The Challenge of Primary Central Nervous System Lymphoma

Julia Carnevale, MD[a], James L. Rubenstein, MD, PhD[b,*]

KEYWORDS

• Aggressive lymphoma • Primary CNS lymphoma • Brain tumor • NF-κB
• High-dose chemotherapy

KEY POINTS

- Long-term survival and cure is feasible in primary central nervous system lymphoma (PCNSL) without whole brain radiotherapy (WBRT).
- WBRT consolidation is associated with severe neurotoxicity, particularly in patients older than 60.
- High-dose chemotherapy is currently under investigation as first-line consolidation.
- There is a need for novel therapies that target key survival pathways in PCNSL, including activation of nuclear factor-κB survival signaling.

INTRODUCTION

Although primary central nervous system lymphoma (PCNSL) remains a rare neoplasm, representing only 2% to 3% of all cases of non-Hodgkin's lymphoma (NHL), the incidence of PCNSL among immunocompetent patients seems to be increasing, particularly among persons age 65 years and older.[1] The characteristic pathobiology of PCNSL is that of an aggressive lymphoma, localized within the central nervous system (CNS) and often disseminated within brain, cranial nerves, leptomeninges, cerebrospinal fluid (CSF), intraocular structures and spinal cord, without overt systemic disease.[2,3]

PCNSL has long been recognized to be an aggressive brain tumor associated with a poor prognosis.[4] Historically known as reticulum cell sarcoma or microglioma,

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[a] Division of Hematology/Oncology, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143, USA; [b] Division of Hematology/Oncology, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, M1282 Box 1270, San Francisco, CA 94143, USA
* Corresponding author.
E-mail address: jamesr@medicine.ucsf.edu

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management principles for this disease have emerged slowly. Beginning in the 1960s, in the absence of prospective data, whole brain radiotherapy (WBRT) was used as the first-line intervention as a means to elicit immediate responses in patients faced with a rapidly deteriorating course; WBRT alone typically resulted in median survival of 12 months. To date, the most significant advance in PCNSL has been the recognition, in the 1970s, of the efficacy of high-dose methotrexate (HD-MTX).[5,6] Several recent prospective trials have demonstrated markedly improved outcomes in PCNSL. Our goal is to highlight significant advances in our understanding of disease biology, diagnosis, staging, and therapeutic management.[7–12]

ETIOLOGY

Risk factors for PCNSL include acquired and/or congenital immunodeficiency states. PCNSL is an AIDS-defining illness associated with a low CD4 cell count (<50 cells/mL) and Epstein–Barr virus (EBV) infection. In systemic AIDS-related lymphomas, EBV infection of the lymphoma may be predictive of secondary CNS involvement.[13] Congenital immunodeficiency states such as Wiskott-Aldrich syndrome, severe combined or common variable immunodeficiency, or ataxia-telangiectasia carry an approximately 4% risk of PCNSL. Posttransplant lymphoproliferative disorder (PTLD) involving CNS develops in 1% to 2% of renal transplant recipients and 2% to 7% recipients of liver, cardiac, and lung transplant recipients. CNS PTLD is associated with EBV in the setting of iatrogenic T-cell immunodeficiency induced by immunosuppressive agents such as mycophenolate mofetil (CellCept, Genentech, San Francisco, CA).[14] Among patients with PCNSL without clinically overt immunosuppression, EBV infection of lymphoma is rare.[15]

CLINICAL FEATURES AND PATHOGENESIS

PCNSL is typically a highly infiltrative neoplasm that has been characterized as a "whole brain disease," particularly at relapse.[16] For this reason, its radiographic appearance typically underestimates disease extent, and like malignant gliomas, PCNSL is not amenable to curative resection.[16] One of the archetypical histologic features of PCNSL is angiotropism; the accumulation of lymphoma cells around tumor vessels, a phenotype that likely disrupts the blood–brain barrier and enables radiographic detection of lesions via pathologic contrast enhancement. PCNSL commonly is diagnosed as a solitary mass, typically with vasogenic edema and mass effect. The frequency of multiple lesions is increased among the immunosuppressed[17] (**Fig. 1**).

Although NHL presenting in the brain is typically classified as PCNSL, subclinical tumor-related clones are often detectable in the blood and bone marrow of PCNSL patients, suggesting that the brain microenvironment might promote malignant progression.[18,19]

Intraocular disease is a common manifestation: 20% of PCNSL patients present with involvement of the retina, uvea, and vitreous. An important principle is that apparently localized intraocular lymphoma (IOL) will disseminate within brain in greater than 80% of cases; therefore, detection of IOL mandates staging of the neuroaxis. Therapies for IOL that address this risk should be strongly considered.[20]

Approximately 95% of PCNSL are large B-cell lymphoma; other include T-cell (2%),[21] Burkitt, lymphoblastic, and marginal zone lymphomas. PCNSL is distinguished from dural-based marginal zone lymphomas because these rarely invade brain parenchyma and typically share overlapping radiographic features on MRI with meningioma.[22]