

# Primary central nervous system lymphoma: presentation, diagnosis, and staging

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✓Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma that affects the brain, spinal cord, leptomeninges, and eyes. The clinical presentation and neuroimaging appearance of PCNSL differ in immunocompetent patients and in those with acquired immunodeficiency syndrome (AIDS). A magnetic resonance (MR) image of the brain in immunocompetent patients with PCNSL typically demonstrates one or more homogeneously enhancing lesions located in the periventricular white matter, characteristically spanning the corpus callosum. In patients with AIDS, multiple ring-enhancing lesions are more common. After neuroimages raising the suspicion of PCNSL are obtained, a definitive diagnosis should be established in both immunocompetent and AIDS patients by performing pathological analysis of cerebrospinal fluid (CSF), vitreous fluid, or a biopsy specimen. Brain biopsy sampling remains the gold standard for PCNSL diagnosis in all patients, although the possibility of establishing routine, minimally invasive diagnostic procedures in which Epstein-Barr virus polymerase chain reaction (PCR) analysis of the CSF and nuclear imaging are used is currently under investigation in the population of patients with AIDS. At the time of diagnosis, the patient should undergo further evaluation, which should include a physical examination, ophthalmic evaluation with a slit-lamp examination, serum lactate dehydrogenase levels, human immunodeficiency virus testing, computed tomography scans of the chest/abdomen/pelvis, bone marrow biopsy sampling, contrast-enhanced brain MR imaging, and lumbar puncture (LP). Testicular ultrasonography studies should be considered in men. In patients who cannot undergo LP or in those with evidence of spinal cord dysfunction, contrast-enhanced MR imaging of the entire spine should be considered.

**KEY WORDS** • primary central nervous system lymphoma • diagnostic criteria • differential diagnosis • magnetic resonance imaging • polymerase chain reaction

**P** RIMARY central nervous system lymphoma is a rare form of extranodal non-Hodgkin lymphoma that affects the brain, spinal cord, leptomeninges, and eyes. Although this entity is rare, PCNSL has been the subject of intensive research since the late 1980s, when Eby, et al.,<sup>28</sup> first reported its rising incidence. A definitive clinical overview of PCNSL was written in 1993 by Fine and Mayer,<sup>38</sup> based on an analysis of 792 immunocompetent patients and 315 with AIDS-related PCNSL whose cases were detailed in 72 English-language articles published between 1980 and 1992. Since this review, many other large case series of PCNSL have been published, comprising more than 1000 cases.<sup>8,14,33,36,42,44,48,49,66,70,72,73,79</sup> This article is a summary of the clinical presentation, differential diagnosis, and “extent of disease” evaluation of PCNSL in immunocompetent and immunocompromised patients.

*Abbreviations used in this paper:* CSF = cerebrospinal fluid; CT = computed tomography; LP = lumbar puncture; MR = magnetic resonance; PCNSL = primary central nervous system lymphoma; PCR = polymerase chain reaction; PET = positron emission tomography; PIOL = primary intraocular lymphoma; SPECT = single-photon emission computed tomography.

## Clinical Presentation

### Age and Sex

In immunocompetent patients, the median age at diagnosis of PCNSL is 60 years, with a male/female ratio of 1.2.<sup>16</sup> The highest risk group appears to be those 60 years of age or older, in whom the incidence has increased disproportionately since the mid-1990s.<sup>55,72</sup> Among patients with AIDS, the typical age at presentation is younger; the mean age is 31 to 36 years.<sup>38,70</sup> In fact, PCNSL has been diagnosed in HIV-positive children as young as 2 years old.<sup>30</sup> Consistent with the population at highest risk for AIDS in the past, the published male/female ratio for AIDS-associated PCNSL in adults is 7.38 to 1.<sup>80</sup> The incidence of PCNSL in patients with AIDS appears to have peaked in the early 1990s, with a decline since then that is reflective of the advent of highly active antiretroviral therapy.<sup>19,86</sup> The incidence of PCNSL also appears to be stabilizing or decreasing slightly in immunocompetent patients with these tumors.<sup>72</sup>

### Predisposing Conditions

The most important risk factor for PCNSL is an alteration in immune system functioning (Table 1). Immunocompromised conditions that predispose patients to

