

Primary Central Nervous System Lymphoma

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• **Primary central nervous system lymphoma (PCNSL) is an uncommon extranodal non-Hodgkin lymphoma. Its incidence has increased during the last 3 decades and has been reported in both immunocompromised and immunocompetent patients. Immunocompromised patients are affected at a younger age compared with immunocompetent patients. It presents with raised intracranial pressure and focal neurologic and neuropsychiatric symptoms. The lesions are typically solitary. The majority of the lesions are located in the periventricular area, whereas in a few cases they are located in the supratentorial area. Diffuse large B-cell lymphomas constitute most PCNSLs, whereas T-cell, low-grade, anaplastic, and Hodgkin lymphomas are rarely encountered. The morphology of PCNSL shows a characteristic angiocentric pattern and is positive for B-cell markers by immunohistochemistry. The differential diagnosis of PCNSL includes central nervous system gliomas, metastatic tumors, demyelinating disorders, subacute infarcts, and space-occupying lesions due to an infectious etiology. The understanding of the molecular mechanisms involved in the pathogenesis of PCNSL and the identification of molecular biomarkers have lagged behind that of systemic nodal lymphomas. Primary central nervous system lymphomas are treated with combined radiotherapies and chemotherapies. The prognosis for PCNSL is worse than for other extranodal lymphomas.**

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PPrimary central nervous system lymphoma (PCNSL) is an uncommon variant of extranodal non-Hodgkin lymphoma that involves the brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease. It does not include systemic lymphomas spreading to the central nervous system (CNS). This entity was first described by Bailey in 1929 (Intracranial sarcomatous tumours of leptomeningeal origin. *Arch Surg.* 1929;18:1359–1402) as “perithelial sarcoma” of the CNS until its lymphoid lineage was clarified. In most patients, PCNSL presents as an intracerebral mass, but occasionally it may present in the orbit, the leptomeninges, or the spinal cord.¹ According to the World Health Organization classification, most PCNSLs are diffuse large B-cell lymphomas (DLBCLs),² whereas T-cell, low-grade, anaplastic, and Hodgkin lymphomas are rarely encountered.^{3,4}

It has been reported in both immunocompromised and immunocompetent patients, and it accounts for 2.7% of all malignant diseases of the CNS. The incidence of PCNSL has increased during the last 3 decades and occurs at a younger age in immunocompromised patients. In human immunodeficiency virus-infected patients, PCNSL occurs at a rate that is 3600-fold higher than the general population. The lifetime risk of developing CNS lymphoma approaches 20% in patients with human immunodeficiency virus infection.⁵ The PCNSL in human immunodeficiency virus-positive patients is often associated with Epstein-Barr virus (EBV), whereas its association with EBV is rare in immunocompetent patients.⁶ The present article will focus on clinical features, gross and microscopic findings, ancillary studies, pathogenesis, differential diagnosis, prognostic markers, and treatment of PCNSL DLBCL. Rare variants of PCNSL are described briefly.

CLINICAL FEATURES

Age and Sex

The median age of occurrence of PCNSL in immunocompetent patients is 53 to 57 years,^{5,6} whereas in immunocompromised patients it is 31 to 35 years.⁷ The sex distribution of this disease is almost equal in immunocompetent patients (male-female ratio, 1.2:1.0), whereas there is a clear male predominance in AIDS-associated PCNSL (male-female ratio, 7.38:1).

Predisposing Conditions

Immunodeficiency is an important risk factor for the development of PCNSL. Apart from AIDS, iatrogenic immune suppression for transplant procedures, congenital immune deficiency, and autoimmune conditions are risk factors for the development of PCNSL. Congenital immunodeficiency syndromes that predispose to lymphoma include ataxia-telangiectasia, Wiskott-Aldrich syndrome, and severe combined and common variable immunodeficiency. Autoimmune diseases that predispose to lymphoma include rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, myasthenia gravis, sarcoidosis, and vasculitis.

Symptoms

The location of the lymphoma in the CNS determines the clinical presentation. In a large series with immunocompetent patients with PCNSL, focal neurologic deficits were the most common presentation in 70% of patients, followed by neuropsychiatric symptoms in 43%, signs of raised intracranial pressure like headache/nausea/vomiting in 33%, seizures in 14%, and ocular symptoms in 4%.⁸

Immunocompromised patients with PCNSL present

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with raised intracranial pressure, personality changes, and neurologic and neuropsychiatric symptoms.

