

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

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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.^{4,5}

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.⁶

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 on 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 negative for CD30, TdT, and MUM-1. CD3 and CD45RO staining highlighted the perivascular T-cell population, while PGM-1 staining highlighted increased histiocytes in the background. The immunohistochemistry findings were consistent with THRLBCL. The results of the immunoglobulin gene rearrangement study were positive for a B-cell clone. The results of his T-cell receptor rearrangement study, Epstein-Barr virus (EBV) *in-situ* hybridization, and HIV testing were negative. The findings from staging evaluations including an ophthalmologic examination, ultrasound of his testicles, and a computed tomography of the chest, abdomen, and pelvis were also unremarkable. These findings were consistent with primary CNS THRLBCL (PCNS-THRLBCL).

The patient was initially treated with high-dose of methotrexate (8 g/m²) and had an excellent response; however due to nephrotoxicity, this treatment was discontinued. He was subsequently treated with rituximab (375 mg/m² every 28 days) and temozolomide (100-200 mg *per os* daily for 5 days based on renal function, every 28 days) until he had a major relapse about nine months later. Due to multiple co-morbidities and poor performance status at the time of relapse, he was transitioned to hospice and subsequently passed away.

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Discussion

Pathologically, our case of PCNS-THRLBCL showed an angiocentric pattern with perivascular cuffing of lymphoid cells, which is characteristically 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 (*SPPI/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

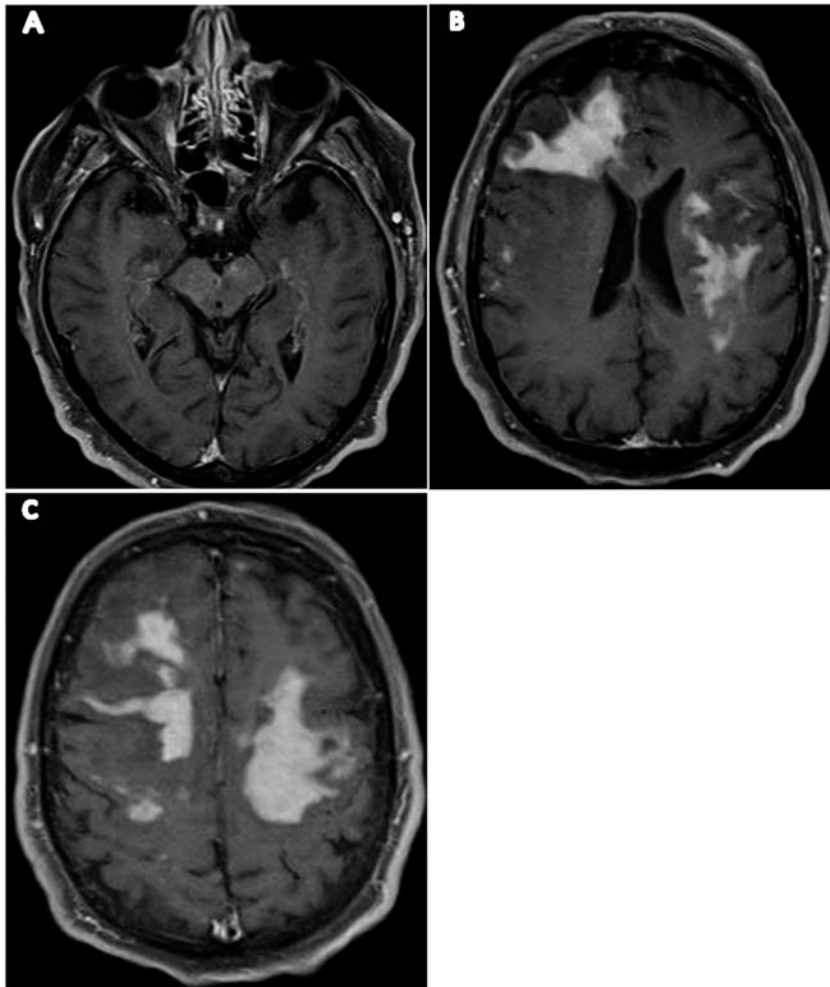


Figure 1. A) Axial T2 flair Magnetic resonance imaging of the brain reveals abnormal enhancement of the cerebral peduncles. B) and C) T1 axial spin echo, peripheral gating, and fat saturated images reveal confluent and patchy areas of enhancement and restricted diffusion in bilateral cerebral hemispheres.

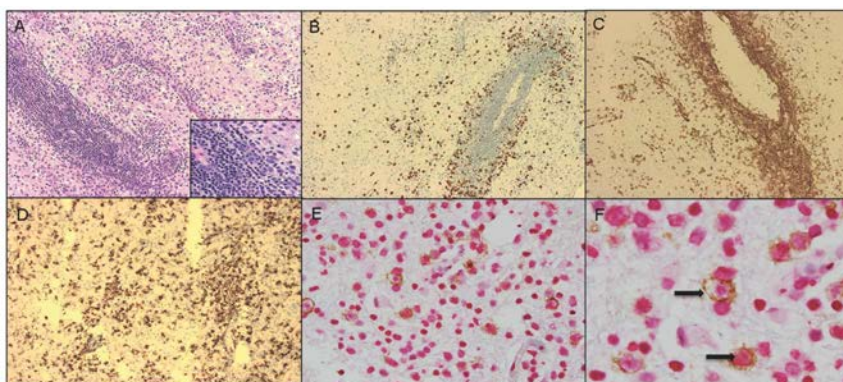


Figure 2. Primary central nervous system T-cell/histiocyte-rich large B-cell lymphoma. A) The brain tissue contains dense perivascular and interstitial lymphoid infiltrate consisting of large atypical cells in a background rich in small lymphocytes and histiocytes (H&E magnification 10 \times ; inset, H&E 40 \times). B) Immunostain of PAX-5 highlights the large atypical cells (10 \times), which confirms the B-cell lineage. C) CD3 stain is positive for many small reactive T cells (10 \times). D) CD68 stain is positive for histiocytes (10 \times). 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 \times ; F, 40 \times).

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.

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