Imaging of lymphoma of the central nervous system in all its shapes and forms

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Learning objectives

Lymphoma of the central nervous system (CNS) encompasses a broad spectrum of clinical and histopathological entities and consequently can demonstrate a variety of radiological appearances. This diversity combined with the rarity of the disease can make correct imaging interpretation challenging. Establishing an early diagnosis has important therapeutic and prognostic implications for patients and radiologists have a vital role to play in this regard.

This educational exhibit aims to increase general radiologists’ knowledge of CNS lymphoma by:

- Discussing the classification of CNS lymphoma
- Reviewing the clinical context and epidemiology of subclassifications
- Describing characteristic MR and CT appearances of subtypes of cerebral lymphoma
- Illustrating case examples encountered at a national neurosurgical tertiary referral centre
- Correlating radiological and histopathological findings
- Introducing the role of advanced MR imaging techniques

Background

Primary CNS lymphoma (PCNSL):

This uncommon type of extranodal Non Hodgkins lymphoma is responsible for 5% of all primary brain tumours. Radiological appearances vary with patients’ immune status and immunodeficiency is the only known risk factor for PCNSL. The majority of cases are diffuse large B cell on histopathological analysis. There has been a reduction in incidence of PCNSL in the HIV population since the introduction of HAART.

Typical symptoms on presentation include neuropsychiatric and raised intracranial pressure manifestations. Seizures are less common than with other brain tumours as principally the subcortical white matter is affected rather than eliptogenic grey matter.

In keeping with the guidelines of the International PCNSL Collaborative Group all patients should have contrast enhanced cranial MRI and CT Thorax, Abdomen and Pelvis as part of the diagnostic evaluation.
Definitive diagnosis is only made with stereotactic biopsy. Beware of treating patients with steroids prior to biopsy as they can obscure the typical histological and radiological appearance of lymphoma. Methotrexate - Cytarabine combination is the reference therapy for PCNSL. Surgical resection is not a viable treatment option due to its infiltrative behaviour and involvement of deep brain locations.

**Secondary CNS Lymphoma**

Secondary CNS involvement by systemic lymphoma is the other major subtype of cerebral lymphoma and is more common than the primary form. It may involve the brain parenchyma or the leptomeninges. The frequency of CNS involvement depends on the histological classification and is more common for NHL than Hodgkins disease. Typically it occurs between 5 - 12 months following systemic diagnosis.

Patients with leptomeningeal disease may present with spinal or cranial neuropathies due to nerve involvement. Headache in patients with meningeal disease is likely due to raised intracranial pressure from metastatic obstruction of CSF absorption. Patients with parenchymal lesions behave clinically in a manner similar to PCNSL.

**Angiocentric Intravascular Lymphoma**

In this rare, but underdiagnosed, form of lymphoma there is angiotropic growth and intravascular proliferation of lymphoid cells. It demonstrates a predilection for CNS and dermatological involvement. Indeed, 50% of patients have skin lesions. Otherwise known as intravascular malignant lymphomatosis, the disease typically affects people in the 6th decade of life who tend to present with symptoms of confusion, memory loss, cognitive decline and occasionally fever. The prognosis is poor with a mean survival time of 10 months.

**T Cell Lymphoma**

The T cell subtype of CNS lymphoma is very rare with a reported incidence of 3.6% of primary CNS lymphomas. They tend to involve the superficial subcortical region and may demonstrate haemorrhage, rim enhancement and cystic areas in keeping with necrosis. There as is an increased incidence in men and systemic B symptoms occur frequently.
Imaging findings OR Procedure details

Primary CNS Lymphoma:

*Immunocompetent Host: Fig. 1 on page 6 Fig. 2 on page 7*

The characteristic radiological features of lymphoma are due to its disruption of the blood-brain barrier, hypercellularity and high nuclear to cytoplasmic ratio. These properties lead to contrast enhancement and high density CT lesions, respectively on imaging studies. PCNSL typically involves the periventricular and superficial regions of the brain. In patients with unimpaired immunological status, PCNSL tends to involve solitary parenchymal lesions that enhance homogenously. Oedema in the surrounding white matter is another common finding.

*Immunocompromised Host: Fig. 3 on page 7*

Multiple lesions are typical in immunodeficient patients and are identified in up to 80% of cases compared with immunocompetent patients where multifocal involvement is seen in only up to 40%. Also, lesions in the immunocompromised tend to exhibit necrotic regions manifesting as irregular or peripheral contrast enhancement. Indeed, ring-like enhancement is identified in 75% of immunodeficient patients compared with 10% in non-immunocompromised. Haemorrhage or calcification in tumours is more frequent in the immunosuppressed and the basal ganglia and corpus callosum are frequently involved sites.