Anatomical Location

Primary CNS lymphoma may present either as an isolated lesion or as a combination of the following features: (1) discrete or diffuse intracranial lesions that are either solitary or multiple, (2) ocular lymphomas with or without other lesions, and (3) leptomeningeal surface and spinal cord lesions. Immunocompetent patients tend to present predominantly with solitary lesions in 70% of cases, compared with 50% in AIDS patients.⁸ The majority of the discrete lesions are supratentorial (85%), and a minority are infratentorial (15%).^{6,8} In 60% of cases, the lesions of PCNSL are primarily located in periventricular areas involving the thalamus, basal ganglia, and corpus callosum. The lobes of the cerebral cortex are involved with following frequency: frontal lobe is involved in 20%, parietal lobe in 18%, temporal lobe in 15%, and occipital lobe in 4%.⁸

Macroscopic Features

The gross appearance of PCNSL in immunocompetent and immunodeficient patients is similar. The size may vary, but most of the lesions are well circumscribed and are greater than 2 cm in diameter. Grossly, the lesions could be firm, homogenous, centrally necrotic, brownish, gray-tan, and yellow with areas of hemorrhage. Their demarcation of the lesions from the surrounding brain is variable. They may resemble gliomas due to the architectural effacement and diffuse borders. Diffuse infiltrating tumors are referred to as *lymphomatosis cerebri*. In AIDS patients, necrotic areas simulating those of cerebral toxoplasmosis are observed. Meningeal lymphoma may mimic meningioma or meningitis or appear microscopically normal.²

Microscopic Features

The PCNSL shows a characteristic angiocentric pattern, forming cuffs of tumor cells within and around cerebral blood vessels. Reticulin preparation shows concentric reticulin fibers around blood vessels. The tumor infiltrates the brain parenchyma as small clusters and as individual cells. The tumor may show areas of necrosis, with viable cells found mainly around blood vessels. The cells lack a cohesive appearance. Most of the PCNSLs show a diffuse growth pattern, whereas a follicular growth pattern has not been observed. A focally prominent reactive astrocytic and microglial response, as well as reactive lymphocytic infiltrates with a predominance of small CD4-positive T cells are common.² The malignant lymphoid cells may be centroblasts or immunoblasts with scant cytoplasm and a variable number of mitotic figures (Figure 1).

Immunohistochemical Profile

Immunohistochemical stains for the diagnostic workup include CD45 (leukocyte common antigen), CD20, CD79a, and CD3. In PCNSL, the large atypical cells are positive for CD20 (B-cell marker), and small benign admixed cells are positive for CD3 (T-cell marker). Glial fibrillary acidic protein staining shows gliosis of the infiltrated brain parenchyma by tumor cells. Most tumors are BCL2 positive (Figure 2). The PCNS DLBCL is further subcategorized into germinal center B-cell and activated B-cell type based on CD10, BCL6, and MUM-1 staining patterns. The BCL6 protein is a zinc-finger transcriptional repressor required for the formation of the ger-

minal center.⁹ A number of studies have shown the expression of BCL6 in PCNS DLBCL (Figure 3).^{10,11} Most PCNSLs (96%) are positive for MUM-1 (a marker of germinal center/early post-germinal center B cells), indicating a late germinal center/early post-germinal center stage of differentiation (Figure 4).¹² A far greater number of PCNSLs express the pattern of an activated B-cell phenotype when compared with systemic DLBCL, and are associated with poor prognosis.¹²

Pathogenesis and Molecular Studies

Since the CNS is devoid of B cells, the understanding of the molecular mechanisms involved in the pathogenesis of PCNSL is quite limited. Due to its association with EBV in immunodeficient individuals, the proposed mechanisms for the development of PCNSL are focused on the body's immunologic response to EBV infection. In immunodeficient patients, EBV is associated with PCNSL, and latent EBV infection of B cells leads to their immortalization and to CNS tropism. In healthy individuals, the EBV-infected B cells are held in check by T cells, and as the immunodeficiency becomes severe, a gradual fall in T cells leads to the proliferation and dissemination of B cells. Another proposed mechanism for the development of PCNSL is the expression of specific adhesion molecules by systemic malignant B cells that could facilitate their homing to the CNS. A B-cell chemokine, BCA-1, has been shown to be expressed at a higher level in PCNSL. A study by Rubenstein et al¹³ showed that certain factors are required for the retention of peripherally derived lymphoma cells in the CNS as well as for the angiocentric pattern in PCNSL. This group has shown that interleukin 4 and STAT6 molecules are involved in the pathogenesis of PCNSL. They also showed that the expression of STAT6 is associated with tumor progression and a shortened survival.

