Distinguishing primary central nervous system lymphoma from other central nervous system diseases: a neurosurgical perspective on diagnostic dilemmas and approaches

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Object. White matter diseases, including demyelinating or inflammatory disorders, may be indistinguishable clinically and radiologically from some central nervous system (CNS) tumors. In such situations, determination of the final diagnosis is difficult. An example is the differential diagnosis of non-acquired immunodeficiency syndrome–related primary central nervous system lymphoma (PCNSL) and multiple sclerosis (MS), a demyelinating disease. Unfortunately, delayed diagnosis and treatment of PCNSL can negatively affect prognosis.

Methods. The authors reviewed the cases of eight patients with PCNSL or MS. In each case, the initial diagnosis (PCNSL or MS) was equivocal. In these cases, conventional diagnostic approaches were not definitive, thus further delaying diagnosis. The initial symptoms, the selected diagnostic tests, and the presumptive as well as final diagnosis for each case are discussed.

The final diagnosis was PCNSL in six cases and MS in two. The uncertainty about the clinical or initial pathological presentation required further diagnostic evaluation in all cases. Two important neurosurgical guidelines are the avoidance of corticosteroid agents and performance of biopsy sampling rather than volumetric tumor resection. High-volume lumbar puncture, slit-lamp examination/vitrectomy, new CNS imaging techniques, and repeated biopsy procedures also proved helpful.

Conclusions. In PCNSL, early definitive diagnosis and treatment are the keys to successful outcomes. Knowledge of strategies essential to early diagnosis lessens the need for brain biopsy sampling, but this procedure is still usually necessary. In such selected cases, biopsy sampling is appropriate even when pathological investigation shows MS rather than PCNSL. Complete resection is not indicated in PCNSL and can lead to additional sequelae.

KEY WORDS • primary central nervous system lymphoma • multiple sclerosis • demyelinating disease • biopsy • slit-lamp examination • vitrectomy • cerebrospinal fluid

Many diseases of the CNS manifest themselves similarly, and may be indistinguishable radiologically. Not uncommonly, this scenario is seen in many diseases like MS, PCNSL, metastatic or primary brain tumors, infections, and acute disseminated encephalomyelitis. These diseases often present with similar signs and symptoms; lack distinguishing features based on clinical history, physical examination, and MR imaging; and often show nonspecific changes in the CSF. A brain biopsy procedure may often be the only diagnostic alternative.

Primary CNS lymphomas exemplify a disease that may share radiological, clinical, and laboratory similarities with many other diseases of the CNS. Patients’ conditions are often diagnosed by the use of biopsy procedures rather than less invasive means of diagnosis such as LP or vitrectomy. Conversely, in some patients the presumptive diagnosis is MS because the CSF findings are not consistent with PCNSL. The prognosis for patients with these diseases relies to a significant extent on their neurological condition prior to the initiation of treatment; hence, an early, definitive diagnosis is the key to successful outcomes, even if occasionally patients with MS undergo brain biopsy procedures.

The purpose of this report is to provide simple diagnostic steps that can be used for patients with lesions in which the differential diagnosis of MS compared with PCNSL is equivocal at the initial presentation. We present patients in whom difficulty was encountered in the establishment of a diagnosis (non-AIDS-related PCNSL, compared with MS) when using conventional diagnostic approaches. In some cases, this had a negative impact on the patient’s clinical course.

Abbreviations used in this paper: BBB = blood–brain barrier; CNS = central nervous system; CSF = cerebrospinal fluid; LP = lumbar puncture; MR = magnetic resonance; MS = multiple sclerosis; PCNSL = primary CNS lymphoma; SPECT = single-photon emission computed tomography.
Clinical Material and Methods

With the approval of the Institutional Review Board of the Oregon Health & Science University, clinical records were selected for eight patients whose final diagnosis was non-AIDS-related PCNSL (in six) or MS (in two), but in whom the diagnosis was equivocal at initial presentation.

Case Reports

Case 1: PCNSL Presenting as MS

In this 55-year-old woman, a left hemiparesis developed acutely. Based on initial MR imaging findings, either PCNSL or MS seemed possible. The CSF analysis showed elevated levels of immunoglobulin G but no oligoclonal bands. The presumptive diagnosis was MS, and high doses of dexamethasone were given. Improvement was short-lived, and a repeated MR image demonstrated progression of the initial lesion (Fig. 1). Results of a stereotactic biopsy procedure proved diffuse large B-cell lymphoma. The patient’s condition improved remarkably with chemotherapy.

