

LETTER TO THE EDITOR

Central nervous system graft-versus-host disease: consider progressive multifocal leukoencephalopathy among the differential diagnoses

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Kamble *et al.*¹ recently provided a review of cases of central nervous system graft-versus-host disease (CNS GVHD). The authors conclude that ‘when relapse of a CNS neoplastic process, opportunistic infections as well as EBV related post-transplant lymphoproliferative disorders (PTLD) among other diagnoses are all excluded by means of thorough studies, the possibility of CNS-GVHD may be entertained’. We discuss here the basis for the requirements to rule out another fatal but potentially curable CNS disease, namely progressive multifocal leukoencephalopathy (PML).

Both original cases reported by Kamble *et al.* had hyperintense white matter lesions (WMLs) on T2-weighted images at magnetic resonance imaging, a finding that in allogeneic hematopoietic stem cell transplant recipients should have encouraged investigations for PML, especially if they had been previously treated with fludarabine² (as for case 2) or rituximab.³ According to consensus terminology,⁴ these patients actually fulfilled the criteria for possible PML. Similarly, 7 of the 10 cases reported in Table 1 had focal or diffuse WML at magnetic resonance imaging.

In their case 1, the authors found negative immunohistochemistry for JC virus (JCV) on cerebral biopsies, but they did not perform PCR, the gold-standard test to exclude PML. In case 2, JCV PCR was performed only on cerebrospinal fluid, but negativity cannot rule out PML, since this test has only a 50% sensitivity for PML in HIV-negative patients.⁵ They also did not report on the occurrence of reactive astrocytes with bizarre atypical nuclei or intranuclear inclusion bodies in oligodendrocytes in the brain biopsies in their case 2. In HIV-negative patients, a less invasive and cheap test for PML is JC viremia, which usually precedes the onset of PML symptoms⁶ (P Duda, personal communication), while being normally absent in healthy controls and transplant recipients.

PML has generally been considered by definition as an invariably progressive disease, and so the fact that eight of the nine presumed CNS GVHD patients with WML survived could have suggested ruling out the diagnosis of PML. Actually, cases of spontaneous resolution without any potential antiviral treatment have been reported in HIV-negative patients.⁷ Furthermore, T-lymphocyte infiltrates in CNS, as reported by Kamble *et al.*, are not pathognomonic of GVHD: they are commonly seen in PML and colocalize with JCV-infected glial cells.⁸ Responses to methylprednisolone pulses

are theoretically expected also in PML via reduction of cerebral edema.

Despite commonly occurring with subcortical WML, PML is a very pleomorphic disease with many described histological variants (including perivascular inflammation and plasma cell infiltrates⁹) and radiological (including mass effect¹⁰) variants, as recently reviewed,¹¹ so that JCV detection in CNS samples (either by PCR or by immunohistochemistry) remains the most sensitive assay.

Given the potential curability of PML,⁵ we feel that this disease should be thoroughly investigated before diagnosing CNS GVHD.

D Focosi¹, RE Kast², F Maggi³, S Galimberti¹,
F Papineschi¹, M Petrini¹ and L Ceccherini-Nelli³

¹Department of Oncology, Transplantation and Advanced Medicine, Division of Hematology, Azienda Ospedaliera Universitaria Santa Chiara, Pisa, Italy;

²Department of Psychiatry, University of Vermont, Burlington, VT, USA and

³Division of Virology, Azienda Ospedaliera Santa Chiara, University of Pisa, Pisa, Italy
E-mail: focosi@icgeb.org

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Response from Dr Kamble and colleagues

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We agree that diagnosis of central nervous system (CNS) GVHD may be controversial and that the diagnosis currently remains one of exclusion. As we stated,¹ the possibility of post transplant progressive multifocal leukoencephalopathy (PML)² was indeed considered in both patients. The diagnosis of ‘possible PML’ has to be entertained in the presence of the typical clinical and radiologic picture of PML in the absence of demonstrable JC virus (JCV) infection. In the immunocompromised host, JCV DNA detection in the cerebrospinal fluid (CSF) has a sensitivity of 72–92% and specificity of 92–100%.³ As one-third of patients may not yield JCV DNA in CSF, brain biopsy with immunohistochemical studies along with tissue JCV DNA amplification by PCR remains the gold standard for diagnosis of PML. We did indeed seek the characteristic pathological changes of PML, namely, JCV-infected glial cells, bizarre astrocytes, lipid-laden macrophages and demyelination, but they were lacking in our cases. Hence the absence of characteristic pathologic changes, the negative JCV studies (negative immunohistochemical stain in case no. 1 and negative CSF PCR in case no. 2), the rapid response to steroids and the exclusion of other etiologies lead one to consider the possibility of CNS

GVHD. While PML is indeed a worthy candidate for consideration in cases of this type, it would be unwise to force this label on all ‘white matter disease of uncertain origin’ in the immunocompromised host. Continued reporting of similar cases may help delineate whether brain tissues truly are targets for the development of GVHD.

RT Kamble¹, C-C Chang² and G Carrum¹

¹Center for Cell and Gene Therapy, Baylor College of Medicine and Methodist Hospital, Houston, TX, USA and

²Department of Pathology, Methodist Hospital, Weill Medical College of Cornell University, Houston, TX, USA

E-mail: kamble@bcm.edu

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