



Primary Intra-Axial Diffuse Large B-Cell Lymphoma in Immunocompetent Patients: Clinical Impact of Molecular Analysis and Histogenetic Evaluation

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Key words

- Central nervous system
- Diffuse large B-cell lymphoma
- Immunocompetent patient
- Immunohistochemistry
- Lymphoid neoplasia
- Pathology

Abbreviations and Acronyms

ABC: Activated B-cell–like subtype

CNS: Central nervous system

DLBCL: Diffuse large B-cell lymphoma

GCB: Germinal center B-cell–like subtype

MR: Magnetic resonance

R-CHOP: Rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone

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INTRODUCTION

Primary central nervous system (CNS) lymphoma is a malignant lymphoid neoplasia arising primarily within the parenchyma of the brain and spinal cord. The most common primary CNS lymphoma is diffuse large B-cell lymphoma (DLBCL),¹⁻³ a high-grade, aggressive neoplasm with poorly understood pathogenesis that can affect both immunocompromised and immunocompetent patients. DLBCL is composed of large B lymphoid cells whose nucleus is twice the size of the nucleus of a normal lymphocyte or equal to or larger than a normal nucleus of a macrophage. Primary CNS DLBCL accounts for almost all intra-axial lymphomas but does not include

Primary central nervous system (CNS) diffuse large B-cell lymphoma (DLBCL) represents less than 1% of non-Hodgkin lymphomas and 2%–3% of brain tumors. Primary CNS DLBCL occurs sporadically in healthy patients. Tumor development and progression have been associated with reduced/absent expression of human leukocyte antigen class I and II proteins; increased expression of CXCR4, CXCL12, CXCR5, and CCR7; mutations of *VH4/34*, *BCL6*, *MYC*, and *PAX5* genes; and rearrangement of immunoglobulin heavy and light chain genes. Generally, DLBCL is a single supratentorial lesion (60%–70%), and stereotactic biopsy and intraoperative examination are the main diagnostic methods. Distinctive histologic features are a diffuse growth pattern and angioinvasiveness. Most neoplastic cells resemble centroblasts and exhibit positive CD20, CD22, PAX5, CD79a, and MUM1 expression. The prognosis of primary CNS DLBCL is less favorable than that of nodal DLBCL, and DLBCL subtype, strong FOXP1 immunoreactivity, *MYC* and *BCL2* overexpression, and *BCL6* translocations are associated with poor prognosis.

dural lymphoma, intravascular large B-cell lymphoma, and immunodeficiency-associated lymphoma.^{2,4-9}

Primary CNS DLBCL represents less than 1% of all non-Hodgkin lymphomas and approximately 2%–3% of all brain tumors. There is a slightly higher incidence in men, and the median age at diagnosis is 60 years. Several studies have reported an increase in CNS DLBCL incidence, but it is unknown whether this is because of improved diagnostic tools or an actual increase in incidence rates.^{3,4,10-14} Morphologic, biological, and clinical studies have defined CNS DLBCL as a heterogeneous group of tumors. A large number of CNS DLBCL cases are identified as DLBCL, not otherwise specified, because of the lack of clear and accepted classification criteria. However, subtype classification can be of prognostic importance in DLBCL. The 2 major subtypes are germinal center B-cell–like subtype (GCB) and activated B-cell–like subtype (ABC) **Figure 1**.^{2,5-7,15-18}

TOPOGRAPHY AND CLINICAL FINDINGS

Primary CNS DLBCL occurs sporadically in healthy patients. Generally, these are single

lesions (60%–70%), and in most cases, the process arises in the supratentorial region (60%), affecting mainly the frontal (15%), temporal (8%), parietal (7%), and occipital lobes (3%). **Figure 2** lesions in the basal ganglia and periventricular region are present in 10% of patients.^{3,4,6,12,19-21} In many cases, magnetic resonance (MR) and computed tomography images exhibit a homogeneous, expansive process with irregular focus of necrosis. MR shows hypointense lesions on T1-weighted images and iso- to hypointense lesions on T2-weighted images with variable edema. **Figure 3** CNS DLBCL can resemble sarcoidosis, glioblastoma, vasculitis, and multiple sclerosis in MR images. Primary DLBCL is generally a homogeneous contrast-enhancing tumor without the ring enhancement observed in glioblastoma or metastatic lesions. Leptomeningeal involvement is observed in 5% of intra-axial CNS DLBCL cases. Intraocular involvement is also a frequent finding (observed in about 20% of cases).^{3,4,6,7,12,14,21-23}

