Primary Central Nervous System Lymphoma

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KEYWORDS

• Primary central nervous system lymphoma • Brain • Non-Hodgkin's lymphoma
• Methotrexate

KEY POINTS

- Primary central nervous system lymphoma (PCNSL) is an aggressive form of Non-Hodgkin's lymphoma restricted to the central nervous system.
- Stereotactic biopsy is the gold-standard for diagnosis of PCNSL.
- Methotrexate-based chemotherapy is the standard induction for PCNSL patient.
- Optimal treatment for relapsed and refractory PCNSL has not been defined.

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive Non-Hodgkin's lymphoma (NHL) confined to the CNS, including the brain, spinal cord, eyes, and leptomeninges. It is a rare disease that makes up approximately 1% to 2% of all NHL cases and about 4% of primary brain tumors.[1–3] Although PCNSL can develop in both the immunocompetent and immunocompromised host, the focus of this article is on the former.

EPIDEMIOLOGY

Data from population-based studies on PCNSL are limited due to its low incidence of 7 cases per 1,000,000 population in the United States per year.[4] Over time, the incidence of PCNSL has fluctuated, with an increase in the 1980s that was thought to be due to the acquired immunodeficiency syndrome (AIDS) pandemic. The incidence

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Neurol Clin 36 (2018) 517–532
https://doi.org/10.1016/j.ncl.2018.04.008
neurologic.theclinics.com

increased until the mid-1990s, when it peaked; it has subsequently declined.[4] In the immunocompetent population, PCNSL tends to occur in older individuals with a median age at diagnosis of 65.[5–7] For unclear reasons, this older population is the only subgroup that continues to have an increasing incidence of PCNSL despite the overall decline reported in the United States.[4,8,9]

PATHOPHYSIOLOGY

Most (>90%) PCNSL cases are diffuse large B cell lymphomas (DLBCLs), a lymphoma histologically indistinct from systemic NHL.[10] PCNSLs are highly proliferative, and demonstrate an angiocentric growth pattern.[10]

Genetic profiling has allowed for lymphomas to be subdivided into classes based on the specific differentiation stage during which malignant transformation is assumed to occur. These groups include germinal center B cell-like (GCB), activated B cell-like (ABC), and type 3. PCNSL displays a unique molecular signature (MUM1+, BCL6+, CD10-), consistent with features of both GCB and ABC types. Most PCNSL cases are considered to be of the ABC immunophenotype, which, in systemic DLBCL, is associated with more aggressive disease and poor prognosis.[10]

In PCNSL, additional mutations in the B cell signaling pathway affect the downstream target nuclear factor kappa B (NFkB), particularly mutations in MYD88.[11] Studies have shown elevated but variable percentages of mutations in these genes from 29% to 86% of patients with PCNSL.[12,13] Interestingly, the increase in mutations in the MYD88 genes has been reported to be significantly more frequent in PCNSL compared with systemic ABC-type DLBCL.[12,13] The presence of this mutation suggests that targeted therapies focused on this pathway may be useful in the treatment of PCNSL.

CLINICAL PRESENTATION

PCNSL can be a diagnostic challenge, as presentation is variable and nonspecific. In a retrospective study of 248 immunocompetent individuals with PCNSL, the most common symptoms on presentation were focal neurologic deficits (70%), neuropsychiatric symptoms (43%), seizures (14%), and symptoms attributable to increased intracranial pressure such as headache, nausea, and vomiting (33%).[6]

Isolated leptomeningeal (LM) lymphoma is rare, comprising only 7% of all cases of PCNSL in immunocompetent hosts. However, LM lymphoma occurs simultaneously with intracranial disease in approximately 15% to 20% of all PCNSL patients.[14] LM disease is asymptomatic in the majority of patients, although cranial nerve palsies have been reported variably in the literature (5%–31% of cases).[15]

In some cases, PCNSL patients will have involvement of the eye or spine. Approximately 10% to 20% of PCNSL cases are found to have intraocular involvement at the time of diagnosis, although isolated intraocular lymphoma is much less common.[16] Typically patients with eye involvement report nonspecific symptoms such as floaters and blurred vision.[5,6] Spinal involvement of PCNSL is rare (<5%) and typically presents with symptoms that localize to the spinal cord such as limb paresthesias, weakness (often asymmetric), bowel or bladder dysfunction, impaired gait, and perineal numbness.[17]

DIAGNOSIS

Imaging

PCNSL has a characteristic appearance on both computed tomography (CT) and MRI due to its hypercellularity and disruption of the blood-brain barrier (**Fig. 1**).[17] On MRI,