Cytogenetic analyses show gains of chromosomes 12, 1, 18, and 7 by comparative genomic hybridization. A study by Kady et al¹⁴ suggests distinct differences between genetic pathways of PCNSL and systemic lymphomas. Their study showed less frequent translocations of immunoglobulin H (IgH), BCL6, and MYC in PCNSL compared with systemic lymphomas. In contrast to systemic lymphomas, homozygous deletion and promoter hypermethylation of *CDKN2A*, which produces p14ARF, have been identified in PCNSL.^{15,16} Unlike systemic lymphomas, mutations of *TP53* are extremely rare in PCNSL.^{15,16}

Differential Diagnosis

Since PCNSL predominantly presents as a single homogenous lesion surrounded by edema on radiologic studies, the differential diagnosis includes a wide range of benign and malignant lesions, which present with a similar radiologic pattern. Malignant lesions include glioblastoma multiforme and metastatic lesions to the CNS from other malignancies, like prostate cancer, small blue cell tumors, or adenocarcinoma of the lung. Benign lesions in the differential diagnosis include subacute infarction, lesions due to demyelinating diseases, or space-occupying lesions due to infectious or parasitic etiologies. Histopathology and immunohistochemical staining of the lesion is crucial to differentiate PCNSL from other lesions.

Malignant gliomas tend to have a greater degree of cellular and nuclear pleomorphism, infiltrative borders, vascular proliferation, and necrosis with pseudopalisading by tumor cells. Anaplastic carcinomas tend to be cohesive