PCNSL include the following: AIDS; iatrogenic immunosuppression for transplant procedures or for autoimmune diseases such as rheumatoid arthritis; and rare congenital immunodeficiency syndromes such as ataxia–telangiectasia, severe combined immunodeficiency, and Wiskott–Aldrich syndrome.<sup>1,47</sup> In patients with AIDS, advanced disease is the most important predisposing factor, demonstrated by a median CD4 cell count in AIDS-associated PCNSL of 30 to 37 cells/mm.<sup>3,9,70</sup>

### *Symptoms and Signs*

As with all masses in the central nervous system, the location of PCNSL lesions determines the clinical presentation. The presenting symptoms and signs in one large case series of 248 immunocompetent patients with PCNSL included the following: focal neurological deficits in 70% of patients; neuropsychiatric symptoms in 43%; headache/nausea/vomiting suggestive of increased intracranial pressure in 33%; seizures in 14%; and ocular symptoms in 4%.<sup>8</sup> Common focal deficits include aphasia, hemiparesis, and ataxia due to discrete intracerebral lesions as well as less common cranial nerve palsies secondary to leptomeningeal deposits. Neuropsychiatric changes such as apathy, depression, slowed thinking, and confusion have been attributed to the infiltration of white matter tracts by PCNSL lesions that involve the periventricular regions or the corpus callosum. The fact that seizures occur as the initial manifestation of PCNSL in less than 15% of immunocompetent patients who have these tumors may be partially explained by the fact that PCNSL lesions less often involve excitable cerebral cortex than do other types of brain tumors.<sup>37</sup>

Of the 41% of patients with PCNSL shown to have leptomeningeal involvement in one series, the leptomeningeal tumor was asymptomatic in the majority. Less than one third of patients with PCNSL who had definite leptomeningeal involvement showed any symptoms or signs characteristic of leptomeningeal tumor.<sup>7</sup> The incidence of cranial nerve palsies among these patients is reported to be 5 to 31%.<sup>10,47</sup>

For the 10 to 20% of immunocompetent patients found to have ocular involvement at the time of PCNSL diagnosis, and for those with the PIOL variant, both eyes are affected in the majority of cases. Such patients' most common visual complaints are "floaters" and blurred vision.<sup>52</sup> Some may experience diminished visual acuity, whereas others may have painful, red eyes, which can be misleadingly suggestive of uveitis or other nonmalignant inflammatory diseases. Twenty percent of patients with ocular lymphoma will be asymptomatic.<sup>11</sup>

The rare spinal cord lesions found in patients with PCNSL are primarily discrete intramedullary nodules that may be single or multiple.<sup>57,60</sup> The symptoms and signs of intramedullary spinal cord lymphoma resemble those of other intramedullary spinal tumors and depend on the lesion's location within the spinal cord. Presenting symptoms may include limb paresthesias and/or numbness, limb weakness (often asymmetrical), impaired gait, and perineal numbness with bladder or bowel dysfunction.

Patients with AIDS who have PCNSL are more likely than immunocompetent patients to present with mental status changes or seizures. The presenting features often

TABLE 1  
*Risk factors for PCNSL*

AIDS
organ transplantation
autoimmune or inflammatory disease requiring continual pharmacological immune suppression
myasthenia gravis
rheumatoid arthritis
systemic lupus erythematosus
sarcoidosis
Sjögren syndrome
vasculitis
hereditary immunodeficiency
severe combined immunodeficiency
common variable immunodeficiency
ataxia–telangiectasia
Wiskott–Aldrich syndrome

occur in a span of only days to weeks in patients with AIDS, as opposed to weeks to months in immunocompetent hosts.<sup>20</sup> In the review by Fine and Mayer,<sup>38</sup> in which the presentation of PCNSL in 315 patients with AIDS was compared with that in 792 immunocompetent patients, focal neurological deficits occurred in approximately 50% of individuals in both groups; mental status changes (including behavioral changes) were seen in 53% of patients with AIDS compared with 35% of immunocompetent patients; and seizures were reported in 27% of patients with AIDS compared with 11% of immunocompetent patients.