Case 2: PCNSL With Trigeminal Neuralgia

In this 49-year-old man, diplopia and right-sided trigeminal neuralgia in the V2 distribution developed subacutely. The MR imaging study revealed a discretely enlarged right cavernous sinus. The patient’s condition was managed with corticosteroid agents because of a presumptive diagnosis of Tolosa–Hunt syndrome, and the treatment resulted in temporary relief. An MR imaging study obtained after symptom recurrence demonstrated an increase in the size of the lesion (Fig. 2). A biopsy sample obtained in the cavernous sinus demonstrated inflammatory changes and necrotic large blue cells. Subsequently, focal-beam radiation (35 Gy) was administered to the cavernous sinus. One year later, a metastatic lesion in the foramina of C-6 was revealed to be PCNSL.

Case 3: Consequences of Preoperative Steroid Treatment in PCNSL

This 11-year-old boy with a left temporal lobe mass presented with abdominal pain, nausea, and tonic-clonic seizures (Fig. 3). Due to significant perilesional edema, high doses of dexamethasone were administered before biopsy sampling was performed; biopsy results showed inflammatory changes only. Biopsy sampling of the lesion was performed via craniotomy 2 months later without corticosteroid premedication, and the final diagnosis was PCNSL.

Case 4: Unusual Presentation of MS Makes Tumor Likely Enough to Justify Biopsy Sampling

This healthy 45-year-old woman suffered a single tonic-clonic seizure. An MR image was obtained, and it revealed multiple enhancing white matter lesions (Fig. 4A and B). Results of CSF analysis were normal. Before stereotactic biopsy sampling was performed, a second MR imaging study was obtained in which iron oxide nanoparticle contrast material was used (Fig. 4C and D). This study demonstrated less enhancement of the lesions compared with the previous gadolinium-enhanced study; these latest results favored MS. Analysis of biopsy samples demonstrated inflammatory changes and demyelination consistent with MS.

Case 5: Demyelinating Disease Simulating Neoplasm

In this 13-year-old girl, a right hemiparesis developed acutely. Left posterior thalamic enhancement was seen on MR imaging (Fig. 5 left). Although results of CSF analysis were normal, a stereotactic needle biopsy revealed inflammatory changes and demyelination. The patient’s con-

Fig. 1. Case 1. The CSF analysis in this patient favored MS; however, the response to dexamethasone was short-lived. Repeated MR imaging demonstrated changes in the right frontal lobe characteristic of tumor (left, T2-weighted; right, after addition of gadolinium). Results of a stereotactic biopsy confirmed PCNSL.

Fig. 2. Case 2. The initial MR images obtained in this patient demonstrated enhancement in the right cavernous sinus. These three T2-weighted sequences, obtained after addition of gadolinium, demonstrate the lesion at three levels, starting from the base. The clinical response to dexamethasone was transient. The first biopsy sample showed necrotic blue cells; PCNSL was confirmed on repeated biopsy sampling performed 1 year later.
dition improved with the use of steroids, but a relapse occurred later with similar MR imaging changes in the opposite thalamus (Fig. 5 right) and oligoclonal bands in the CSF, findings consistent with MS.

Case 6: The Importance of “Floaters” in PCNSL

This 63-year-old woman reported “floaters” and blurry vision. An enhancing area in the right cerebellum extending into the pons was demonstrated on MR imaging (Fig. 6). Further management of her condition included plans for an open biopsy procedure. However, a slit-lamp examination performed before surgery showed abnormalities, and a subsequent vitrectomy demonstrated diffuse large B-cell lymphoma. The diagnosis of PCNSL with ocular involvement was made, and a cerebellar biopsy procedure was avoided.

Case 7: Complete Resection Is not Indicated in PCNSL

This 60-year-old man with mild sensory deficits in his left hand underwent a gross-total resection of a right premotor cortex mass in which the presumptive diagnosis was glial tumor (Fig. 7 left). However, pathological evaluation showed diffuse large B-cell lymphoma. The patient was temporarily hemiparetic after the procedure. A follow-up MR imaging study obtained 1 month postsurgery demonstrated recurrent tumor in the surgical cavity (Fig. 7 center). The patient achieved complete remission after 1 year of high-dose methotrexate administered in conjunction with BBB disruption (Fig. 7 right).

Case 8: The Risk Associated With Aggressive Resection in PCNSL

This 58-year-old woman underwent resection of a lesion that was presumed to be a corpus callosum glioma (Fig. 8). Pathological investigation revealed PCNSL. The patient experienced postoperative fevers and neurological decline after starting nonmyelosuppressive chemotherapy. A fungal infection at the surgical site was diagnosed. No further chemotherapy could be administered due to her poor performance status, and the patient died of progressive neurological decline.