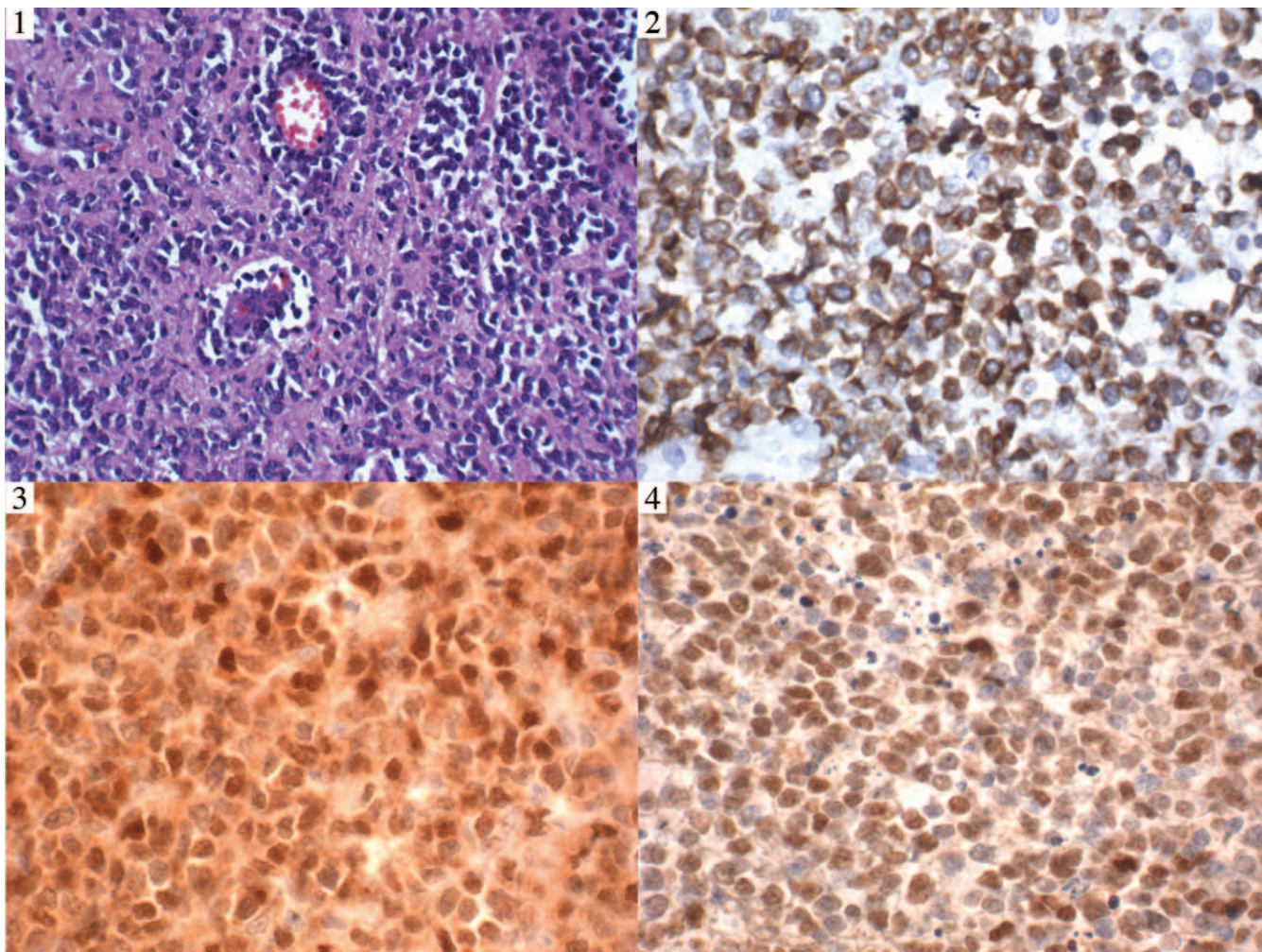


Figure 1. Primary central nervous system diffuse large B-cell lymphomas showing a characteristic angiocentric pattern, forming cuffs of tumor cells within and around cerebral blood vessels and consisting of centroblasts (hematoxylin-eosin, original magnification $\times 100$).

Figure 2. A case of primary central nervous system diffuse large B-cell lymphoma. Immunohistochemical staining for BCL2. Tumor cells show strong staining for BCL2 (original magnification $\times 100$).

Figure 3. Primary central nervous system diffuse large B-cell lymphoma. Immunohistochemical staining for BCL6. Lymphoma cells are positive for BCL6 (original magnification $\times 100$).

Figure 4. A case of primary central nervous system diffuse large B-cell lymphoma. Immunohistochemical staining for MUM-1. Tumor cells show strong nuclear staining for MUM-1 (original magnification $\times 100$).

and lack perivascular reticulin deposition. A macrophage-rich lesion may be due to an infarction or a demyelinating disorder. Axons are destroyed in infarctions compared with their preservation in demyelinating disorders. Small cell carcinomas show nuclear molding, a feature not seen in PCNSL. Immunohistochemical stains, glial fibrillary acidic protein, and phosphotungstic acid hematoxylin accentuate the fibrillary pattern in gliomas. Leukocyte common antigen (CD45) confirms the diagnosis of lymphoma. Cytokeratin may be useful in detecting undifferentiated carcinomas. In immunodeficient patients, a parasitic infestation due to toxoplasmosis needs to be ruled out.

Treatment and Prognosis

The favorable prognostic factors described to date include a single, well-circumscribed intracranial lesion, the absence of meningeal or periventricular tumor, the absence of immunodeficiency, and age younger than 60 years.² Patients with diffuse mixed and small noncleaved

cell lymphomas do better than those with large immunoblastic and large noncleaved or cleaved lymphomas.¹⁷

The primary treatment for PCNSL includes a combination of chemotherapy containing high-dose methotrexate followed by radiotherapy. With the combined radiotherapy and chemotherapy approach, immunocompetent patients show a response rate of 85%, with a median survival of 17 to 45 months.² Patients with AIDS have a poorer prognosis, with median survival of 13.5 months, even when treated with multimodal therapy.¹⁸ The dramatic response to corticosteroids is usually temporary.