### *Time From Symptom Onset to Diagnosis*

The mean period between onset of symptoms and the diagnosis of PCNSL is 3 months in immunocompetent patients and 2 months in those with AIDS.<sup>37</sup> Administration of corticosteroid agents can delay or confound the diagnosis due to cytolysis of lymphoma cells.<sup>85</sup>

### *Anatomical Distribution of Lesions*

PCNSL can present in four distinct anatomical distributions in both immunocompetent patients and in those with AIDS: 1) discrete or diffuse intracranial mass lesions that are solitary or multiple, often in contact with ventricular or meningeal surfaces; 2) leptomeningeal disease; 3) ocular lymphoma with or without other lesions; and 4) rare spinal cord lesions.

Discrete intracranial PCNSL lesions differ in number in immunocompetent compared with AIDS patients. In immunocompetent patients with PCNSL, lesions are solitary approximately 70% of the time.<sup>8</sup> In contrast, AIDS-associated PCNSL lesions are just as likely to be multiple as solitary.<sup>38</sup> The distribution of intracranial lesions follows that of other adult primary brain tumors: approximately 85% of discrete lesions are found in supratentorial compared with 15% in infratentorial sites.<sup>8,14</sup> Of all intracranial lesions, more than 60% are periventricular (involving the basal ganglia, thalamus, or corpus callosum), and 12% of discrete PCNSL masses arise in the corpus callosum, a site that is particularly suggestive for this tumor type as a diagnosis. With respect to lobar location, lesions are more often located in the frontal (20%), parietal (18%), and temporal lobes (15%) than in the occipital lobes (4%).<sup>8</sup>

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Primary leptomeningeal lymphoma, defined as PCNSL limited to the meninges without cerebral parenchymal disease or systemic lymphoma, is rare and comprises approximately 7% of all cases of PCNSL in immunocompetent patients.<sup>59</sup> Leptomeningeal involvement of intracranial PCNSL, on the other hand, is more common and has been reported in up to 41% of cases, either by findings obtained using clinical diagnostic modalities (positive CSF cytology, leptomeningeal enhancement on MR imaging) or by postmortem pathological findings.<sup>7</sup>

The PIOL variant is a rare subset of PCNSL involving the vitreous, retina, choroid, or optic nerve. In addition to those with PIOL, 10 to 20% of immunocompetent patients are found to have ocular involvement at the time of PCNSL diagnosis.<sup>32,76</sup> Subsequent to diagnosis and treatment, cerebral lymphoma develops in the majority of patients with PIOL, with the percentage varying according to the length of the follow-up period.<sup>52</sup>

The spinal cord is the least common site of involvement in patients with PCNSL. Rare cases have been documented, comprising less than 1% of all patients with PCNSL.<sup>57,60</sup> Spinal cord lesions in cases of multifocal PCNSL may arise from two routes of spread: direct invasion from the caudal brainstem and dissemination via the CSF. Primary intramedullary spinal lymphoma is exceedingly rare, with fewer than 20 cases published in the literature.<sup>15,50,75,81</sup> Fifty-two biopsy-proven cases of primary spinal epidural lymphoma have been described.<sup>67</sup>

### Diagnosis

#### Neuroimaging Modalities

Primary central nervous system lymphoma has a characteristic appearance on both CT and MR imaging studies due to its hypercellularity, high nuclear/cytoplasmic ratio, and disruption of the blood–brain barrier. Masses most commonly appear isodense or hyperdense on CT scans and enhance homogeneously after the intravenous administration of contrast material (Fig. 1). On MR imaging, most lesions are hypointense to gray matter on T<sub>1</sub>-weighted images, iso- or hyperintense on T<sub>2</sub>-weighted images, and enhance moderately to markedly after gadolinium administration (Fig. 2).<sup>6,13,23,41</sup> Linear enhancement at the margins of a lesion, tracking along Virchow–Robin perivascular spaces, is highly specific for PCNSL (Fig. 3).<sup>6</sup> A

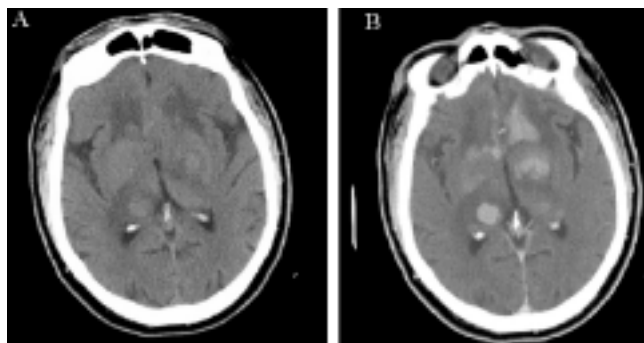


FIG. 1. Head CT scans demonstrating the appearance of PCNSL before (A) and after (B) the administration of contrast material.

