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The Multiple Faces of Nervous System Lymphoma. Atypical Magnetic Resonance Imaging Features and Contribution of the Advanced Imaging

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Primary central nervous system lymphoma (PCNSL) is an uncommon variant of extranodal non–Hodgkin lymphoma, which involves the brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease. In addition to a detailed history and physical examination, the evaluation of patients suspected of having a PCNSL should include a contrast-enhanced magnetic resonance imaging. Occassionaly, PCNSL shows peculiarities on magnetic resonance imaging, which delay the diagnosis and thus the start of treatment. It is essential that radiologists be aware of these less common presentations such as isolated spine or meningeal lymphoma, angiocentric lymphoma, ocular lymphoma, and Epstein-Barr virus–associated lymphoma. Advanced neuroimaging (diffusion and perfusion sequences, spectroscopy-magnetic resonance, and positron emission tomography metabolic imaging) are useful techniques for the differential diagnosis of PCNSL with processes such as brain glioblastoma, multiple sclerosis, and metastases and brain abscesses, especially in atypical presentations. In this article, a review of unusual radiological findings for PCNSL in immunocompetent patients is made, highlighting the usefulness of functional and metabolic imaging for establishing an early presumptive diagnosis, which reduces delays in treatment.

Introduction

Primary central nervous system lymphomas (PCNSLs) constitute 1%-6% of malignant central nervous system (CNS) tumors.

In recent years, a combination of therapies (radiotherapy and chemotherapy) has achieved longer survival, but their use is determined by the histologic confirmation of the disease. Steroid use is common among patients with symptomatic brain lesions, and these drugs reduce the diagnostic performance of biopsies, thereby delaying the final diagnosis. These facts highlight the radiologist's role in establishing a reliable presumptive diagnosis of PCNSL.

The aim of this article is to explain the atypical radiological presentations of PCNSL as well as to highlight the use of advanced imaging for the differential diagnosis with other processes such as glioblastoma multiforme (GBM), pseudotumoral demyelinating plaques, and brain abscesses.

Definition and General Characteristics

In immunocompetent patients, PCNSLs are mostly B-cell non–Hodgkin lymphomas.[1] A small fraction of PCNSLs are T-cell lymphomas, which behave in a clinically and radiologically similar manner. Isolated CNS Hodgkin lymphomas occur in $<0.5\%$ of cases.[2]

PCNSLs are mostly high-grade non–Hodgkin lymphomas restricted to the CNS, spine, meninges, and eyes. Their incidence is greater in immunocompetent patients (0.3% per 100,000 individuals/y) in contrast to what occurs in immunosuppressed patients, in whom the immunomodulatory therapies have reduced the onset of brain lymphomas.

The prognosis is usually poor with mean survival rates without treatment ranging from 1.5-3 months. Their clinical and radiological manifestations are very similar to those of relapses or metastases of a systemic lymphoma in the brain or meninges (secondary CNS lymphoma). A staging study is always essential to rule out this cause.

In immunocompetent patients, PCNSLs occur during the sixth to seventh decade of life and usually present with focal neurologic symptoms or increased intracranial pressure. However, symptoms depend on the location of the lesions, sometimes reaching large sizes such as in the corpus callosum.

Imaging findings are because of the histologic findings of PCNSL and include considerable cell proliferation, angiotropic growth-forming vascular tubes, with or without vessel wall invasion, disruption of the blood-brain barrier, and predilection for ventricular or meningeal surfaces. In addition, tumor cells are usually accompanied by T lymphocytes and reactive astrocytes.

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In immunocompetent patients, the classic or typical appearance of PCNSL is a solid hemispherical mass with intense homogeneous enhancement.[3] The most common locations are periventricular white matter, near the ependymal or meningeal brain surface (Fig 1), basal ganglia, corpus callosum, and to a lesser extent, cerebellum. Brainstem, major deep white matter tracts, and medulla are uncommon locations. These lesions are usually infiltrative with moderate perilesional edema and normally there is no evidence of necrosis, hemorrhage, or calcifications (in the absence of prior treatment). Enhancement after the intravenous administration of gadolinium is variable—homogenous, incomplete ring-like, perivascular and ependymal linear enhancement patterns have been described, although other infrequent patterns such as multiple ring-enhancing lesions and absent contrast enhancement have also been reported.

In this article, unusual radiological findings for PCNSL in immunocompetent patients are reviewed, showing atypical and uncommon forms of presentation such as angiocentric lymphoma, isolated meningeal or spinal lymphoma, and Epstein-Barr virus (EBV)–associated lymphoma, highlighting the usefulness of functional and metabolic imaging for establishing an early presumptive diagnosis, which reduces delays in treatment.

