MR imaging of primary central nervous system lymphoma in immunocompetent patients: A pictorial review

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Learning objectives

To illustrate the wide spectrum of typical and atypical MR imaging appearances of primary brain lymphoma in immunocompetent patients and to highlight the role of contrast-enhancement pattern, diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) in its early recognition.

Background

INTRODUCTION:

Both systemic and primary nervous system lymphoma (PNSL) may involve the neuroaxis. These aggressive non-Hodgkin lymphomas (NHL) are caused by B-lymphocytes.

They account for less than 1% of lymphomas and for 2% to 6% of all primary brain tumors; they may arise from different parts of the brain. The reported incidence is increasing and this cannot be explained by increased imaging alone.

Although systemic lymphoma can present as focal enhancing masses, it more typically manifests as disseminated leptomeningeal disease (Fig 1).

Primary central nervous system lymphoma is a rare form of non-Hodgkin lymphoma that is frequently misdiagnosed. It most often affects intraaxial brain parenchyma but can also affect the spinal cord, leptomeninges, and eyes. It is restricted entirely to these localizations with no systemic disease.

Supratentorial brain is by far the most frequently involved site, but infratentorial brain can also be affected.

CLINICAL FEATURES:

Immunocompetent patients have a mean age of 60 years and male predominance.

The prodrome is relatively short as most cases are diagnosed within 1 or 2 months after the onset of symptoms. The presentation is determined by location and size and may
include nonspecific focal neurologic deficits. CSF will show high proteins and low glucose but no suggestive cytology.

The clinical presentation and neuroimaging appearance of PNSL differ in immunocompetent patients and in those with acquired immunodeficiency syndrome (AIDS).

Contrast-enhanced MR is the most sensitive imaging technique and MR findings should precede corticosteroid therapy and facilitate stereotactic biopsy instead of resection.

Survival is significantly worse than in patients with similar types of extranodal NHL. Status at the time of diagnosis is a poor prognostic factor, as are involvement of deep brain structures and increased patient age, serum lactate dehydrogenase, and CSF proteins.

Images for this section:

**Fig. 1:** Leptomeningeal affectation as systemic lymphoma manifestation
To avoid an unnecessary extensive surgery in PCNSL, the diagnosis should be suspected after MRI. Patients should undergo contrast-enhanced T2- and T1-weighted images, and DWI; PWI is recommendable. Proton-MR-spectroscopy (1H-MRS) could be added as supplementary sequence.

1. LOCATION

Lobar white matter, periventricular white matter, and deep grey nuclei involvement are the most typical. Involvement of the corpus callosum and other interhemispheric connection fibers is also common.

The cerebellum, orbits, and cranial nerves may also harbor the tumor. Other, infrequently involved sites are the brainstem, cavernous sinuses, pineal gland, and pituitary gland (Figs.1 and 2).

2. NUMBER

PCNSL tends to present as a homogeneously enhancing solitary periventricular or subcortical mass, characteristically spanning the corpus callosum; however, lesions can also be multifocal.

The frontal lobe, the corpus callosum, and the basal ganglia are commonly affected in patients with single or multiple lesions.

Multifocal tumors tend to be smaller, but there is no difference in the perifocal edema and signal characteristics accompanying single and multiple tumors (Fig. 3).

3. CT/ MR CHARACTERISTICS

-CT: The initial study for most patients is unenhanced CT, which is then followed by contrast-enhanced CT. The classical CT appearance is a hyperdense lesion with uniform moderate enhancement.

(Fig. 4).

-MR SIGNAL
At MR imaging, tumors usually have intermediate-to-low signal intensity on T1-weighted images and are either isointense or hypointense relative to the gray matter on T2-weighted images.

Calcifications or hemorrhage and cyst formation within the tumor are rarely seen.

(Fig.5)

Subependymal involvement should be sought.

According to the literature, edema is usually mild.

In the cases diagnosed at our center, calcifications were more common and edema was more significant (Fig. 6).

**-ENHANCEMENT PATTERNS**

Most lesions show intense enhancement. Unenhanced lesions are extremely unusual.

Contrast-enhanced images show variable morphologic enhancement patterns:

Homogeneous enhancement (Fig. 7a). A notch has been reported in some homogeneously enhancing lesions. (Fig. 7b)

'Open-ringlike' enhancement is thick and not uniform (Fig 7 c-d), contrasting with that seen in multiple sclerosis, which is thin and uniform (Fig. 7e).

This notch sign and the open-ringlike enhancement have been proposed as specific patterns.

Ringlike enhancement with internal necrosis is frequent in immunocompromised but extremely rare in immunocompetent patients.

**-FUNCTIONAL IMAGING:** Diffusion restriction, low ADC values, and increased perfusion are useful features for diagnosis and follow-up.

Diffusion imaging: The high cellularity of lymphoma restricts the normal movement of water molecules. This appears as tumor hyperintensity on DWI and hypointensity on ADC maps. ADC values have been related with outcome and vary with the response to chemotherapy.

Diffusion tensor imaging (DTI) takes advantage of the preferential water diffusion along the longitudinal axes, so high cellularity correlates with a decrease in fractional anisotropy (FA).

FA and ADC values of primary cerebral lymphoma are significantly lower than those of
glioblastoma multiforme (GBM); thus, it is possible to differentiate lymphomas from GBM and anaplastic astrocytoma.

Restricted diffusion is a consistent imaging finding (90% on pretreatment scans) in CNS lymphoma in immunocompetent patients and is variable on post-treatment scans. (Fig 8)

-Perfusion Imaging: early studies show increased regional cerebral blood volume (rCBV).