Affected patients can show clinical signs of focal neurologic deficits (50%–80%) or neuropsychiatric symptoms (20%–30%). Leptomeningeal involvement

and increased intracranial pressure are associated with nausea, vomiting, headache, and asymmetrical cranial neuropathy. Stereotactic biopsy and intraoperative examination are the main diagnostic methods and can avoid extensive surgery. Corticosteroids should be avoided prior to biopsy because they have a substantial negative impact on diagnosis.^{1,3,4,7,11,12,18,19,24} In the case of a typical DLBCL histology, a bone marrow biopsy is not essential if positron emission tomography-computed tomography scan has excluded systemic disease, blood parameters are normal, and serum monoclonal protein is undetectable. In most cases without leptomeningeal involvement, cerebrospinal fluid analysis usually shows nonspecific lymphocytic pleocytosis without atypical lymphocytes. The prognosis of primary CNS DLBCL is much less favorable than that of nodal DLBCL, suggesting 2 distinct entities. Metastasis to other organs and systems are very uncommon. Most patients with CNS DLBCL die within 2 years. At autopsy, only about 5% of cases exhibit a secondary focus of involvement in the viscera.^{1,2,6,7,10,25-27}

MORPHOLOGY AND IMMUNOPHENOTYPE

On gross examination, primary DLBCLs are soft, gray, ill-defined, predominantly deep-seated tumors. Most primary CNS DLBCLs are supratentorial lesions and exhibit a diffuse growth pattern. A distinctive histologic feature of this tumor is the angiocentricity and/or angioinvasiveness, especially at the periphery of the lesions. Typical DLBCL also forms dense infiltration zones and less cellular areas. Most neoplastic cells resemble centroblasts and may be intermingled with small reactive lymphocytes, macrophages, and reactive glial cells. Neoplastic nuclei are round to oval, occasionally notched, and have prominent nucleoli. The cytoplasm is often poorly delineated, and nuclear to cytoplasmic ratios are high. **Figure 4** foamy histiocytes and areas of necrosis are common findings.^{2-4,7,11,15,25,26,28} Treatment with high-dose corticosteroids has been associated with vanishing tumors. Mitotic and apoptotic figures are frequent. Primary DLBCL lacks vascular proliferation and perinecrotic palisading. At the ultrastructural level, the tumor is

characterized by an absence of intermediate filaments, specific organelles, and intercellular junctions.^{2-4,7,11,15,25,26,28-30}

Neoplastic large B cells recapitulate the differentiation process of normal B cells. Normal B-cell development begins with precursor B cells (B lymphoblasts), which undergo V(D)J rearrangement of immunoglobulin genes as they differentiate into cytoplasmic μ^+ pre-B cells, immature IgM^+ B cells, and finally mature, surface immunoglobulin-positive (IgM^+ IgD^+) naive B cells. Naive B cells (CD5^+) are found in the peripheral blood, primary lymphoid follicles, and follicle mantle zones.^{2,6,7,11,15,25,26,30-32}

Most cases of CNS DLBCL show positive immunoreexpression for CD19, CD20, CD22, PAX5, OCT2, BOB1, and CD79a.^{2,6,7,11,15,25,26,30-32} **Figures 5 and 6** strong expression of MUM1/IRF4 occurs in about 90% of cases, and BCL-2 and BCL-6 positivity occurs in 60%–80% of cases. **Figure 7** surface and/or cytoplasmic immunoglobulin can be demonstrated in 50%–75% of the cases. MYC positivity is found in about 30% of cases, CD10 positivity is found in 10%–20% of cases, and CD5 positivity is found in 5%–10% of cases. Tumor cells are negative for CD1a, CD2, CD3, CD4, CD7, CD8, CD13, CD33, T-cell receptors, and myeloperoxidase. The proliferative index, evaluated by Ki-67 expression, typically ranges from 50% to 80%.^{2,6,7,11,15,25,26,30,33-36}