RARE PRIMARY CNS LYMPHOMAS

T-Cell Lymphomas

T-cell PCNSL is occasionally seen, and case reports have been described in the literature. The reported incidence of T-cell PCNSL in Western countries is 2%.¹⁹ The largest series of T-cell PCNSL included 45 patients from 7 countries

(The International Primary CNS Lymphoma Corroborative Group).²⁰ In this study, a supratentorial lesion was most commonly seen. T-cell origin was ascertained by immunophenotyping and T-cell receptor gene rearrangement studies. The morphology showed an "angiocentric" pattern in 28% of the cases. The cell size ranged from small to medium in 50% of the cases and either "pleomorphic" or "medium to large" cells in the other 50% of the cases.²⁰

Anaplastic Large Cell Lymphoma

Primary or secondary CNS anaplastic large cell lymphomas (ALCLs) are extremely rare, and only 20 cases have been reported in the literature.²¹ There is no association between ALCL and immunodeficiency disorders or immunosuppression. Most cases occurred in patients younger than 22 years, and a minority of cases after 50 years.²² Primary CNS ALCL is notable for dural or leptomeningeal involvement.

The morphology of ALCL shows large cells with pleomorphic nuclei and multiple prominent nucleoli. The majority of the lymphomas are positive T-cell markers, and staining for CD45, CD30, and epithelial membrane antigen is variable. The majority (60%–85%) of ALCLs show t(2;5) that fuses ALK (anaplastic large cell kinase) on chromosome 2, with the nucleophosmin on chromosome 5. This can be detected immunohistochemically by reactivity with ALK-1 antibody. The morphologic variants include lymphohistiocytic and small cell types. The morphologic and immunohistochemical variability makes its diagnosis a challenge.²² Metastatic carcinoma, sarcoma, and melanoma are in the differential diagnosis. Epithelial membrane antigen, cytokeratin, S100, and lymphoid markers are used to differentiate ALCL from other tumors. Multifocal disease, ALK-1 negativity, tumor necrosis, and elderly patients are associated with a bad prognosis.

Low-Grade Lymphoma

Low-grade lymphomas are extremely rare and constitute 3% of PCNSLs. Supratentorial localization is common. The International Primary CNS Lymphoma Study Group recently published a series of low-grade PCNSLs.²³ Of the 40 patients with low-grade PCNSL, 32 (80%) were of B-cell lymphoma type, and 8 (20%) were of the T-cell type.²³ T-cell lymphomas showed a similar angiocentricity compared with DLBCL, and they were diagnosed by the presence of T-cell markers and the absence of B-cell markers. The low-grade lymphomas showed an indolent behavior compared with the high-grade DLBCLs. There was no difference in the prognosis between B-cell and T-cell low-grade lymphomas. A low-grade PCNSL should be differentiated from inflammatory processes, like viral encephalitis and multiple sclerosis. Nonneoplastic processes are composed mainly of reactive T cells, whereas most lymphomas are composed predominantly of B cells. T-cell receptor and IgH gene rearrangement studies are helpful in diagnosis.

Primary Hodgkin Lymphoma

This entity is rare in the CNS. Secondary involvement of the brain or meninges is an uncommon complication of systemic Hodgkin lymphoma. The lesions are dura based in most cases. Identification of Reed-Sternberg cells or their variants in the appropriate nonneoplastic background and immunoreactivity of Reed-Sternberg cells for CD30 and CD15 confirms the diagnosis. Epstein-Barr vi-

rus genes and proteins may occur even in immunocompetent patients.²⁴

Primary Intraocular Lymphoma

Primary intraocular lymphoma involves the retina, the vitreous, and the optic nerve. The majority of the cases present bilaterally and develop intracerebral disease during the course of progression. Most of the primary intraocular lymphomas are DLBCLs and show positive B-cell markers. Vitreous cytology and chorioretinal biopsy are necessary for the diagnosis and show a malignant lymphoid infiltrate between the retinal pigment epithelium and the Bruch membrane.

CONCLUSION

The incidence of PCNSL is increasing. Diffuse large B-cell lymphoma is the most common type of PCNSL, the majority of which are activated B-cell type. The molecular mechanisms involved in pathogenesis of PCNSL are not yet understood fully. There is an urgent need to discover new therapeutic targets and drugs to improve the clinical outcome of patients with PCNSL.

