Imaging features of primary brain lymphoma

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Learning objectives

The main goal of this study is:

- To describe the radiologic findings of primary brain lymphoma (PBL).
- To illustrate the typical and atypical advanced MR imaging features of PBL.
- To know differential diagnosis of PBL.
Background

PBL is defined as lymphoma in the central nervous system (CNS) without primary tumor elsewhere. It is less common than secondary CNS involvement by systemic lymphoma.

PBL causes approximately 5% of all primary brain tumors [1].

PBL is a diffuse large B-cell lymphoma in 90% of cases and is usually high grade. Less common PBL histological types are Burkitt's lymphoma and T-cell lymphoma.

PBL occurs sporadically or in association with congenital or acquired immunodeficiency disorders.

A remarkable increase of PBL incidence was observed in the last decade. This was mainly due to their association with human immunodeficiency virus infection and partly due to advancement of neuro-imaging techniques.

The etiology of PBL remains unclear: The CNS is devoid of endogenous lymphoid tissue [1].

PBL has been associated with Epstein-Barr virus and cytomegalovirus infection [1-3].

The only established risk factor for PBL is immunodeficiency and PBL is the most common brain tumor in this population. AIDS accounts for the largest group of immunocompromised patients with primary CNS lymphoma (PCNSL) and is an AIDS-defining diagnosis [1].

Systemic dissemination is unusual and occurs in only 6% of the patients. Nevertheless complete staging procedures including clinical examination, computed tomography (CT) of the thorax and abdomen and cerebrospinal fluid examination (CSF) is recommended [4].

A wide variety of clinical presentation is encountered: focal neurologic deficits, altered mental status, disturbance of intellectual function, signs of increased intracranial pressure, seizure [4].

Since the clinical and neuroimaging presentation of PBL can be varied and the differential diagnostic possibilities are therefore large, no patient should be treated for PBL without definitive cytological proof of diagnosis, either by CSF cytology, or brain biopsy.

Brain biopsy: Stereotactic brain biopsy is the most appropriate method for the diagnosis of PBL. However, open brain biopsy may be necessary in those patients who have lesions located in areas of the brain that are difficult to access (eg, brainstem). If possible, the procedure should be performed before corticosteroids have been administered.
Patients

- Prospective study of 11 patients with PBL proven histologically, enrolled in our University Hospital center from January 2009 to December 2011.

- All the patients were immunocompetent. The mean age was 53 years. In other publications, PBL usually occurred in the sixth decade [5].

- They had a variety of symptoms including:

  Signs of increased intracranial pressure (n=8),
  focal neurological deficits (n=5),
  and signs of Coma (n=3).

Imaging analysis (our study)

MRI study of the brain was performed in all the patients either immediately or after a cranial CT scan (n=8).

MRI evaluation was done on a 1.5T, including conventional sequences, diffusion-weighted sequences, MR spectroscopy (MRS) and MR perfusion.

- Location:
  - Most lesions are supratentorial (n=9),
  - periventricular locations (n=5),
  - both fronto-parietal lobes were observed in 2 cases,
  - and leptomeningeal involvement was found in one patient.

- Characteristic of MRI findings:
  - Predominance of lesions with intense enhancement,
  - DWI: Restricted diffusion with low ADC values,
  - MRS: elevated lipid and lactate peaks and decreased in the NAA peak.
  - No necrosis lesion was detected.

Histological confirmation was obtained using stereotactic biopsy.

These findings will be widely compared to proven literature data:
General Features [1,6]

Best diagnostic clue: Enhancing lesion within basal ganglia, and periventricular white matter.

_location:

- 90% supra tentorial: Frontal and parietal lobes most common (Figure 1),
- Deep gray nuclei commonly affected (Figure 2),
- Lesions cluster around ventricles (Figure 3), GM-WM junction,
- Often involve, cross corpus callosum (Figures 4, 5),
- Frequently abut, extend along ependymal surfaces (Figure 5),
- Infratentorial, sellar, pineal region uncommon,
- May involve leptomeninges or dura, more commonly in secondary lymphoma (Figure 6).