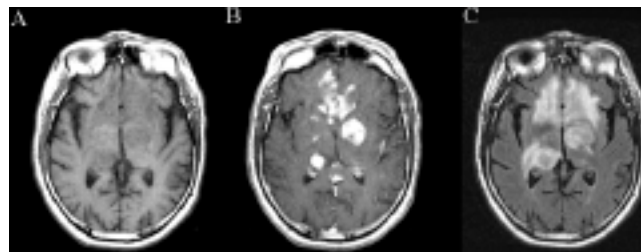


FIG. 2. Brain MR images obtained in the same patient, demonstrating the hypodense appearance on a T<sub>1</sub>-weighted image obtained before administration of contrast material (A), enhancement on a T<sub>1</sub>-weighted image obtained after administration of contrast agent (B), and hyperdense appearance on a T<sub>2</sub>-weighted image (C).

high T<sub>2</sub> signal is often seen surrounding the lesion and extending along adjacent white matter tracts, representing tumor-associated vasogenic edema. Because of the relative restriction of water diffusion within PCNSL, lesions may appear hyperintense on diffusion-weighted images and hypointense on apparent diffusion coefficient maps, a characteristic shared by acute ischemic stroke, cerebral abscess, and several other high-grade neoplasms (Fig. 4). Evidence of hemorrhage, calcification, or necrosis within a PCNSL lesion may be seen, but is rare before treatment. As with other high-grade neoplasms, proton MR spectroscopy reveals a decreased *N*-acetylaspartate peak and an increased choline/creatine ratio.<sup>58</sup> In addition, a high lipid resonance on MR spectroscopy may differentiate PCNSL from glioma.<sup>43,77</sup>



FIG. 3. A T<sub>1</sub>-weighted MR image obtained after administration of contrast material in a different patient with PCNSL, demonstrating enhancement that tracks along the Virchow–Robin perivascular spaces (arrow).

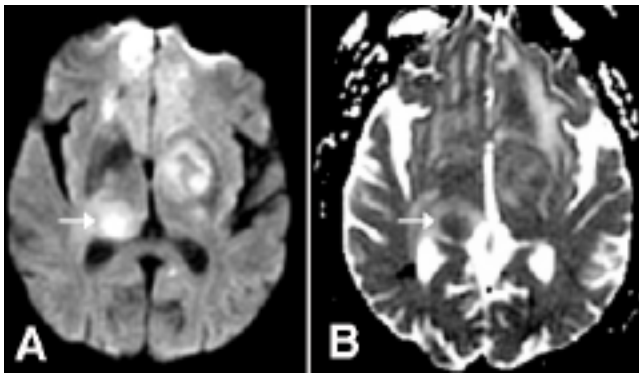


FIG. 4. Diffusion-weighted image (A) and apparent diffusion coefficient map (B) obtained in the same patient as in Figs. 1 and 2, demonstrating restricted diffusion within the right thalamic lesion (arrows).

A PCNSL in an immunocompromised host shares many of the neuroimaging features described earlier. As with immunocompetent patients, individuals with AIDS may demonstrate lesions in the cerebral hemispheres, deep gray matter of the basal ganglia and thalami, corpus callosum, brainstem, cerebellum, and spinal cord. Multifocal disease and basal ganglia involvement seem to be more common in patients with AIDS than in those without the syndrome, however.<sup>84</sup> The signal characteristics on CT and MR imaging are more variable, with lesions often appearing hypodense on CT and hyperintense on  $T_2$ -weighted MR images. In addition, lesions may be heterogeneously enhancing or ring-enhancing on images obtained after administration of contrast material, contrary to the homogeneous enhancement pattern seen in most immunocompetent hosts. This variability in neuroimaging appearance leads to difficulty in distinguishing PCNSL from other AIDS-related mass lesions, most notably toxoplasmosis, by using structural imaging alone. Adjunctive imaging modalities, including  $^{201}\text{Tl}$ -enhanced SPECT scanning, PET scanning, MR spectroscopy, and MR perfusion, can be used in an attempt to differentiate between PCNSL and toxoplasmosis.<sup>18,29,51,64</sup>

The role of cranial PET scanning in the diagnosis and assessment of treatment in patients with PCNSL is not well defined, and there has been limited systematic study. The PET modality may be incorporated into treatment assessment algorithms, especially in patients with nonenhancing tumors or in those with minimal residual contrast enhancement on MR images or CT scans after completion of therapy.

