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Editorial

Primary Central Nervous System Lymphoma: 'The Great Imitator'

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Primary central nervous system lymphoma (PCNSL) is colloquially called 'the great imitator' due to its diverse radiographic appearances that mimic a variety of other lesions such as high-grade glioma, tumefactive demyelination, infection and granulomatous disease. In this context, it is important to consider the radiographic and clinical nuances of diagnosing this rare and enigmatic entity. In this monograph, we crystallize key elements of our clinical thought process and offer selected references from the literature to guide the reader in cultivating their fund of knowledge on this subject.

Contrast-enhanced magnetic resonance imaging (MRI) remains the preferred modality to noninvasively evaluate PCNSL and other intracranial pathologies. PCNSL most commonly presents as a solitary lesion in the supratentorial white matter, often contacting a CSF surface such as the pia or ventricle. Approximately one-third of cases present with multiple lesions. PCNSL less commonly occurs in the infratentorial compartment and rarely the spinal cord. PCNSL lesions are usually iso- to hypointense to gray matter on T1-weighted imaging, with variable intensity on T2-weighted sequences. Lesions are typically diffusion-restricting with avid, homogeneous contrast-enhancement, well-defined borders and marked surrounding vasogenic edema. Ring enhancement is rare in immunocompetent patients but may be present in up to 75% of immunocompromised patients. Uncommon features include central necrosis and meningeal enhancement. Calcification, hemorrhage, and neovascularization have been reported in PCNSL but are generally characteristic of other pathologies [1]. Advanced MRI modalities such as diffusion tensor imaging and spectroscopy may also help to distinguish PCNSL from high-grade glial tumors, but have yet to gain widespread clinical use [2].

The importance of diffusion-weighted imaging (DWI) sequences in formulating neurological differential diagnosis also bears specific mention. Prior to the widespread use of DWI in the mid-1980s onwards, diagnostic and radiographic response assessments for neoplastic, ischemic and other lesions were based upon computed tomography (CT) scan findings. The advent of DWI dramatically improved the sensitivity and specificity of neuroimaging, particularly when used in conjunction with apparent diffusion coefficient (ADC) maps and T2-weighted imaging. For a lesion to be designated 'diffusion restricting', it must show a high (bright) signal on DWI and corresponding low (dark) signal on ADC. These must be distinguished from lesions that are bright on both sequences, a finding known as 'T2 shine-through'.

The most common cause of restricted diffusion is acute cerebral infarction, due to energy depletion and cell death that limit diffusion of intracellular water molecules. High viscosity and cellularity as seen in pus or highly cellular neoplasms may also lead to diffusion restriction. Other causes include infection, toxic/metabolic insult, seizure, traumatic brain injury and demyelination, though the latter may also cause increased diffusion. We propose a structured diagnostic approach to diffusion restriction called the 'risks, time and space' model. 'Risks' include immunosuppression, infectious history, toxin exposure, and metabolic disease. 'Time' refers to the acute vs chronic onset of symptoms and radiographic progression of lesions over time. Finally, 'space' denotes the anatomic distribution of lesions. Variations of this approach have been elegantly outlined by other authors [3].

Even if imaging is highly suggestive of the diagnosis, histopathologic analysis of lesional tissue remains the gold standard for diagnosing PCNSL. Patients with characteristic clinical presentations and radiographic findings often proceed directly to neurosurgical biopsy by open or stereotactic techniques. Cerebrospinal fluid (CSF) or vitreous fluid may be obtained prior to biopsy in atypical cases or when there is a high clinical suspicion for other pathologies. Importantly, intracranial hypertension, obstructive hydrocephalus and mass effect from space-occupying lesions may be contraindications to lumbar puncture, and in rare cases may necessitate open biopsy with subtotal or gross total resection.

Comprehensive baseline evaluation is critical to establishing the extent of disease, screening for metastatic systemic lymphoma mimicking PCNSL, and determining treatment eligibility. This includes CSF cytology, flow cytometry, cell counts and chemistries, although these studies are frequently nonspecific or negative upon initial evaluation. Additional studies include ocular slit lamp examination, full-body positron emission tomography (PET)/CT scan, serum lactate dehydrogenase (LDH), hepatic and renal function testing, human immunodeficiency virus (HIV) screening, bone marrow aspiration and biopsy, and testicular ultrasound for men. Notably, corticosteroids should be avoided during initial workup because they may cause regression of lesions on MRI and interfere with histopathologic analysis [2].

The two most widely used prognostic scoring systems specific to PCNSL have been formulated by the International Extranodal Lymphoma Study Group (IELSG) and Memorial Sloan-Kettering (MSK) Cancer Center. These two schemes predict median overall survival ranging from 1.1 to 8.5 years. Age and performance status are the most important prognostic factors, and also help to determine the choice of therapy. Although there is substantial variation between different practitioners, induction therapy typically includes high-dose methotrexate (HD-MTX)-based combination chemotherapy regimens as well as rituximab. Immunocompetent patients achieving complete radiographic response typically receive consolidation therapy with further HD-chemotherapy, autologous stem cell transplantation, non-myeloablative chemotherapy and/or reduced-dose whole-brain radiation therapy (WBRT). However, radiation is often reserved for salvage chemotherapy due to high rates of irreversible neurotoxicity, particularly in younger patients.

Unfortunately, more than half of the patients who initially respond to HD-MTX-based therapy eventually relapse. Overall survival following relapse is typically 2 - 4 months. Treatment strategies for relapsed PCNSL remain under investigation. Because surgical resection has not been definitively shown to affect survival, the role of surgery is typically limited to establishing an initial diagnosis, and rarely for confirming recurrence. Resection should be deferred if lymphoma is encountered on intraoperative histopathologic analysis, unless surgical relief of mass effect is required [2].

Although the treatment of PCNSL remains challenging, there is reason for optimism as we enter the exciting era of molecularly targeted treatment of central nervous system neoplasms. However, theoretical and practical clinical management paradigms remain unchanged. Clinicians must also leverage interdisciplinary collaboration between neuro-oncologists, neuro-radiologists, neurosurgeons, pathologists, primary care providers and other specialists to provide timely, standard-of-care treatment for this disease [4,5].

Disclosure

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