_morphology:

- Multiple lesions (Figure 7) or solitary mass (Figure 8),
- May be circumscribed (Figure 8) or infiltrative (Figure 5).

Most lesions are supratentorial, and involve central hemispheric or periventricular white matter. Proximity to the sub arachnoid / subependymal space is a common finding and may provide a diagnostic clue (Figure 9).

The sites of involvement include: frontal lobe (20-43 %) (Figure 9), basal ganglia (13-20%): (Figures 2, 3), corpus callosum (10%) (Figure 4), posterior fossa (13%) and the spinal cord, in only 1%-2% of patients [6].

Primary dural lymphoma is a rare subtype of PCNSL that differs biologically from other PCNSLs because it arises from the dura mater [7].

PCNSL May rarely involve leptomeninges, retina, vitreous humour and optic nerve.

CT Findings(Figures 7, 10):

- Non-Enhanced CT:
A round or oval iso-/ hyper dense lesion.

A negative CT examination does not exclude CNS lymphoma and there is a reported 13-38% false-negative rate (Figure 10 B)

• Contrast-Enhanced CT:
  Common: moderate-to-marked contrast enhancement [6]
  Uncommon: heterogeneous or absent contrast enhancement.

**MR Findings**

1. **T1** :

Hypo- or iso intense lesions (Figures 1, 2).

2. **T2**:

  • Hyper or iso-intense (Figures 1, 2).
  • Mild surrounding edema is typical (Figure 11).

3. **FLAIR** (Figure 12):

  • Homogeneous, isointense/hypointense to cortex. May be hyperintense.
  • Mild surrounding edema is typical.

4. **DWI** (Figures 4):

  • Because PBLs are highly cellular tumors, water diffusion is often restricted, making them appear hyperintense on DWI
  • and hypointense on ADC maps [8].

5. **T1 C+** (Figure 13):

  • Common: moderate to marked contrast enhancement.
  • Uncommon: heterogeneous or absent contrast enhancement.
  • The pattern of enhancement could be categorized as solid, irregular, linear (Figure 9), punctate, patchy and rim (ring)-like [9].
6. **T2*GRE** (Figure 14):

- Hemorrhage or internal calcification within the tumor is quite a rare finding [9].
- May see blood products or calcium as areas of "blooming" (immunocompromised)

7. **Magnetic resonance spectroscopy** (Figures 15, 16):

- MRS provides information on metabolic change in vivo. It demonstrates an exaggerated lipid peak in a solid mass with high Choline /Creatine ratios.
- Elevation of lipid peak is typically a signature of cell death; however, a lipid-dominated spectrum is found in PCNSL that is not macroscopically necrotic and due to macrophage content [10, 11].

8. **MR perfusion** [12, 13]:

- PBLs demonstrate low cerebral blood volume (CBV) [Figure 17] and a characteristic intensity time curve, which is related to a massive leakage of contrast media into the interstitial space (Figures 18 and 19 from [14, 15]). Furthermore, maximum relative CBV (rCBV) measured in tumor tissue, calculated as a ratio to contralateral normal-appearing WM, is typically lower in lymphomas than in other brain tumors. This characteristic finding can help to differentiate glioblastomas and metastases from lymphomas. In one study, rCBV of PBLs was 1.72, while that of high-grade gliomas was 4.86. In another study, primary and secondary CNSLs showed relatively low values for the maximum rCBV ratio.
- MR perfusion should be measured before steroid administration at it induces a reduction in blood tumour barrier permeability and regional cerebral blood volume.

**BRAIN BIOPSY**

Stereotactic brain biopsy is the most appropriate method for the diagnosis of PBL. However, open brain biopsy may be necessary in those patients who have lesions located in areas of the brain that are difficult to access (eg, brainstem). If possible, the procedure should be performed before corticosteroids have been administered.
In summary, a stereotactic-guided biopsy for multiple or deep-seated lymphomas is a safe operative procedure with minimal morbidity and no mortality.

**DIFFERENTIAL DIAGNOSIS**

1. **Glioblastoma multiforme (Figure 20):**
   - "Butterfly glioma" involving corpus callosum,
   - Hemorrhage common,
   - Enhancement typically heterogeneous,
   - Necrosis with ring enhancement in 95%,
   - PBLs lesions often have more restricted diffusion and lower ADC values than high-grade gliomas.