### Differential Diagnosis

In the immunocompetent patient population, a solitary lesion that infiltrates the corpus callosum, enhances homogeneously, and is associated with only a moderate amount of edema is highly suggestive of PCNSL.<sup>13</sup> In addition to PCNSL, however, a single homogeneously enhancing lesion surrounded by edema may also represent glioma, metastasis, a subacute infarct, or a focal demyelinating lesion. Diffuse periventricular disease with no discrete mass is a less common presentation of PCNSL and may be misdiagnosed as multiple sclerosis.<sup>27</sup>

For patients with AIDS, the differential diagnosis of multiple ring-enhancing lesions on CT or MR imaging includes both PCNSL and toxoplasmosis cerebri. These two diseases have a similar appearance on CT and MR imaging, and a similar prevalence in patients with AIDS (2–13% for PCNSL and 3–10% for toxoplasmosis).<sup>3</sup> Although PCNSL may have more of a propensity for white matter and subependymal spread than toxoplasmosis, this finding is not definitive.<sup>4</sup> The presence of multiple lesions does not distinguish toxoplasmosis from PCNSL; approximately 50% of AIDS-associated PCNSL cases also present as multiple lesions on neuroimaging studies.<sup>4,38</sup> Other diseases in the differential diagnosis of AIDS-associated intracranial lesions, such as progressive multifocal leukoencephalopathy, can typically be distinguished from PCNSL by their characteristics on gadolinium-enhanced MR images. Unlike PCNSL, progressive multifocal leukoencephalopathy rarely enhances after gadolinium administration.

### Diagnostic Studies

After structural neuroimaging of the brain implicates PCNSL, a definitive diagnosis must be established prior to treatment (Table 2). In one prospective study of 96 immunocompetent patients with PCNSL, 15% were diagnosed based on CSF cytological findings alone, 5% on vitrectomy alone, and 78% with the aid of surgery.<sup>7</sup>

#### Cerebrospinal Fluid

As in all cases of intracranial mass lesions, an LP for CSF examination should only be performed in patients with PCNSL who are not at risk for herniation. Examination of CSF includes the following: 1) basic studies such as cell count, protein, and glucose levels; 2) cytological and flow cytometry studies; and 3) PCR for clonal immunoglobulin gene rearrangements (or, in AIDS patients, PCR to identify Epstein-Barr virus DNA). The CSF cytological study is at present the diagnostic test most commonly performed, with PCR gaining broader use.

#### Studies of CSF in Immunocompetent Patients With PCNSL

**Basic CSF Studies.** In PCNSL, basic CSF parameters can be normal or only slightly abnormal. In a study of the CSF profile of 96 immunocompetent patients with PCNSL, a mild pleocytosis was present in only slightly more than half of them. Specifically, CSF obtained using an LP in 70 immunocompetent patients with PCNSL showed the following: 1) an elevated white blood cell count (defined as more than seven cells/mm<sup>3</sup>) in 54% of patients, with the median value for the white blood cell count at eight cells/mm<sup>3</sup>; 2) elevated protein concentration in 67% of patients, with a median value of 69 mg/dl; and 3) low glucose concentration (< 38 mg/dl) in 10% of patients.<sup>7</sup> Although sometimes they implicate the disease, basic CSF laboratory values will be normal in a large number of PCNSL cases.

**Cytological Studies of CSF.** A CSF cytology study is sufficient to confirm the diagnosis of PCNSL in a significant percentage of cases (Fig. 5). The incidence of positive CSF cytological findings in the immunocompetent patient population with PCNSL has been reported to be between



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TABLE 2  
*Diagnostic evaluation of patients with PCNSL*

Diagnostic Study	Evaluation
laboratory	HIV serology lactate dehydrogenase
neuroimaging	contrast-enhanced brain MRI contrast-enhanced spinal MRI* SPECT or PET scans†
LP for CSF	body CT scans of chest, abdomen, & pelvis cell count & total protein cytology & flow cytometry PCR for immunoglobulin heavy-chain clonal rearrangements
ocular evaluation	PCR for Epstein–Barr virus‡ slit-lamp examination serial color photography of posterior pole of the eye‡ chorioretinal biopsy, fine needle aspiration, or vitrectomy‡
biopsy sampling	bone marrow aspirate stereotactic brain biopsy sampling

\* Use in patients with spinal symptoms.

