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LETTER TO THE EDITOR

Central Nervous System Manifestations of Graft-Versus-Host Disease

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To the Editor,

Graft-versus-host disease (GvHD) of the central nervous system (CNS) is an infrequent complication of allogeneic hematopoietic stem cell transplantation (HSCT), officially recognized as a distinct entity in 2010 [1–3]. Despite increasing recognition, significant gaps remain in its understanding.

We describe eight patients diagnosed with CNS GvHD at our center, detailing clinical presentation, imaging, histopathology, and outcomes. Patients were identified through our institutional database and diagnosed based on neuroimaging, neuropathology, or published criteria [3].

The median age at diagnosis was 64 years (61–67), with a median onset of 141 days post-HSCT (112–229). Six patients had concurrent GvHD in other organs, with skin, liver, and lung involvement being the most common. Neurological symptoms included cognitive and behavioral disturbances ($n=6$), motor impairment ($n=3$), speech difficulties ($n=2$), seizures ($n=1$), visual disturbances ($n=1$), and cerebellar dysfunction ($n=1$). CSF analysis showed pleocytosis in five patients, with a median white cell count of 8.5/μL (reference <5 cells/μL). Microbiological workup was negative in all cases. Magnetic resonance imaging (MRI) findings predominantly showed confluent and patchy white matter abnormalities with restricted diffusion, suggesting small vessel vasculopathy (Figure 1a,b). Histopathology ($n=6$) revealed widespread astrocytosis, perivascular CD3+ T lymphocyte infiltration, and marked microglial activation (Figure 1c–e). Optic nerve and spinal cord demyelination was observed in three cases.

Seven patients received corticosteroids (median duration: 83 days), with four also receiving additional immunosuppressants (mycophenolate mofetil: 3, azathioprine: 1). Four patients showed partial clinical response, three had disease progression, and one relapsed. The median overall survival post-diagnosis was 183 days (95% CI: 87–915). Only two patients survived beyond one year, both with persistent neurological deficits. The primary cause of death in all cases was attributed to CNS GvHD.

Neurological complications after HSCT, including CNS GvHD, present a significant clinical challenge with considerable morbidity and mortality [2–4]. The 2010 consensus criteria for diagnosing CNS GvHD require concurrent chronic GvHD in other

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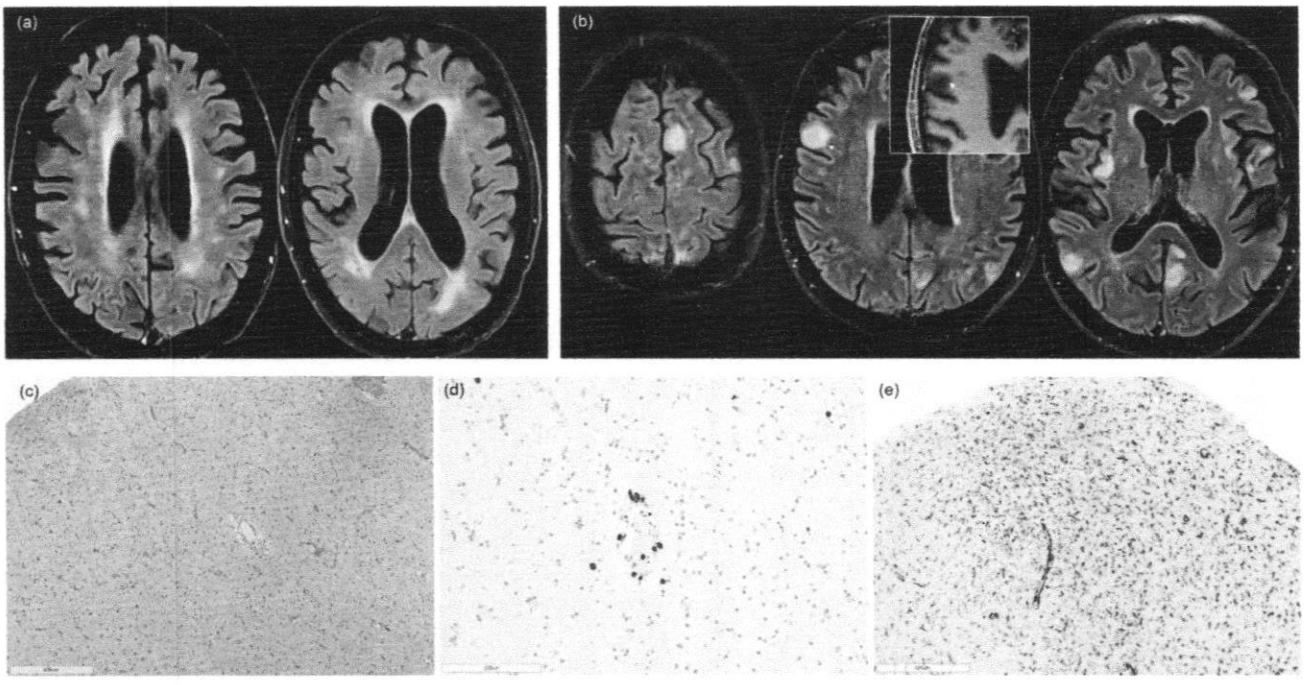

FIGURE 1 | (a) Axial T2-weighted fluid-attenuated inversion recovery image (FLAIR) images show patchy hyperintensity in the periventricular deep white matter of the cerebral hemispheres. (b) Axial T2-weighted fluid-attenuated inversion recovery image (FLAIR) images show multiple lesions involving cortex and subcortical white matter in the cerebral hemispheres. Inset: Contrast-enhanced T1-weighted image shows no associated contrast enhancement. (c) Histopathology findings: Hematoxylin and Eosin (H&E) staining of the brain shows widespread reactive astrocytosis, more pronounced in the white matter (d) CD3 immunostaining highlights Tlymphocytes around blood vessels (e) CD163 immunostaining highlights the exuberant activation of microglia.

organs; however, Lambert et al. [4] reported that 59% of patients lacked prior or concurrent non-CNS GvHD, a finding also observed in two patients from our cohort. The heterogeneous clinical presentation, including confusion, seizures, and behavioral changes, complicates diagnosis. Consistent with previous reports, behavioral disturbances were the most common symptom in our study. Pathophysiologically, alloreactive T lymphocytes likely infiltrate the CNS, causing neuroinflammation [5]. Recent murine studies have shown that acute CNS GvHD is driven by cytokines from microglia, while chronic GvHD involves macrophages from donor bone marrow [6].

CNS GvHD typically occurs during the tapering of immunosuppression [2]. In our study, symptoms appeared earlier (median 141 days), likely due to early tapering of immunosuppressive therapy, as half of the cohort received PTCy-based GVHD prophylaxis, which is associated with a shorter time to immunosuppression discontinuation [7]. Treatment is challenging, with high relapse rates, and corticosteroids remain the primary treatment. Emerging therapies like ruxolitinib and ibrutinib have shown promise, though their efficacy in CNS GvHD remains limited [8, 9]. The median survival was 183 days, and only two patients survived beyond one year with persistent neurological deficits. Our data highlight the need for a high index of suspicion for CNS GvHD in patients with unexplained neurological symptoms post-HCT. Multicenter collaborative studies are essential to better understand the pathophysiology and improve treatment responses for this rare complication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request.

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