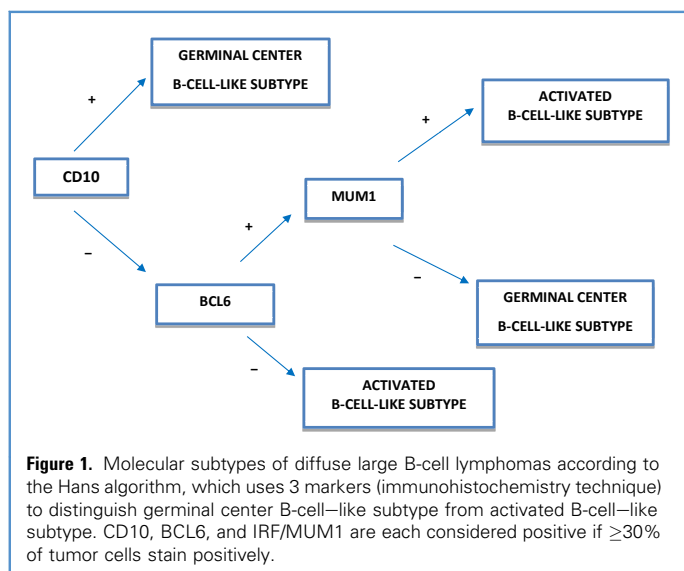
The Hans algorithm (**Figure 1**) classifies nodal DLBCL into 2 subtypes that have

different prognoses and genetic characteristics: GCB and ABC DLBCL. GCB DLBCL is associated with better survival than ABC DLBCL. Unfortunately, most CNS DLBCL resemble nodal ABC DLBCL. Subtype classification is based on 3 immunohistochemistry markers: CD10, BCL-6, and MUM1. Some CNS DLBCL cases show coexpression of CD10 and MUM1 and others are negative for the 3 markers, but the clinical significance of these variants is unclear.^{2,6,7,11,15,25,26,30,33-36}

Differential diagnosis in immunocompetent patients includes high-grade infiltrative gliomas (particularly anaplastic oligodendroglioma and glioblastoma), other lymphomas, metastatic carcinoma, inflammatory disorders, and vasculitis.^{4,7,11-13,16,18}

ETIOLOGY AND GENETICS

The etiology of CNS DLBCL in immunocompetent patients remains unknown. Possible risk factors are B-cell-activating conditions (e.g., rheumatoid disease), systemic lupus erythematosus, Sjogren syndrome, cigarette smoking, high body mass index, and hepatitis C infection.^{1,3,11,12,17,20,23,29,31,37} Epstein-Barr virus infection is generally absent in immunocompetent patients with CNS DLBCL. However, even in the absence of an active Epstein-Barr virus infection, immunoglobulins produced by mutated naive B cells can regulate and interact with



microglia, astrocytes, and endothelial cells, probably by ligation with MHC class I molecules, promoting positive B-cell receptor signaling and consequently activation, proliferation, and survival of transformed B cells.³⁸

Distinct mechanisms are involved in the malignant transformation of B cells, including chromosomal translocation, aberrant somatic hypermutation of oncogenes, mutation of tumor suppressor genes, gain and loss of genetic material, and gene inactivation by DNA methylation (Figure 2).^{1,3,11,12,17,20,23,29,31,37} CNS DLBCL may show decreased or absent expression of human leukocyte antigen class I and II proteins, which allows the neoplastic cells to escape an immune attack. Neoplastic cells may interact with endothelial cells via interleukin-4 to create a favorable microenvironment for tumor growth.^{1,3,11,12,17,20,23,29,31,37}

Expression of CXCR4, CXCL12, CXCR5, CXCL13, and CCR7 allows interaction of neoplastic B cells with endothelial cells, reactive astrocytes, and microglia. CNS DLBCL is associated with different somatic hypermutations and open reading frame mutations.^{2,5,9,17,20,30,37-40} The VH4/34, BCL6, MYC, PAX5, ARHH, and PIM1 genes are recurrently mutated. Frequent cytogenetic abnormalities include BCL6 translocations; 6q deletions; BCL2 amplification; gains at 12q, 22q, and 18q21; and homozygous/hemizygous deletions affecting the CDKN2A (p16INK4a) pathway. Immunoglobulin heavy and light chain gene rearrangements are commonly detected.^{2,5,9,17,20,30,37-40}