† Use in immunocompromised patients.

‡ Use in patients with ocular involvement. Biopsy procedures, aspiration, or vitrectomy might be considered in lieu of stereotactic brain biopsy sampling if the likelihood of achieving a histopathological diagnosis is considered high.

26 and 31%.<sup>38</sup> In the study of 96 immunocompetent patients with PCNSL cited earlier, 15% were diagnosed based on results of CSF cytology studies.<sup>7</sup> Prior to sampling of their CSF, most of the patients had been treated with corticosteroid agents, which may lyse lymphoma cells and thus decrease the sensitivity of CSF cytology studies in PCNSL cases.

Serial CSF samples may be required to make a diagnosis of PCNSL based on CSF cytological findings: two thirds of patients with PCNSL who have positive CSF findings have negative cytological results initially. Even PCNSL lesions that involve the leptomeninges may not exfoliate sufficient malignant cells into the CSF to render cytological analysis a successful diagnostic tool.<sup>7</sup> It is the small number of morphologically recognizable malignant cells typically found in the CSF of patients with PCNSL that accounts for the low incidence of positive findings on CSF cytology studies. Performing flow cytometry may increase the sensitivity of CSF cytological analysis, as reported by Hegde et al.<sup>45</sup> Other conventional CSF tests that may establish monoclonality involve immunohistochemical studies in which antibodies are used against B-cell markers and immunoglobulin light chains.<sup>62</sup>

**Use of PCR Studies for CSF Analysis.** Examination of the CSF by using PCR studies is an important complement to cytological studies, given the relatively low incidence of positive CSF cytological findings in PCNSL. Since 1989, PCR analysis with consensus primers to the V and J regions of the immunoglobulin heavy-chain gene has been used to detect clonal rearrangements. Demonstration of clonal immunoglobulin gene rearrangements can establish monoclonality of a lymphocyte population in the CSF and thus confirm the diagnosis of PCNSL.<sup>39,78,83</sup> A PCR examination can also be performed on vitrectomy specimens for suspected PIOL.<sup>24</sup>

The sensitivity and specificity of PCR evaluation of the CSF as a diagnostic tool for PCNSL remain to be definitively established. In different reports, sensitivity has been calculated as 90 or 96%.<sup>78</sup> However, in one prospective study of 76 patients with PCNSL, researchers found monoclonal PCR products in only eight samples by using automated fluorescent fragment analysis.<sup>40</sup>

## *Studies of CSF in Patients With AIDS-Associated PCNSL*

Patients with AIDS who have intracranial lesions should undergo CSF examination prior to biopsy sampling, provided there is no danger of herniation. Positive cytological findings and/or PCR detection of Epstein–Barr virus DNA in the CSF may establish the diagnosis of PCNSL in AIDS patients and obviate the need for a biopsy procedure. In one study the incidence of positive results on CSF cytology was 23% (three of 13) for patients with AIDS-associated PCNSL compared with 31% (79 of 255) for the immunocompetent individuals.<sup>38</sup>

The PCR analysis of CSF for Epstein–Barr virus DNA appears to be a sensitive and specific test for AIDS-associated PCNSL.<sup>5,22,25</sup> In a prospective study of 122 HIV-positive patients with focal cerebral lesions, including 40 patients with AIDS-associated PCNSL, investigators reported that PCR detection of Epstein–Barr virus DNA in CSF was 80% sensitive for AIDS-associated PCNSL (positive in 27 of 34 patients with AIDS-associated PCNSL) and 100% specific.<sup>21</sup> Lower specificity has been reported in a recent retrospective study, however: of seven patients with positive results for Epstein–Barr virus on PCR analysis of the CSF, only two had PCNSL.<sup>54</sup> Alternative diagnoses included toxoplasmosis (two), HIV encephalopathy (two), and cryptococcoma (one).