Uncommon Radiological Presentations

In rare cases, PCNSLs appear as an isolated spinal or ocular lymphoma and diffuse leukoencephalopathy without contrast-enhancing lesions, which may progress evolving to an intravascular infiltration such as in angioblastic or angiocentric lymphoma, or more rarely as an exclusive leptomeningeal lymphomatosis. EBV-PCNSL has also recently been reported and exhibits peculiarities on imaging studies.

Isolated Spinal Lymphoma

Spinal involvement, both primary and secondary, is very uncommon; occurring in 1% of PCNSLs and 3% of systemic CNS lymphoma, when there is massive systemic involvement.[2] The most common intramedullary location is the cervical cord, followed by the thoracic cord then the lumbar cord. Most are solitary lesions, however, there may be multiple lesions throughout the spinal cord.

The imaging findings are similar to those of the intracerebral PCNSL lesions—slightly and poorly defined expansive intramedullary masses, with patchy and multifocal areas of contrast enhancement (Fig 2). These lesions are usually infiltrative, with involvement of both white and gray matter. Tumoral cysts and syringomyelia is not a common finding. Absence of necrosis and hemorrhage is the rule.

Although infrequent, spinal cord lymphoma must be included in the list of differential diagnoses in spinal cord contrast-enhancing lesions in those patients with symptoms evolving over several days or weeks—tumoral infiltration of the spinal cord generally is restricted to a short segment of the medullary parenchyma, exhibiting a more expansive appearance; expansive demyelinating lesions are often marginated lesions with peripheral gadolinium enhancement and rarely affect gray matter; medullary ischemic lesions course with an acute onset and absent enhancement is usually observed.

Ocular Lymphoma

Isolated ocular lymphoma is considered a highly rare subtype, the incidence of which is unknown, and may pose a significant diagnostic problem for the clinician as well as for the radiologist.

In immunocompetent individuals, the peak incidence is between the fifth and the seventh decade, although disease may occur at a younger age in the immunocompromised population.

Ocular PCNSL can be asymptomatic, but the clinical presentation is mostly steroid-resistant uveitis with reduced vision. Up to 80% of patients usually develop intracerebral lesions or contralateral ocular involvement.

The diagnosis is determined by a cytologic analysis of a vitreous humor aspirate.

Ocular lymphoma can appear as nodular enhancing lesions in the maculla or as thickening of the uvea, although radiological findings are very subtle and the diagnostic performance of magnetic resonance imaging (MRI) is very low.[4]

The diagnosis is often made late in most of cases, inducing delayed therapeutic management with poor visual prognosis and life-threatening complications. Differential diagnosis should be made with infectious uveitis (viral, tuberculosis, and syphilis) and noninfectious uveitis such as idiopathic posterior uveitis, sarcoidosis, or Behçet syndrome.

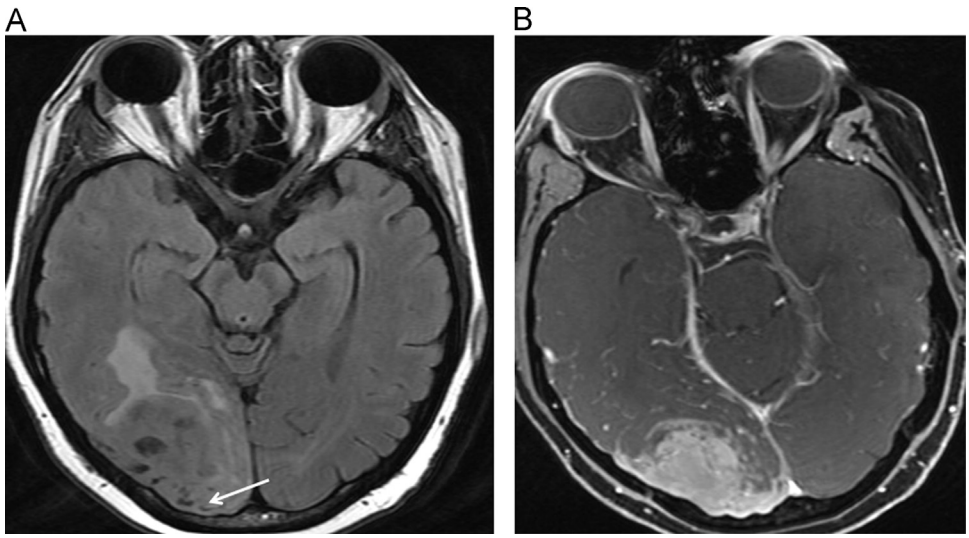

Fig. 1. Common presentation of PCNSL. Solitary or multiple infiltrative parenchymal masses. Iso–high-signal intensity lesion on T2-weighted image with considerable mass effect due to underlying edema. (A) Right occipital corticosubcortical lesion extending to the meningeal surface (arrow). (B) Postcontrast T1-weighted images show homogeneous mass enhancement as well as meningeal and tentorial linear enhancement.