Extranodal Lymphoma of the Central Nervous System and Spine

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KEYWORDS

• Primary central nervous system lymphoma • Intravascular lymphoma • Lymphomatosis cerebri
• Lymphomatoid granulomatosis • Posttransplantation lymphoproliferative disorder
• Immunosuppression

KEY POINTS

- Central nervous system lymphoma is rare, comprising approximately 6% of all brain tumors.
- Strong affiliation with immunocompromised status is common but it may arise in those with normal immune systems as well.
- Hyperattenuation on computed tomography, mild hypointensity on T2-weighted magnetic resonance imaging, enhancement on postcontrast studies, and periventricular location are characteristic imaging manifestations.
- Less common variant forms include intravascular lymphoma, lymphomatosis cerebri, lymphomatoid granulomatosis, and posttransplantation lymphoproliferative disorder.
- Extranodal lymphoma of the spine is more often caused by secondary dissemination from systemic disease and less often the primary site of origin.

EXTRANODAL LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM

Once an extremely rare brain neoplasm, primary central nervous system lymphoma (PCNSL) and its less common variants now comprise 6% of all primary brain tumors, primarily driven by its firm affiliation with immunocompromised population groups. This single factor and the advent of acquired immunodeficiency syndrome (AIDS) in the late 1970s and early 1980s led to a remarkable surge in prevalence that continued into the early 1990s. For reasons that defy explanation, the prevalence of the disease in the immunocompetent populations groups also increased (albeit to a lesser extent) during this same period.

Because the tumor is known for its dense cellularity and periventricular location, it is often initially characterized on computed tomography (CT) and magnetic resonance (MR) imaging, placing the radiologist on the front line in suggesting the diagnosis and helping guide a multidisciplinary team in management strategies. This article reviews a broad spectrum of clinical, etiologic, and pathologic features that frequently intersect with common radiologic findings of this disease.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

PCNSL is a form of extranodal non-Hodgkin lymphoma involving the brain, leptomeninges, spinal

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cord, or ocular globes.[1] Although still rare, the prevalence of the disease increased substantially during the past 4 decades, with a striking threefold increase between 1973 and 1984, primarily related to the advent of AIDS and the increasing utility of immunosuppression in the setting of solid organ and autologous stem-cell transplantation. This underscores its strong connection for those who are immunocompromised from congenital or acquired immunodeficiency, including those with autoimmune disorders.[1,2] However, its prevalence has also increased among those who are immunocompetent for reasons that are poorly explained. Since a peak in 1993 and in conjunction with the introduction of highly active antiretroviral therapy, the annual incidence of PCNSL has declined in those with AIDS, although its incidence is not significantly changed for those 60 years or older, another higher risk group.[2,3] PCNSL now accounts for approximately 6% of all brain tumors, placing it as the fourth most common primary brain tumor overall.[1,2]

Clinical

Patients with PCNSL present with nonspecific clinical signs and symptoms with a paucity of "B" symptoms (fever, weight loss, and night sweats) so commonly seen in systemic lymphoma. In a multicenter review of 248 patients with primary cerebral lymphoma (96% as PCNSL), most (70%) presented with focal neurologic deficits, whereas neuropsychiatric symptoms (43%), symptoms related to increased intracranial pressure (33%), seizures (14%), and ocular symptoms (4%) were less common.[4] Other studies have shown ocular involvement (commonly with floaters, blurred vision, and painful red eyes) in up to 20% of patients with PCNSL.[1] Accordingly, slit-lamp examination should be included as part of the diagnostic evaluation.[1]

Besides standard neuroimaging (described later in this article), contrast-enhanced CT of the chest, abdomen, and pelvis is recommended in all patients and clinical and ultrasonographic evaluation of the testicles should be considered in older men.[1] As up to 13% of patients with PCNSL have occult extraneural disease, bone marrow biopsy is also recommended.[1]

Cerebrospinal fluid (CSF) analysis plays an important role in the initial and continuing assessment of patients with PCNSL. Increased white blood cell count and protein concentration with lowered CSF glucose levels compared with serum glucose levels are common.[1] Although initial CSF evaluation is often normal, positive cytology is frequently seen on follow-up lumbar punctures.[5]

Prognosis is especially poor for patients with PCNSL who are older than 60 years, have a performance status greater than 1 (Eastern Cooperative Oncology Group performance status scale), elevated serum lactate dehydrogenase (LDH), high CSF protein concentration, and location of the tumor within the deep regions of the brain (periventricular, basal ganglia, brainstem, and/or cerebellum). Those who have 1 to 3 of these features had a 2-year survival rate of 48%, whereas those with 4 to 5 showed only 15% survival rate. In contrast, those patients with none of these parameters had an 80% 2-year survival rate.[6]

Etiology and Pathology

The etiology of PCNSL remains unknown. Several associations beyond immunosuppression have been identified. Epstein-Barr virus (EBV) genome is present in 95% of tumor cells in immunocompromised patients but in fewer than 20% of those with normal immune systems.[2] Some evidence suggests a possible role of the JC virus as a cofactor.[2] Genetic evidence supports the hypothesis that PCNSL is derived from germinal center B cells.[2] Overexpression of numerous genes, most prominently B-cell lymphoma 6 (BCL-6) protein, is linked with PCNSL.[2] This marker is also associated with nearly 7 times longer median survival than those with tumors that did not show expression of this protein.[1]

Whether PCSNL arises in the brain or outside the brain is unresolved. Current hypotheses include development of adhesion molecules on transformed B cells outside the brain, preservation of lymphoma cells in the brain as a "safe haven," and expansion of a polyclonal inflammatory lesion in the brain into a monoclonal state.[2] Historically, the brain has been recognized for its lack of a classic lymphatic drainage system and fueled controversy regarding the histogenesis of PCNSL in such a structure. Recently, Louveau and colleagues[7] reported the discovery of functional lymphatic vessels lining the dural sinuses that has altered this perspective and other assumptions about neuroimmunology.

On gross pathology, the tumor shows frequent but not invariable demarcation from normal brain with most lesions occupying a periventricular location (**Fig. 1**E). More diffuse involvement of the brain, as is typical in glial neoplasms, also may be seen but is less conspicuous.[2] Single lesions are reported in 66% of cases overall but multiple lesions share nearly equal prevalence in the immunocompromised and tend to show more necrosis than in the immunocompetent population.[2,8]

Nearly all (95%) of PCNSLs are classified as diffuse large B-cell lymphoma (DLBCL) and express characteristic immunohistochemical markers for that cell lineage, such as CD19 and