## *Ocular Evaluation*

Ocular evaluation that includes slit-lamp examination must be performed as part of the assessment in any patient suspected of having PCNSL or the PIOL variant. A cellu-

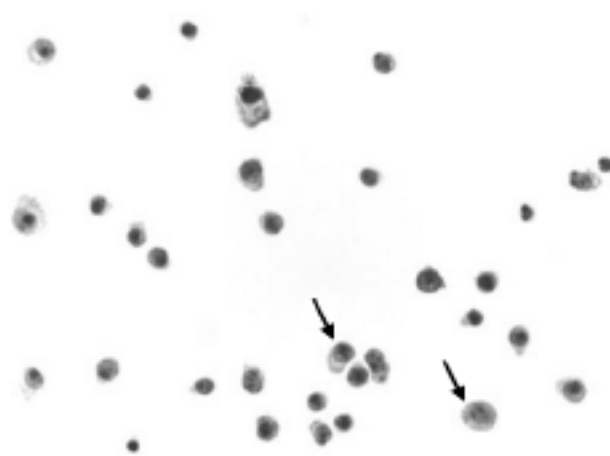


Fig. 5. Photomicrograph showing positive cytopathological results in a CSF specimen obtained in a patient with leptomeningeal involvement from PCNSL. The specimen contains several lymphocytes (arrows) with malignant features including pleomorphic nuclei, coarse chromatin, and excess cytoplasm. H & E, magnification unknown.

lar infiltrate in the vitreous, with or without subretinal infiltrates, is typically seen in patients with ocular lymphoma. The disease may also involve the retina, subretinal pigment epithelium, or optic nerve. Patients with PIOL rarely demonstrate involvement of the conjunctiva or orbit. For any patient in whom ocular symptoms and slit-lamp examination findings raise the suspicion of ocular lymphoma, gadolinium-enhanced MR imaging of the brain and orbits should be performed. If neuroimaging demonstrates that LP poses no danger of herniation, CSF should be obtained for cytological and PCR analysis.

If serial CSF examinations yield negative cytological results and PCR studies of CSF are inconclusive, then vitrectomy may establish the diagnosis of PCNSL by demonstrating malignant lymphocytes in the eye. The vitrectomy should be performed in the eye with the worst vision or the most severe vitritis. In addition to vitrectomy, chorioretinal biopsy sampling or fine-needle aspiration of a subretinal lesion may be performed. Special handling of the specimen is required because lymphoma cells in the vitreous degenerate rapidly.

In a manner analogous to CSF analysis, the vitreous specimen can also be subjected to flow cytometry and/or immunohistochemical investigation in an effort to establish monoclonality. Cytokine levels may demonstrate elevated interleukin-10 and an interleukin-10/interleukin-6 ratio greater than 1.0.<sup>12</sup> The PCR analysis can be used to detect clonal rearrangements of the VDJ regions of immunoglobulin heavy-chain genes of vitreal lymphoma cells.<sup>24</sup> If the patient has received corticosteroid drugs prior to the procedure, a false-negative result is possible.

### Biopsy Procedures

**Biopsy Sampling in Immunocompetent Patients With PCNSL.** Stereotactic brain biopsy sampling is the standard procedure for obtaining tissue adequate for pathological diagnosis of cerebral lymphoma.<sup>82</sup> Biopsy specimens insufficient for diagnosis can be avoided by targeting the center of the suspected lesion.

Advantages of stereotactic brain biopsy procedures over open craniotomy include minimal skin incision, the option of local anesthesia, a short postoperative recovery period, and most important, relatively low morbidity and mortality rates. In addition, resection of cerebral parenchymal PCNSL lesions confers no survival benefit for patients. In fact, resection may be associated with lower survival,<sup>8</sup> and there is a theoretical risk of inadvertent seeding of the leptomeninges with tumor cells. For these reasons, the least invasive procedure that yields a diagnostic surgical specimen is preferable.

**Biopsy Sampling in Patients With AIDS-Associated PCNSL.** The diagnostic accuracy of stereotactic brain biopsy sampling for AIDS-associated intracranial lesions ranges from 88 to 96%.<sup>17,31,53,61,65,87</sup> The morbidity and mortality associated with this procedure is higher in AIDS patients compared with immunocompetent individuals due to the higher frequency of hemorrhagic complications in patients with AIDS.<sup>74</sup> With regard to the efficacy of stereotactic brain biopsy sampling specifically for the diagnostic question of PCNSL compared with *Toxoplasma* encephalitis, the decision pathway has been controversial. In the absence of positive cytopathological

findings in CSF, early brain biopsy sampling should be considered in patients who have the following characteristics: 1) neurological deterioration; 2) negative serological results for *Toxoplasma* and neuroimaging features atypical for toxoplasmosis; 3) discordant results between PCR of the CSF for Epstein-Barr virus and thallium-enhanced SPECT scans, if other infectious origins are not suspected; and 4) improvement during a brief trial of therapy for toxoplasmosis.<sup>4,56</sup>