Discussion

Non-AIDS-related PCNSL frequently presents with multiple enhancing lesions in the periventricular white matter and with signs and symptoms that are similar to many CNS diseases such as MS, metastases, malignant gliomas, and inflammatory diseases. The incidence is approximately 3.8 cases per million persons per year. 

Primary central nervous system lymphoma is frequently diagnosed late because more common CNS diseases are considered first. A PCNSL is a high-grade malignancy. Survival time is shorter in patients with coexisting ocular lymphoma, involvement of deep structures of the brain, meningeal disease, low Karnofsky performance status (< 70), high CSF protein levels, elevated lactate dehydrogenase, age greater than 60 years, and at relapse. Early diagnosis can significantly affect the prognosis because PCNSL is highly chemo- and radiosensitive, and chemotherapy with or without radiation significantly improves the outcome. Survival time without treatment is very short.
Multiple sclerosis is a multifocal white matter disease. Together with a typical clinical history, a CSF analysis can help confirm the diagnosis. Unfortunately, the changes observed in the CSF, such as elevated levels of immunoglobulin G and oligoclonal bands, are nonspecific. Elevated immunoglobulin G (40–85% of patients) and oligoclonal bands (0–27%) can also be found in PCNSL. Elevated protein levels (>80%) and increased cellularity (40%) are also common, although marked pleocytosis is rarely seen. All of these findings are also present in other inflammatory diseases of the CNS. If the clinical signs and symptoms, imaging studies, and CSF analysis are consistent with MS, treatment with steroid agents is normally the next step. Patients often improve after only one dose. However, patients with PCNSL also respond rapidly to steroid drugs, thus complicating the diagnosis, and perhaps delaying it until recurrence.

If PCNSL compared with MS is the differential diagnosis, a high-volume LP should be obtained, and in addition to conventional cytological studies, material should be reserved for flow cytometry and, if possible, polymerase chain reaction studies (Fig. 9). Multiple CSF samples may be needed for establishment of the diagnosis. These additional LPs should be done as soon as possible to avoid delays in diagnosis. When there is leptomeningeal involvement, the LP site is important. Patients with periventricular lesions have fewer false-negative findings when the puncture is done from an Ommaya reservoir or shunt (if available); conversely, in patients with spinal and/or radicular symptoms, an LP may be preferable. In Cases 1, 4, and 5, the CSF analysis was either equivocal or normal; thus, biopsy sampling was the next logical step to confirm the diagnosis.

Cases 2 and 3: Importance of Avoiding Steroids Before Brain Biopsy, LP, and Slit-Lamp Examination/Vitrectomy

Diseases such as PCNSL, MS, other inflammatory disorders, and even gliomas may have similar, dramatic clinical and radiological responses to steroid agents. A PCNSL may even disappear on imaging studies (the “ghost tumor” effect). Steroid drugs should not be administered before diagnostic procedures are completed unless it is absolutely necessary (when PCNSL is in the differential diagnosis and the patient’s condition will tolerate it). The patients in Cases 2 and 3 exemplify how the effect of steroid medications can render the pathological diagnosis impossible, thus delaying the diagnosis and necessitating a repeated biopsy procedure. A PCNSL can cause demyelination; therefore, biopsy tissue samples that are devoid of malignant B lymphocytes due to the effects of steroid drugs may be falsely interpreted as confirming a demyelinating disease. Furthermore, a PCNSL can present as T-cell-rich B-cell lymphoma, and in these cases, administration of steroid agents may lead to biopsy samples consisting of T cells and cells with demyelination only.

When cranial nerves are affected, a variety of skull base pathological entities should be considered. Inflammatory processes tend to have a subacute onset and good response to steroid therapy. Because skull base procedures are complex and many are associated with higher complication rates compared with stereotactic needle biopsy, avoiding a biopsy procedure can be beneficial in a select subgroup of patients in whom CSF assessment and slit-lamp examination in the absence of steroid therapy yield the diagnosis (Fig. 9).

Cases 4 and 5: MS can Mimic a Neoplasm, and new Imaging Techniques and/or Biopsy Sampling can be Useful in Differential Diagnosis

The patient in Case 4 presented with a single tonic-clonic seizure, which was suggestive of tumor rather than MS. The results of MR imaging also implicated PCNSL or metastatic disease (Fig. 4A and B). Results of CSF studies were negative for MS, malignant cells, and the presence of HIV. An MR image obtained with an iron oxide–based nanoparticle contrast agent demonstrated less enhancement of the lesions compared with the study obtained after addition of gadolinium contrast, which is suggestive of MS...
Analysis of stereotactic biopsy samples confirmed MS.
Although the prevalence of epilepsy in patients with MS is higher compared with the general population, seizures are rarely observed in MS.10,27,34 An isolated seizure without neurological deficits is also unusual for PCNSL; rather, a progressive neurological decline over a period of months prior to diagnosis is common.8,21,22 In this patient (Case 4), the clinical presentation was not typical for MS or PCNSL, and based on imaging findings, either diagnosis seemed possible. Therefore, diagnosis based on results of a biopsy procedure was the logical next step.