References

1. Central Brain Tumor Registry of the United States. *Primary Brain Tumors in The United States 1995–1999: Statistical Report*. Chicago, Ill: Central Brain Tumor Registry of the United States; 2002–2003.
2. Kleihues P, Cavenee WK. *Pathology and Genetics of Tumours of the Nervous System*. Lyon, France: IARC Press; 2000. *World Health Organization Classification of Tumors*.
3. Aubrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005;23:5034–5043.
4. Aubrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering cancer center prognostic model. *J Clin Oncol*. 2006;24:5711–5715.
5. Schabert M. Epidemiology of primary CNS lymphoma. *J Neurooncol*. 1999;43:199–201.
6. Camilleri-Broet S, Martin A, Moreau A, et al. Primary central nervous system lymphomas in 72 immunocompetent patients: pathologic findings and clinical correlations. *Am J Clin Pathol*. 1998;110:607–611.
7. Fine HA, Mayer RJ. Primary central nervous system lymphoma. *Ann Intern Med*. 1993;119:1093–1104.
8. Bataille B, Delwail V, Menet E, et al. Primary intracerebral malignant lymphoma: report of 248 cases. *J Neurosurg*. 2000;92:261–266.
9. Dent AL, Shaffer AL, Yu X, Allman D, Staudt LM. Control of inflammation, cytokine expression and germinal center formation by BCL-6. *Science*. 1997;276:589–592.
10. Braaten KM, Betensky RA, de Level L, et al. BCL-6 expression predicts improved survival in patients with primary central nervous system lymphoma. *Clin Cancer Res*. 2003;9:1063–1069.
11. Lin CH, Kuo KT, Chuang SS, et al. Comparison of the expression and prognostic significance of differentiation markers between diffuse large B-cell lymphoma of central nervous origin and peripheral nodal origin. *Clin Cancer Res*. 2006;12:1152–1156.
12. Camilleri-Broet S, Criniere E, Broet P, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. *Blood*. 2005;107:190–196.
13. Rubenstein JL, Fridlyand J, Shen A, et al. Gene expression and angiotropism in primary CNS lymphoma. *Blood*. 2006;107:3716–3723.
14. Kady FM, Law ME, Porter-Umphrey AB, et al. The frequency of specific chromosomal abnormalities in primary central system lymphomas (PCNSL) differs from systemic diffuse large B-cell lymphoma (DLBCL), suggesting a distinct pathogenesis. Poster presented at: United States and Canadian Academy of Pathology; March 24–30, 2007; San Diego, Calif.
15. Nakamura M, Shimada K, Konishi N. Histopathology, pathogenesis and molecular genetics in primary central nervous system lymphomas. *Histol Histopathol*. 2004;19:211–219.
16. Rubenstein JL, Treseler P, O'Brien JM. Pathology and genetics of primary central nervous system and intraocular lymphoma. *Hematol Oncol Clin North Am*. 2005;19:705–717.
17. Miller DC, Hochberg FH, Harris NL, et al. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma: the Massachusetts General Hospital experience 1958–1989. *Cancer*. 1994;74:1383–1397.
18. Chamberlain MC. Long survival in patients with acquired immune deficiency syndrome related primary central nervous system lymphoma. *Cancer*. 1994;73:1728–1730.
19. Ferreri AJ, Reni M, Pasini F, et al. A multicenter study of treatment of primary CNS lymphoma. *Neurology*. 2002;58:1513–1520.

20. Shenkier TN, Blay JY, O'Neill BP, et al. Primary CNS lymphoma of T cell origin: a descriptive analysis from the international Primary CNS Lymphoma Collaborative Group. *J Clin Oncol*. 2005;23:2233–2239.

21. Rupani A, Modi C, Desai S, Rege J. Primary large cell anaplastic cell lymphoma of central nervous system—a case report. *J Postgrad Med*. 2006;51:326–327.

22. George DH, Scheithauer BW, Aker FV, et al. Primary anaplastic large cell

lymphoma of the central nervous system: Prognostic effect of ALK-1 expression. *Am J Surg Pathol*. 2003;27:487–493.

23. Jahnke K, Korfel A, O'Neill BP, et al. International study on low-grade primary central nervous system lymphoma. *Ann Neurol*. 2006;59:755–762.

24. Klein R, Mullges W, Bendszus M, Woydt M, Kreipe H, Roggendorf W. Primary intracerebral Hodgkin's disease: report of a case with Epstein-Barr virus association and review of literature. *Am J Surg Pathol*. 1999;23:477–481.

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