Expression of MHC II genes in CNS DLBCL predicts a favorable outcome after chemotherapy. Expression of BCL-6, IMO2, and CD10 has been associated with favorable outcome, whereas expression of MUM1, cyclin D2, p53, CD5, FOXP1, ICAM1, HLA-DR, and BCL-2 are related to poor prognosis.^{2,5,9,20,30,33,36-39,41,42} Strong FOXP1 positivity, MYC and BCL2 overexpression, BCL6 translocations, and high Ki-67 index are associated with unfavorable prognosis.^{2,6,7,11,15,25,26,30,33-36}

Braggio et al.³⁸ demonstrated that biallelic inactivation of TOX and PRKCD was recurrent in CNS DLBCL but not in systemic DLBCL, suggesting a specific role for these genes in primary lymphoma pathogenesis. They also identified a high prevalence of MYD88 mutations and biallelic loss of CDKN2A.

Current treatment modalities for CNS DLBCL include radiotherapy, intrathecal therapy, systemic therapy, or a combination of these strategies. Rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP) or methotrexate–temozolomide–rituximab are the preferred chemotherapeutic regimens, but limited blood–brain barrier permeability impairs the therapeutic response to these drugs. Adverse effects of chemotherapy include white matter damage, axonal loss, myelin swelling, reactive astrocytosis, necrosis, and mononuclear cell reaction.^{2,5,9,20,30,33,36-39,41-43} The accurate distinction between GCB subtype and ABC subtype should be made for all cases of DLBCL because it is an important predictive factor. Preliminary data suggest that the

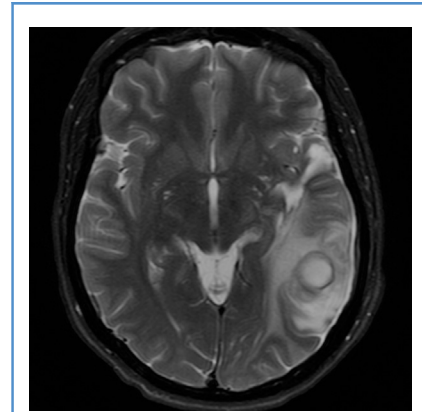
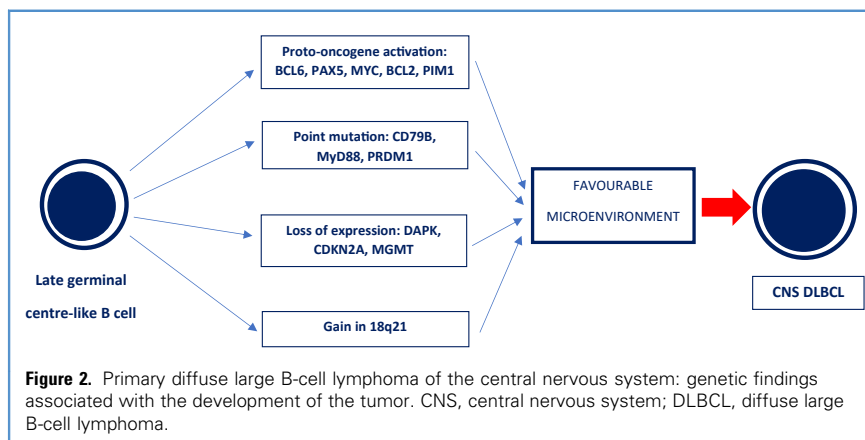


Figure 3. Primary central nervous system diffuse large B-cell lymphoma: postcontrast T2-weighted magnetic resonance imaging exhibiting an expansive solid mass in the right parietal lobe, with surrounding edema and homogeneous contrast enhancement.

addition of bortezomib, lenalidomide, and ibrutinib to R-CHOP is preferentially seen in the ABC subtype. MGMT methylation in CNS DLBCL has been associated with a better course in elderly patients submitted to temozolomide monotherapy. The inclusion of whole-brain radiation may improve outcome, but increases the risk of neurotoxicity.^{30,33,36-39,41-46}