2. **Demyelination: Demyelinating pseudotumor(Figure 21):**
   - Younger patients,
   - May involve corpus callosum,
   - Often incomplete, "horseshoe-shaped" enhancement open towards cortex.

3. **Acute disseminated encephalomyelitis (Figure 22):**
   - Acute disseminated encephalomyelitis (ADEM) is an acute, monophasic inflammatory demyelinating disease affecting the CNS, which usually follows an infection or vaccination. The disease is characterised by multifocal WM lesions on neuroimaging.
   - CT Scan is generally normal at onset and usually becomes abnormal 5-14 days later. The typical computed tomographic appearance is that of low attenuation, multifocal lesions in the subcortical WM.
   - Demyelinating lesions of ADEM are better visualised by MRI, which usually exhibit no mass effect and can be seen scattered throughout the white matter of the posterior fossa and cerebral hemispheres. Involvement of the cerebellum and brainstem is more common in children.
   - Characteristic lesions seen on MRI appear as patchy areas of increased signal intensity on conventional T2-weighted images and on FLAIR sequence. Few MRI lesions may enhance after gadolinium administration. Extensive perifocal oedema may be seen.

4. **Secondary CNS Lymphoma (Figure 23):**
• Typical location: Leptomeninges +++
• Superficial cerebral lesion; communicating hydrocephalus.
• Leptomeningeal, subependymal, dural, or cranial nerve contrast enhancement.
Fig. 1: 52 years-old-man, confusion. Axial T1 and T2 WI showing a large ill-defined fronto-parietal lobe mass in the right periventricular region, hypointense in T1 WI and hyperintense in T2 WI. Note the hyperintense perifocal surrounding vasogenic oedema.

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Fig. 2: 56 years old women. Left hemiparesis, epilepsy. Axial T2 WI reveals a hyper intense infiltrative lesion involving the right basal ganglia causing compression of the third ventricle and resulting in obstructive hydrocephalus.

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**Fig. 3:** 50 years old man increased intracranial pressure. Sagittal T1 WI without contrast and T2 WI showing a large area of decreased signal in T1 WI and hyper intense in T2 in the frontal lobes and periventricular lesions.

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![Image](image1)

**Fig. 4:** 62 years old women. Signs of increased intracranial pressure. Homogeneous hypointense T1 WI and hyperintense T2 WI mass in the splenium of the corpus callosum causing compression of the ventricles. DWI reveals high signal within the lesion, representing restricted diffusion (low ADC) due to the high cellularity of the tumor.

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**Fig. 5:** 47 years-old-man, signs of coma. Large hyperintense T2 and FLAIR lesion involving the left periventricular white mater and corpus callosum, extending along ependymal surface. Note the additional periventricular right lesion (arrowheads).

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**Fig. 6:** 55 years old man. Progressive left hemiparesis. Non contrast cerebral CT scan showing an hyperattenuated right parasagittal frontal lobe lesion with marked enhancement in post contrast series.

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**Fig. 7:** 48 years old man with increased intra cranial pressure. Axial cranial CT and MRI showing multiple focal lesions in the basal ganglia and frontal left lobe with solid enhancement, associated to periventricular white matter vasogenic edema and mass effect displacing the midline.

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**Fig. 8:** 43 year’s old women, with right hemiparesis. Hypo intense T1 and hyper intense T2 well circumscribed left posterior frontal lobe lesion.

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Fig. 9: 78 years old man. Signs of coma. FLAIR and post contrast T1 WI sequence demonstrating a PBL involving both frontal lobes, and corpus callosum. It has spread across the corpus callosum and through the subependymal space.

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Fig. 10: (A) same patient as figure 9. Multifocal PCNSL, unenhanced CT shows high-attenuation lesions in basal ganglia and corpus callosum (arrowheads). The corresponding post-contrast CT image shows marked homogenous enhancement. (B) negative CT examination with corresponding T2 WI showing a well-circumscribed lesion (confirmed PBL).