The typical perfusion-imaging feature for lymphoma is a low regional tumor blood volume (rTBV) compared with that of primary high-grade neoplasms, so differentiation between lymphoma and primary high-grade glial neoplasms is feasible. (Fig. 9).

-The spectroscopy spectrum of PCNSL is not specific, occurring in a variety of high-grade malignancies. Some patients with high metabolite accumulation show increased activity at PET but PET-CT but normally it does not add useful information to MRI atypical findings.

4. SPECIAL FORMS:

-Intravascular lymphoma: nonspecific imaging features similar to other vasculitides (fig 10).

-Neurolymphomatosis: Primary lymphoma that affects cranial and peripheral nerves and roots.

5. IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS:

The main difference between immunocompetent (IC) and immunocompromised (ID) patients is the enhancement pattern:

-IC: hyperdense in noncontrast CT because of high cellularity. On MR, they are iso/ hypointense on T1-weighted sequences and iso/hypointense on T2-weighted sequences. After the administration of contrast material, two-thirds will show moderate to intense enhancement and mild to moderate edema. Uncommonly, no enhancement is seen.

-ID: It is more likely to occur in an atypical location. Calcifications or blood can be seen more often. Nearly half of all ID patients will have heterogeneous enhancement with necrosis inside and marked peritumoral edema; others will have no enhancement (fig 11).
6. DIFFERENTIAL DIAGNOSIS:

In immunocompromised patients, the diagnosis can be easier if we know about the patient's immunodeficiency. In immunocompetent patients with no clinical suspicion, the differential diagnosis can be oriented by some imaging findings:

- Signal intensity: low signal on T2-weighted images and no blood products.
- Corpus callosum and interhemispheric fibers: the main differential diagnosis is with glioblastoma multiforme.
- Extra-axial disease: common in systemic lymphoma, PNSL usually spares extra-axial space.
- Diffusion: restriction is not totally specific because other focal lesions can be bright on diffusion but ADC values are especially low in PNSL compared to other lesions. ADC minimal values are lower in lymphomas than in GBMs and AAs.
- Perfusion: In PNSL perfusion can show mild increase or even decrease. It shows less perfusion than gliomas with lower rCBV(max) values, but more than infections.

7. TREATMENT AND MANAGEMENT:

PNSL is highly sensitive to both radiation therapy and chemotherapy, including corticosteroids (CS). That is the reason why CS can interfere with the correct diagnosis. Most of responses to CS are transient and develop later resistance (Fig. 12 a and b).

High-dose methotrexate has improved the response rate and patient survival. (12 c-f)

The criteria for evaluating the response to treatment depend on size evaluation of enhancing lesions. The response is usually classified as complete response, unconfirmed complete response, partial response, or progressive disease.

Response to treatment entails a 50% decrease in the greater axis or in two axes. Patients should be monitored for at least for 10 years.

Images for this section:
Fig. 1: Supra-infratentorial lesions

Most lesions are supratentorial but 10% are infratentorial.
Fig. 2: Interhemispheric fibers affectation

Only two primary brain tumors can involve the interhemispheric fibers: lymphoma and glial tumors. Figure a shows anterior commissure involvement by PNSL and figure b shows a high grade glial tumor.
Fig. 3: Uni-multifocal lesions

NNSL is not always a solitary mass (a). 30-50% of immunocompetent patients have multiple lesions like in the two different patients shown in b and c.
Fig. 4: CT in lymphoma

CT is the initial study for most patients. Classically, lymphoma is hyperdense on unenhanced CT and shows uniform and moderate enhancement after contrast administration.
**Fig. 5:** MRI signal

MR imaging shows:
- Intermediate-to-low signal intensity on T1-weighted images (a).
- Either isointense or hypointense signal relative to the gray matter on T2-weighted images (b and c).
- Calcifications /hemorrhage in untreated patients are rarely seen but possible (b and d).
In the literature it is described as mild (a-b), but significant edema was common in our series (c-d).

**Fig. 6:** Perilesional edema
**Enhancement patterns**

Homogeneous enhancement (a) is the most common. A notch can be present in homogeneously enhancing lesions as a specific sign (arrow in b).

'Open ringlike' enhancement is specific too. It is thick and not uniform (c-d), unlike in multiple sclerosis where it is thin and uniform (e).

**Fig. 7:** Enhancement patterns
Both DWI and DTI show restriction: hyperintensity in diffusion (a, d) and hypointensity in ADC (b-c and e). ADC and FA values can have prognostic value and differentiate PSNL from GBM.

**Fig. 8:** Diffusion: DWI and DTI
Fig. 9: Perfusion

Early studies show increased rCBV (arrow in a) but less than in GBM (arrow in c); this may help differentiate between them.
Fig. 10: Intravascular lymphomatosis.

Diffuse subtle signal change in white matter that mimics leukoencephalopathy with no contrast enhancement. This 29-year-old woman with rapidly fatal neurological deficit was diagnosed postmortem.
**Fig. 11**: Immunocompetent and immunocompromised
Images a and b show very good response to corticosteroid therapy after 20 days. Images from c-f show response to chemotherapy in gadolinium-enhanced and T2-FFE sequences. Hemorrhagic changes are not unusual in posttreatment studies.

Fig. 12: Response to treatment
Conclusion

Although brain biopsy is the gold standard for diagnosis, conventional, enhanced and diffusion-perfusion MR imaging may allow earlier detection of PCNSL and facilitate optimal management.

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