PROGNOSIS AND WORLD HEALTH ORGANIZATION 2016 CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM

CNS DLBCL cases exhibit a remarkably worse outcome than patients with systemic DLBCL. Older patients, MYC overexpression, high Ki-67 index, and ABC subtype are major negative prognostic factors, and are associated with reduced survival. Most reports describe a median progression-free survival of about 12 months and an overall survival of approximately 3 years.^{1,2,22,30,35,42,45} The 2016 World Health Organization Classification of Tumors of the Central Nervous System uses molecular data and histologic findings to define tumor entities like WNT-activated/SHH-activated medulloblastomas and IDH-wildtype/IDH mutant glioblastomas. In this new classification, no specific molecular and histologic data can substantially differentiate CNS DLBCL from systemic DLBCL, or explain the worse



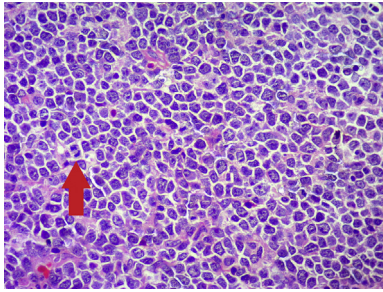


Figure 4. Histologic features of primary central nervous system diffuse large B-cell lymphoma (hematoxylin-eosin stain; original magnification, 200 \times). The lymphoma cells are large, with relatively abundant cytoplasm and irregular cleaved nuclei. The nuclei are usually round, centrally located, with chromatin clumped or condensed under the nuclear membrane. Note the diffuse pattern of infiltration, which is characteristic of this high-grade lymphoid malignancy. The arrow indicates an atypical mitotic figure.

prognosis from CNS lesions at this moment.^{2,47-49}

Otani et al.⁵⁰ evaluated 26 cases of primary CNS DLBCL submitted to continuous intrathecal injection therapy of methotrexate combined with conventional therapy, and found a response rate for all patients of 92.3%. They also found median progression-free survival and median overall survival equal to 59.4 and 93.8 months, respectively.⁵⁰ The authors suggested that better prognosis in patients treated with continuous intrathecal injection therapy of methotrexate can be associated with



Figure 5. Representative photomicrograph showing positive immunoexpression for CD20 in primary central nervous system diffuse large B-cell lymphoma cells (original magnification, 100 \times). Note the distinct membrane staining of the neoplastic cells for CD20 antibody (arrow).

stable concentration of methotrexate in the cerebrospinal fluid.⁵⁰ Rae et al.⁵¹ analyzed the relationship between craniotomy, prognostic factors, and survival for primary central nervous system lymphoma using a case-control design, and determined that craniotomy was associated with increased median survival over biopsy (19.5 vs. 11.0 months), independent of subsequent radiation and chemotherapy ($P < 0.001$, data based on National Cancer Database-Participant User File). Abranso et al.⁵² reported a case of DLBCL, germinal-center subtype, arising in the CNS, with a BCL2 rearrangement and multiple copies of MYC and BCL6. The patient was refractory to infusional chemotherapy (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab) and was enrolled to CD19-directed chimeric antigen receptor T-cell therapy. One month later, positron emission tomography-computed tomography scan and brain MR imaging revealed complete remission of intra-axial lesions.⁵² Ferreri et al.⁴³ evaluated 12 HIV-negative patients who developed primary CNS DLBCL and received treatment consisting of 6 courses of conventional doses of R-CHOP preceded by NGR-hTNF infusion. The authors tested the hypothesis that NGR-hTNF can break the blood-brain barrier, which could favor the response to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone therapy.⁴³ Ferreri et al.⁴³ described that tumor necrosis factor- α coupled with NGR, a peptide targeting CD131 vessels, induces endothelial permeabilization and improves tumor access of cytostatics. In this series, R-CHOP preceded by low-dose NGR-hTNF was not associated with unexpected toxicity and resulted in tumor regression in 9 of 12 patients with primary central nervous system lymphoma.⁴³ Kim et al.⁵³ reported 98 cases of primary CNS DLBCL and demonstrated that PD-L1 expression in the tumor microenvironment is positively correlated with infiltration of CD8+ or PD-1+ TILs. In this series, tumoral PD-L1 expression was related to a poor prognosis, and a large number of CD8+ or PD-1+ TILs were associated with a good prognosis, suggesting that PD-L1-mediated immune evasion is important for tumor progression in primary central nervous system DLBCL.⁵³

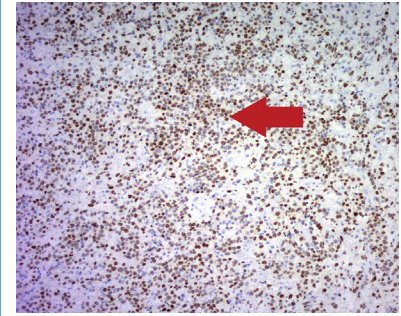


Figure 6. Primary central nervous system diffuse large B-cell lymphoma: neoplastic cells showing strong nuclear positivity (arrow) for MUM1 antibody (original magnification, 100 \times).