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Fig. 11: A same patient as figure 8, B same patient as figure 4. Mild perifocal edema much less extensive than is seen with primary glial tumors or metastases (arrowheads).

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Fig. 12: same patient as figure 4, coronal FLAIR sequence shows a homogeneous isointense mass compared to the cortex in the splenium of the corpus callosum (arrow) with a mild surrounding edema (arrowhead).

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**Fig. 13:** different types of enhancements. (A) moderate and heterogeneous enhancement. (B) same patient as figure 7: multifocal strong patchy homogeneous enhancement. (C) same patient as figure 5: punctuate nodular enhancement.

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**Fig. 14:** Same patient as figure 4, aggravation of the headaches + altered mental status one month after intrathecal chemotherapy. Hyperintense T1 WI lesion involving the entire corpus callosum. Detection and diagnosis was best with T2*-weighted gradient-echo images.

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**Fig. 15:** Same patient as in figure 7, the single voxel, short Time Echo MRS demonstrates an exaggerated lipid peak in a solid mass. Lipid peaks are typically demonstrated in necrotic lesions, but in solid PCNSL lesions the peak is due to the increased macrophage content. MRS demonstrates also a decreasing value of NAA and elevation of choline.

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**Fig. 16:** Same patient as in figure 4, MRS (TE 35 ms and 144 ms) demonstrates an exaggerated lipid peak, increased concentration of choline and decreased concentration of N-acetyl aspartate in this solid mass.

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**Fig. 17:** Same patient as in figure 4. Enhanced T1-WI MRI demonstrates a homogeneously enhancing mass in the splenium of the corpus callosum causing compression of the ventricles. On visual evaluation of the cerebral blood volume (CBV) map, there is a weak increase of relative cerebral blood volume despite the intense contrast enhancement, which indicates no significant localized neoangiogenesis.

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Fig. 18: multimodal MRI of a large deep right frontal periventricular lesion, showing a strong homogeneous enhancement with peripheral oedema. MRI perfusion indicates increasing of the intensity of the signal above the baseline attesting the high blood-brain barrier permeability with no significant neoangiogenesis [14].

Fig. 19: Multimodality cerebral MRI of a middle-aged man with a PCNS lymphoma. T1 WI with contrast showing a homogeneous enhancing of two lesions in contact with the ventricles. MRI perfusion of the major lesion shows a weak increase of relative cerebral blood volume, which indicates no significant localized neoangiogenesis (no red area in the lesion). The first pass of the bolus agent curve indicates high blood-brain barrier permeability [15].


Fig. 20: CT and MRI of a left frontal glioblastoma. Post-contrast T1WI shows an irregular ring-like enhancement. T2 WI shows a high signal mass surrounded by peritumoral edema Post-contrast FLAIR image clearly demonstrates the ring-like enhanced tumor.
**Fig. 21:** Tumefactive oval bilateral centrum semiovale mass, hyperintense on T2 WI, with an open ring-enhancing pattern of contrast uptake. Typical pseudotumoral form of multiple sclerosis.
**Fig. 22:** Axial FLAIR (a), T2-WI (b), and DWI (c) showing multiple, asymmetric, patchy hyperintense lesions of acute disseminated encephalomyelitis. Post-contrast T1 WI sequence (not shown) shows simultaneous nodular enhancement of all the lesions.

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**Fig. 23:** Post contrast axial T1 WI showing optic nerves and leptomeningial enhancement in a secondary CNSL.
Conclusion

CNS lymphomas may have a characteristic appearance on traditional CT and MR imaging; however, none of these imaging characteristics will unequivocally differentiate CNS lymphomas from other neoplasms (eg, metastases from other malignancies, malignant gliomas, meningiomas) or non-neoplastic diseases (eg, multiple sclerosis, stroke, cerebral toxoplasmosis, pyogenic abscess). Furthermore, the typical imaging characteristics may not be present. DWI, perfusion MR imaging, and MR spectroscopy are increasingly used in clinical radiologic practice and may help to differentiate CNS lymphomas from other lesions of the brain.

Stereotactic biopsy performed at an earlier stage, gives immunophenotypic characterization with far less aggressive procedure than open surgical biopsy, and plays a major role in the therapeutic decision-making process.
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