### Extent of Disease Evaluation

After the diagnosis of PCNSL has been established with analysis of CSF, a vitreal aspirate, or a biopsy specimen, an extent of disease evaluation should be performed in every patient. Full ocular evaluation, including a slit-lamp examination, should be done in every patient, because asymptomatic ocular involvement is not uncommon and specific treatment is indicated for ocular lymphoma.<sup>32</sup> In addition, in patients who are deemed eligible for LP, the CSF should be collected for cell count, chemistry, cytopathology, flow cytometry, and PCR tests. The serum lactate dehydrogenase level should be measured in every case because this parameter is an important prognostic factor in patients with PCNSL.<sup>34</sup> Because PCNSL occurs so commonly in patients with AIDS, HIV serological studies should be requested for every apparently immunocompetent patient in whom PCNSL is diagnosed. Evaluation of cognitive function is important both at diagnosis and in follow-up visits to gauge the benefit of therapy and to monitor for treatment-related neurocognitive decline.<sup>2</sup>

Given the rarity of spinal cord involvement, enhanced spinal MR imaging is indicated only in cases in which clinical suspicion of spinal cord tumor is high.<sup>26</sup> However, contrast-enhanced MR imaging of the entire spine should be considered in patients who cannot undergo an LP due to the presence of increased intracranial pressure. In this situation, spinal imaging may identify leptomeningeal deposits of tumor, and this could affect subsequent management.

Evidence of systemic lymphoma has been found at the time of diagnosis in up to 8% of patients initially thought to have isolated PCNSL.<sup>35,63,69,71</sup> For this reason, complete systemic staging, including CT scans of the chest, abdomen, and pelvis and bone marrow biopsy sampling with aspirate has been recommended by the International Primary CNS Lymphoma Collaborative Group.<sup>2</sup> Use of testicular ultrasonography should be considered in men to rule out occult testicular lymphoma that has metastasized to the brain. Whole-body PET or PET-CT scanning may be incorporated into routine extent of disease evaluations in the future.

Systemic dissemination of lymphoma is found over time in 7 to 10% of patients with PCNSL, generally in the terminal stages of the disease or at postmortem examination. In such cases, lymphoma may be found in the lymph nodes and visceral organs of the abdomen/retroperitoneum, mediastinal lymph nodes, lungs, bone marrow, or testes. The clinical significance of late-disease, systemic deposits of lymphoma is controversial.<sup>46,68</sup> During the course of disease, if a patient with PCNSL presents with new ocular or other CNS symptoms and signs, reevaluation—for example, with repeated slit-lamp examination or LP—is indicated.<sup>11,76</sup>

## Conclusions

The clinical presentation and neuroimaging appearance of PCNSL differ in immunocompetent and AIDS patients and are nonspecific in both. Magnetic resonance imaging of the brain revealing a homogeneously enhancing, single lesion that infiltrates the corpus callosum is highly suggestive of PCNSL in immunocompetent patients, whereas multiple ring-enhancing lesions are more common in patients with AIDS. After neuroimages are obtained that raise the suspicion of PCNSL, a definitive diagnosis should be established in both immunocompetent and AIDS patients by analysis of CSF, vitreous fluid, or biopsy specimens. Brain biopsy sampling remains the gold standard for PCNSL diagnosis in all patients, although the possibility of routine, minimally invasive diagnosis by using PCR analysis of the CSF and nuclear imaging is currently under investigation. At the time of diagnosis, the patient should undergo an evaluation of the extent of disease that includes the following: a physical examination; ophthalmic evaluation with a slit-lamp examination; serum lactate dehydrogenase evaluation; HIV testing; chest/abdomen/pelvis CT scans; bone marrow biopsy sampling; contrast-enhanced brain MR imaging; and LP. In patients who cannot undergo LP or in those with evidence of spinal cord dysfunction, a contrast-enhanced MR image of the entire spine should be considered.

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