T-cell/histiocyte-rich large B-cell lymphoma presenting as a primary central nervous system lymphoma

Pooja Advani,1 Jason Starr,1,2 Abhisek Swaika,1 Liuyan Jiang,3 Yushi Qiu,4 Zhimin Li,4 Han W. Tun1,4
1Division of Hematology and Oncology, Department of Internal Medicine, Mayo Clinic, Jacksonville; 2Cancer Specialists of North Florida, Jacksonville; 3Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville; 4Department of Cancer Biology, Mayo Clinic, Jacksonville, FL, USA

Abstract

Primary central nervous system (PCNSL) lymphoma is an aggressive extranodal non-Hodgkin lymphoma, and most cases are classified as diffuse large B-cell lymphoma (DLBCL) by histology. T-cell/histiocyte-rich large B-cell lymphoma (TCRLBCL) represents a distinct subtype of diffuse large B-cell lymphoma and is characterized by the presence of scattered large neoplastic B-cells in a background of abundant T-cells and histiocytes. This is in contrast to the dense perivascular cuffing of neoplastic B-cells in classic DLBCL. T-cell/histiocyte-rich large B-cell lymphoma should be considered in PCNSL cases in which neoplastic B-cells are sparse and scattered. Immunohistochemistry will help identify the B-cells and surrounding infiltrate rich in T-lymphocytes and histiocytes. Future studies exploring the biology of TCRLBCL and the crosstalk between the neoplastic cells and the surrounding inflammatory infiltrate may provide exciting prospects for future therapies for TCRLBCL.

Introduction

Primary central nervous system lymphoma (PCNSL) accounts for approximately 3-4% of newly diagnosed primary CNS tumors and is most frequently a diffuse large B-cell lymphoma (DLBCL) (95% of cases).1 T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), formerly described as a rare variant of DLBCL, is now recognized as a specific sub-type of DLBCL in the 2008 WHO classification and represents 1-3% of all DLBCL cases.2,3 THRLBCL frequently involves extranodal sites, such as the spleen, liver, and bone marrow.4

We report an interesting case of THRLBCL presenting as a primary CNS lymphoma, which to the best of our knowledge, has not been reported in literature. It is probable that THRLBCL is a very rare type of PCNSL. It is also possible that it is under recognized because a low density distribution of lymphoma cells in PCNSL has previously been described.5

Case Report

The patient was a 73-year-old white man who presented to us with a two-month history of progressive abulia, apraxia, right-sided weakness, and significant weight loss. Magnetic resonance imaging (MRI) of the brain demonstrated confluent and patchy regions of abnormal enhancement of the bilateral cerebral white matter, corpus callosum, bilateral cerebral peduncles, and leptomeningeal margin of the pericallosal sulcus (Figure 1). Cytology of the cerebrospinal fluid revealed a predominance of small CD3+ lymphocytes and a few scattered large CD20+ lymphoma cells. Pathology of a stereotactic-guided right frontal lobe biopsy revealed few scattered large lymphoma cells surrounded by numerous histiocytes and T lymphocytes. Lymphoma cells were positive for CD20, CD79a, PAX-5 and BCL-6 (Figure 2) but were characterized by the presence of scattered large neoplastic B-cells in a background of abundant T-cells and histiocytes. This is in contrast to the dense perivascular cuffing of neoplastic B-cells in classic DLBCL. T-cell/histiocyte-rich large B-cell lymphoma should be considered in PCNSL cases in which neoplastic B-cells are sparse and scattered. Immunohistochemistry will help identify the B-cells and surrounding infiltrate rich in T-lymphocytes and histiocytes. Future studies exploring the biology of TCRLBCL and the crosstalk between the neoplastic cells and the surrounding inflammatory infiltrate may provide exciting prospects for future therapies for TCRLBCL.

Discussion

Pathologically, our case of PCNS-THRLBCL showed an angiocentric pattern with perivascular cuffing of lymphoid cells, which is characteristic seen in classic PCNSL.7,8 However, the majority of lymphoid cells in the perivascular cuffing were T lymphocytes with few large B lymphoma cells. Histiocytes were predominantly away from perivascular cuffing. Our group has shown that osteopontin (SPP1/OPN) is the most upregulated gene in PCNSL compared to non-CNS DLBCL by gene expression analysis.9 We showed that OPN is expressed by large B lymphoma cells with predominant nuclear pattern in our case of PCNS-THRLBCL, as in classic PCNSL (Figure 2E,F).9 As such, OPN expression is a marker of various subtypes of PCNSL, including classic primary CNS diffuse large B-cell lymphoma, primary CNS lymphoma with features in between diffuse large B-cell lymphoma and Burkitt lymphoma, and PCNS-THRLBCL.10 Infiltrating immune cells were also shown to express OPN. Currently, we are conducting functional genomic studies to elucidate the role of OPN in CNS lymphoma.

We propose that PCNS-THRLBCL should be considered in PCNSL cases in which lymphoma cells are scattered. Immunohistochemistry should be undertaken to show abundant infiltration by histiocytes.
and T lymphocytes. The best therapeutic option for PCNS-THRLBCL is not known at present. In our patient, the response to high-dose methotrexate appeared to be excellent, although he was only able to get one treatment due to nephrotoxicity. As immune cells are abundant in this type of lymphoma, treatments such as immunomodulatory therapy, which can turn these immune cells against the lymphoma cells, should be tested. Our group has shown that pomalidomide can switch the polarization status of lymphoma-associated macrophages from pro-tumorigenic M2 to anti-tumorigenic M1.11

Currently, we are testing pomalidomide in relapsed/refractory PCNSL in a Phase 1 study (ClinicalTrials.gov identifier: NCT01722305).

Conclusions

In summary, we describe the first case of T-cell/histiocyte-rich large B-cell lymphoma presenting as a primary CNS lymphoma. Our case emphasizes the importance of expert histopathologic review to diagnose this unique subtype of NHL characterized by scattered neoplastic cells in an immune-rich milieu. Future studies are needed to help elucidate whether the immune system can be leveraged to improve the therapeutic landscape of T-cell/histiocyte-rich large B-cell lymphoma.

References


Figure 1. A) Axial T2 flair Magnetic resonance imaging of the brain reveals abnormal enhancement of the cerebral peduncles. B) and C) T1 axial spin echo, peripheral gating, and fat saturated images reveal confluent and patchy areas of enhancement and restricted diffusion in bilateral cerebral hemispheres.

Figure 2. Primary central nervous system T-cell/histiocyte-rich large B-cell lymphoma. A) The brain tissue contains dense perivascular and interstitial lymphoid infiltrate consisting of large atypical cells in a background rich in small lymphocytes and histiocytes (H&E magnification 10×; inset, H&E 40×). B) Immunostain of PAX-5 highlights the large atypical cells (10×), which confirms the B-cell lineage. C) CD3 stain is positive for many small reactive T cells (10×). D) CD68 stain is positive for histiocytes (10×). E,F) Dual immunohistochemistry was performed using antibodies specific to CD20 and osteopontin (OPN). Both CD20 (membranous pattern) and OPN (predominantly nuclear) are positive in the large neoplastic B cells (see arrows) (E, 20×; F, 40×).