FINAL CONSIDERATIONS

Primary DLBCL is an uncommon brain tumor that occurs sporadically in healthy adult patients. Generally, CNS DLBCL is a single lesion (60%–70%) affecting mainly the frontal lobe (15%), and stereotactic biopsy is the criterion standard to establish the final diagnosis. Although the etiology of the lesion in immunocompetent patients remains unknown, neoplastic cells recapitulate the differentiation process of normal B cells, and tumor development has been associated with reduced/absent expression of human leukocyte antigen class I and II proteins; increased expression of CXCR4; mutations of VH4/34, BCL6, MYC, and PAX5 genes; and rearrangement of immunoglobulin heavy and light chain genes. Prognosis of primary CNS DLBCL is much less favorable than that of nodal DLBCL, and future therapies

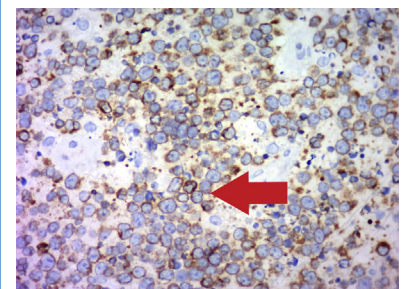


Figure 7. Positive expression of BCL-2 in primary central nervous system diffuse large B-cell lymphoma cells (original magnification, 400 \times). Note the membranous/cytoplasmic pattern exhibited by neoplastic cells (arrow).

based on the use of drugs able to penetrate the blood–brain barrier can improve survival.^{1,2,5,7,9,16,23,29,36,41-43}

