial. This patient manifested GVHD of the skin and liver pre-mortem. However, these were successfully treated before death. No GVHD of the bowel was identified due to extensive post-mortem autolysis. GVHD involving the brain is rare. There are a few reports of post bone marrow transplant patients with MRI evidence of predominately white matter changes in addition to leptomeningeal and gray matter changes whose imaging and neurologic status resolved following corticosteroid therapy. These patients are presumed to have had GVHD of the CNS. However, histologic confirmation by biopsy or autopsy is quite rare. The characteristic histology of donor inflammatory cell damage in multiple organs is strongly supportive of GVHD in this patient. Furthermore, the pattern of a perivascular and subendothelial lymphohistiocytic inflammatory infiltration of cerebral vessels matches earlier descriptions of patients with brain involvement by GVHD. There was no evidence of a viral cytopathic effect nor were there any microglial nodules. Immunohistochemistry for VZV was also negative. In addition, some reports have also identified a predominately intraparenchymal CD8+ lymphocyte population as described here. One unusual feature in this patient is the short interval (< 3 months) between engraftment and CNS GVHD. Most other reports describe several months to years prior to the onset of CNS symptoms. This discrepancy is likely due to the overall short survival of this patient. The lack of donor cell DNA in the brain by PCR is a reflection of prolonged formalin fixation (several weeks). GVHD of the CNS is rare and treatable. The lack of awareness of this unusual entity is partly due to a declining autopsy rate, particularly in post bone marrow transplant recipients, and a lack of recognition by pathologists.