Similarly, the clinical presentation of the patient in Case 5 favored a tumor; a demyelinating process in this pediatric patient seemed less likely. Biopsy sampling revealed demyelination and inflammatory changes, and together with the relapsing–remitting clinical course and typical CSF findings, the diagnosis of MS was eventually established.

In 90% of PCNSL, a diffuse and dense gadolinium enhancement with varying degrees of perilesional edema is seen on MR imaging. Sixty percent of the patients have a single (typically periventricular) lesion.23 Nevertheless, exceptions to this typical presentation have been reported.17 Furthermore, patients with PCNSL can even present with normal findings on MR imaging.25 The new modalities of MR spectroscopy and SPECT scanning have been used in the differential diagnosis of demyelination and tumor.17 Both studies can be especially useful in the differential diagnosis of lesions located in areas of high risk for sequelae postsurgery.32

Iron oxide nanoparticles are a new family of MR imaging contrast agents with a long plasma half-life that can be used to visualize inflammatory reactions in CNS lesions. They cross BBB defects and pool in the interstitial space, where they are phagocytosed by macrophages and reactive astrocytes. Lesions enhance when both a defective BBB and inflammation are present. When iron oxide nanoparticles are used, lymphomas and malignant gliomas tend to enhance more and MS tends to enhance less when compared with gadolinium studies, and thus, they may be useful in the differential diagnosis of malignant neoplasms versus MS, as demonstrated in the patient in Case 4.26 Use of these particles, or other specialized MR imaging techniques such as MR spectroscopy or perfusion MR imaging, may provide additional information, but their effectiveness is still uncertain.

Case 6: Slit-Lamp Examination and Vitrectomy can Avoid Brain Biopsy Sampling

Ocular lymphoma is a manifestation of PCNSL that often presents with “floaters” or blurry vision. A slit-lamp examination is required in every patient suspected of having PCNSL, especially when these typical symptoms are noted. If results of the examination are abnormal, a vitrectomy, which is less invasive than brain biopsy sampling, is indicated (Fig. 9). In the patient in Case 6, the brain biopsy procedure was avoided because the diagnosis was established through vitrectomy.

Cases 7 and 8: Surgery in PCNSL Is for Diagnostic Purposes Only

The purpose of surgery in PCNSL is establishment of a
diagnosis rather than cytoreduction.\(^8,25\) Because PCNSL can resemble glioma on imaging studies, the lesion is sometimes reached through a conventional craniotomy with the expectation of total or subtotal resection. Due to the more invasive nature of resection, the preliminary diagnosis based on the frozen tumor sections should be established before proceeding with surgery if the differential diagnosis includes PCNSL.

**Conclusions**

Demyelinating diseases, especially MS, are part of the most important differential diagnoses of PCNSL, although PCNSL can mimic many different intracranial pathological entities. Both PCNSL and MS are multifocal white matter lesions that can share the features of similar CSF findings\(^2,12,35,39\) and dramatic response to steroid drugs.\(^39\) A systematic diagnostic approach reduces the possibility of confusing these two diseases and can improve outcomes through rapid establishment of the diagnosis. The LP procedure (high-volume and repeated if necessary) and slit-lamp examination/vitrectomy are diagnostic procedures that can obviate the need for surgical biopsy sampling. Complete resection is not indicated and can lead to unnecessary and serious side effects.

New imaging techniques like SPECT scanning, MR spectroscopy, perfusion MR imaging, and iron nanoparticle imaging studies can help in the differential diagnosis of neoplastic compared with inflammatory lesions and should be further investigated. Corticosteroid drugs should be avoided before diagnostic procedures are completed, due to their cytolytic effects on malignant lymphocytes.\(^39\) In patients treated preoperatively with steroid agents, if the tissue sample does not show tumor, multiple LPs and/or a second biopsy procedure should be considered if there is clinical or radiological evidence of disease progression or recurrence. Early definitive diagnosis of PCNSL is the key; if it has not been established, patients who have MS may appropriately undergo brain biopsy sampling as part of their evaluation to rule out PCNSL when it is part of the differential diagnosis.

**References**

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