REFERENCES

- Fox CP, Philips EH, Smith J, et al. Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma. *Br J Haematol.* 2019;184:348-363.
- Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127:2375-2390.
- Langner-Lemervier S, Houillier C, Soussain C, et al. Primary CNS lymphoma at the first relapse/progression: characteristics, management, and outcome of 256 patients from the French LOC network. *Neuro Oncol.* 2016;18:1297-1303.
- Bataille B, Delvail V, Menet E, et al. Primary intracerebral malignant lymphoma: report of 248 cases. *J Neurosurg.* 2000;92:261-266.
- Chapuy B, Roemer MG, Stewart C, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood.* 2016;127:869-881.
- Liu J, Wang Y, Liu Y, et al. Immunohistochemical profile and prognostic significance in primary central nervous system lymphoma: analysis of 89 cases. *Oncol Lett.* 2017;14:5505-5512.
- Ichiki A, Carreras J, Miyaoka M, et al. Clinicopathological analysis of 320 cases of diffuse large B-cell lymphoma using the Hans classifier. *J Clin Exp Hematop.* 2017;57:54-63.
- Zahid MF, Khan N, Hashmi SK, et al. Central nervous system prophylaxis in diffuse large B-cell lymphoma. *Eur J Haematol.* 2016;97:108-120.
- Four M, Cacheux V, Tempier A, et al. PD1 and PDL1 expression in primary central nervous system diffuse large B-cell lymphoma are frequent and expression of PD1 predicts poor survival. *Hematol Oncol.* 2017;35:487-496.
- Olson JE, Janney CA, Rao RD, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. *Cancer.* 2002;95:1504-1510.
- Plasswilm L, Herrlinger U, Korfel A, et al. Primary central nervous system (CNS) lymphoma in immunocompetent patients. *Ann Hematol.* 2002;81:415-423.
- Aki H, Uzunaslan D, Saygin C, et al. Primary central nervous system lymphoma in immunocompetent individuals: a single center experience. *Int J Clin Exp Pathol.* 2013;6:1068-1075.
- Harley B, Shivapathasundram G, Astradsson A, et al. An unusual presentation of cerebellar lymphoma. *J Clin Neurosci.* 2018;57:177-180.
- Birsan R, Blanc E, Willems L, et al. Prognostic value of early 18F-FDG PET scanning evaluation in immunocompetent primary CNS lymphoma patients. *Oncotarget.* 2018;9:16822-16832.
- Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103:275-282.
- Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemotherapy with methotrexate, cytarabine, thiopeta, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomization of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol.* 2016;3:e217-e227.
- Hayashi Y, Iwato M, Arakawa Y, et al. Homozygous deletion of INK4a/ARF genes and overexpression of bcl-2 in relation with poor prognosis in immunocompetent patients with primary central nervous system lymphoma of the diffuse large B-cell type. *J Neurooncol.* 2001;55:51-58.
- Rudresha AH, Chaudhuri T, Lakshmaiah KC, et al. Primary central nervous system lymphoma in immunocompetent patients: a regional cancer center experience. *South Asia J Cancer.* 2017;6:165-168.
- Correa DD, Marin L, Harder H, et al. Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines. *Ann Oncol.* 2007;18:1145-1151.
- Ekstein D, Ben-Yehuda D, Slysarevsky E, et al. CSF analysis of IgH gene rearrangement in CNS lymphoma: relationship to the disease course. *J Neurol Sci.* 2006;247:39-46.
- Puligundla CK, Bala S, Karnam AK, et al. Clinicopathological features and outcomes in primary central nervous system lymphoma: a 10-year experience. *Indian J Med Paediatr Oncol.* 2017;38:478-482.
- Sugita Y, Muta H, Ohshima K, et al. Primary central nervous system lymphomas and related diseases: pathological characteristics and discussion of the differential diagnosis. *Neuropathology.* 2016;36:313-324.
- Zhang X, Chen QH, Farmer P, et al. Central nervous system lymphoma in immunocompetent patients: The North Shore-Long Island Jewish Health System Experience. *J Clin Neurosci.* 2013;20:75-79.
- Sharma MC, Gupta RK, Kaushal S, et al. A clinicopathological study of primary central nervous system lymphoma & their associations with Epstein-Barr virus. *Indian J Med Res.* 2016;143:605-615.
- Chang C, Lin CH, Chang AL, et al. Primary central nervous system diffuse large B-cell lymphoma has poorer immune cell infiltration and prognosis than its peripheral counterpart. *Histopathology.* 2015;67:625-635.
- Giannini C, Dogan A, Salomão DR. CNS lymphoma: a practical diagnostic approach. *J Neuropathol Exp Neurol.* 2014;73:478-494.
- Preusser M, Woehrer A, Koperek O, et al. Primary central nervous system lymphoma: a clinicopathological study of 75 cases. *Pathology.* 2010;42:547-552.
- He M, Zuo C, Wang J, et al. Prognostic significance of the aggregative perivascular growth pattern of tumor cells in primary central nervous system diffuse large B-cell lymphoma. *Neuro Oncol.* 2013;15:727-734.
- Hattab EM, Martin SE, Al-Khatib SM, et al. Most primary central nervous system diffuse large B-cell lymphomas occurring in immunocompetent individuals belong to the non germinal center subtype: a retrospective analysis of 31 cases. *Mod Pathol.* 2010;23:235-243.
- Kluin PM, Deckert M, Ferry JA. Diffuse large B-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Haematopoietic and Lymphoid Tissues.* 4th ed. Geneva, Switzerland: WHO Press; 2017:300-302.
- Nguyen-Them L, Costopoulos M, Tanguy ML, et al. The CSF IL-10 concentration is an effective diagnostic marker in immunocompetent primary CNS lymphoma and a potential prognostic biomarker in treatment-responsive patients. *Eur J Cancer.* 2016;61:69-76.
- Nomura M, Narita Y, Miyakita Y, et al. Clinical presentation of anaplastic large-cell lymphoma in the central nervous system. *Mol Clin Oncol.* 2013;1:655-660.
- Song MK, Chung JS, Joo YD, et al. Clinical importance of Bcl-6-positive non-deep-site involvement in non-HIV-related primary central nervous system diffuse large B-cell lymphoma. *Neurooncol.* 2011;104:825-831.
- Raoux D, Duband S, Forest F, et al. Primary central nervous system lymphoma: immunohistochemical profile and prognostic significance. *Neuropathology.* 2010;30:232-240.
- Lukas RV, Stupp R, Gondi V, et al. Primary central nervous system lymphoma – part 1: epidemiology, diagnosis, staging, and prognosis. *Oncology (Williston Park).* 2018;32:17-22.
- Brunn A, Nagel I, Montesinos-Rongen, et al. Frequent triple-hit expression of MYC, BCL2, and BCL6 in primary lymphoma of the central nervous system and absence of a favorable MYC (low) BCL2 (low) subgroup may underlie the inferior prognosis as compared to systemic diffuse large B-cell lymphomas. *Acta Neuropathol.* 2013;126:603-605.
- Montesinos-Rongen M, Purschke FG, Brunn A, et al. Primary central nervous system (CNS) lymphoma B-cell receptors recognize CNS proteins. *J Immunol.* 2015;195:1312-1319.
- Braggio E, Van Wier S, Ojha J, et al. Genome-wide analysis uncovers novel recurrent alterations in primary central nervous system lymphomas. *Clin Cancer Res.* 2015;21:3986-3994.
- Booman M, Szuhai K, Rosenwald A, et al. Genomic alterations and gene expression in primary diffuse large B-cell lymphomas of immunoprivileged sites: the importance of apoptosis and

- immunomodulatory pathways. *J Pathol.* 2008;216:209-217.
40. Alvarez R, Dupuis J, Plonquet A, et al. Clinical relevance of flow cytometry immunophenotypic of the cerebrospinal fluid in patients with diffuse large B-cell lymphoma. *Ann Oncol.* 2012;23:1274-1279.
 41. Venetz D, Ponzoni M, Schiraldi M, et al. Perivascular expression of CXCL9 and CXCL12 in primary central nervous system lymphoma: T-cell infiltration and positioning of malignant C cells. *Int J Cancer.* 2010;127:2300-2312.
 42. Lukas RV, Gondi V, Stupp R, et al. Primary central nervous system lymphoma – part 2: modern therapeutic management and future directions. *Oncology (Williston Park).* 2018;32:e11-e19.
 43. Ferreri AJM, Calimeri T, Conte GM, et al. R-CHOP preceded by blood-brain barrier permeabilization with engineered tumor necrosis factor- α in primary CNS lymphoma. *Blood.* 2019;134:252-262.
 44. Nowakowski GS, Laplant B, Habermann TM, et al. Lenalidomide can be safely combined with R-CHOP (R2CHOP) in the initial chemotherapy for aggressive B-cell lymphomas. *Leukemia.* 2011;25:1877-1881.
 45. Offner F, Samoilova O, Osmanov E, et al. Front-line rituximab, cyclophosphamid docorubicin, and prednisone with bortezomib (VR-CAP) or vincristine (R-CHOP) for non-GCB DLBC. *Blood.* 2015;126:1893-1901.
 46. Kurzwelly D, Glas M, Roth P, et al. Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status. *J Neurooncol.* 2010;97:389-392.
 47. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of Central Nervous System: a summary. *Acta Neuropathol.* 2016;131:803-820.
 48. Cambruzzi E. Medulloblastoma, WNT-activated/SHH-activated: clinical impact of molecular analysis and histogenetic evaluation. *Childs Nerv Syst.* 2018;34:809-815.
 49. DeWitt JC, Mock A, Louis DN. The 2016 WHO classification of central nervous system tumors: what neurologists need to know. *Curr Opin Neurol.* 2017;30:643-649.
 50. Otani R, Yamada R, Kushihara Y, et al. Continuous intrathecal injection therapy of methotrexate is a therapeutic option in primary CNS lymphoma [e-pub ahead of print]. *J Clin Neurosci* <https://doi.org/10.1016/j.jocn.2019.08.083>, accessed October 21, 2019.
 51. Rae AI, Mehta A, Cleney M, et al. Craniotomy and survival for primary central nervous system lymphoma. *Neurosurgery.* 2019;84:935-944.
 52. Abranson JS, McGree B, Noyes S, et al. Anti-CD19 CAR T cells in CNS diffuse large-B-cell lymphoma. *N Engl J Med.* 2017;377:783-784.
 53. Kim S, Nam SJ, Park C, et al. High tumoral PD-L1 expression and low PD-1+ or CD8+ tumor-infiltrating lymphocytes are predictive of a poor prognosis in primary diffuse large B-cell lymphoma of the central nervous system. *Oncoimmunology.* 2019;8:e1626653.

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