Secondary CNS Lymphoma:

*Parenchymal Involvement: Fig. 4 on page 8*

There are two main imaging patterns of secondary CNS lymphoma. Meningeal involvement affects two thirds of patients while parenchymal lesions are seen in the other third. Parenchymal metastases can be single or multiple, typically enhance and tend to be seen in superficial or periventricular locations. It is not possible to distinguish PCNSL from secondary parenchymal lymphoma on the basis of current MR imaging techniques.
Leptomeningeal Involvement: Fig. 5 on page 9 Fig. 6 on page 10 Fig. 7 on page 11

Imaging features include leptomeningeal, subependymal, avid nodular dural or cranial nerve enhancement, superficial cerebral lesions or communicating hydrocephalus. However, if MRI is performed following lumbar puncture, beware that the puncture may induce dural enhancement which can be falsely interpreted as meningeal enhancement due to disease involvement.

Angiocentric Intravascular Lymphoma: Fig. 8 on page 11 Fig. 9 on page 12 Fig. 10 on page 12

Characteristic radiological features of this rare subtype of lymphoma include multifocal T2 hyperintensity in the supratentorial deep white matter or grey white matter interface. The enhancement pattern is variable with punctate, gyriform, linear and nodular appearances described. Meningeal enhancement may also be observed. Diffusion restriction on diffusion weighted imaging has also been reported. Gradient echo sequences may demonstrate blooming due to the presence of blood products.

Diagnosis is often made at post mortem with small cortical infarcts of varying ages and some haemorrhagic, identified on gross pathological specimens. Microscopically, lymphoid tumour cells distend small vessels. Minimal perivascular extension into adjacent brain parenchyma occurs.

T Cell Lymphoma: Fig. 11 on page 13 Fig. 12 on page 14

As already outlined, the vast majority of CNS lymphomas are B Cell histologically. This is a case of T Cell Hodgkins lymphoma which only very rarely is seen in the central nervous system. Appearances cannot be distinguished radiologically at present, histopathological and immunohistochemical analysis is relied upon for diagnosis.

Differential Diagnosis: Fig. 13 on page 14 Fig. 14 on page 15 Fig. 15 on page 16 Fig. 16 on page 16
Unfortunately, no appearance on traditional imaging unequivocally distinguishes lymphoma from other brain lesions. The differential diagnosis includes other metastases, malignant glioma, meningioma, M.S, stroke, pyogenic abscess and cerebral toxoplasmosis.

Figure 13 shows ring enhancing lesions in the right centrum semiovale and left basal ganglia. These were biopsy proven primary CNS lymphoma in an immunocompromised individual. Figure 14 is a histologically proven case of cerebral toxoplasmosis with ring enhancing lesions seen in the left centrum semiovale and left basal ganglia highlighting how lymphoma may mimic other pathological entities.

Figures 15 and 16 show a case of lymphoma involving the corpus callosum on CT and glioblastoma multiforme of the corpus callosum on MRI, again with strikingly similar appearances.

**Future Directions**

Other advanced MR techniques, including diffusion tensor imaging and perfusion imaging as well as metabolic imaging with PET/CT and SPECT are identifying increasingly specific findings in CNS lymphoma. It is hoped these improvements will eventually yield sufficiently specific morphologic and biologic data to make an accurate diagnosis non-invasively. They may also play a role in planning new targeted therapies, and monitoring treatment response. Fig. 17 on page 17

**Images for this section:**

![Images of brain scans](image_url)
Fig. 1: (From left to right): Confluent hyperintensity in the centrum semiovale on FLAIR (stars). Contrast enhanced T1 MRI reveals small foci of enhancement (arrows). Lesions show diffusion restriction [bright on DWI (circled) # and low on ADC (not shown)].

Fig. 2: (From left to right): Contrast enhanced T1 MR shows enhancing lesion in the left cerebral peduncle of midbrain. (circle) Hyperintense FLAIR abnormality in left cerebral peduncle (thin arrow) and periventricular region (thick arrow). Incidental note of arachnoid cyst in the left temporal fossa (star).
Fig. 3: (left top&bottom): Non-contrast CT shows multifocal hyper dense lesions in a periventricular location with surrounding low attenuation vasogenic edema (diamonds). (mid top&bottom): These masses demonstrate enhancement post contrast on T1 MRI. (stars). (right top): There is periventricular hyper-intensity on FLAIR. (right bottom): The largest lesion shows diffusion restriction - high signal on DWI (circle).
**Fig. 4:** Coronal T1 MRI post contrast shows right frontal extra-axial mass with enhancement of dura in the midline and particularly in the right frontoparietal region (arrows) There is surrounding low signal parenchymal edema (star). Axial T2 MRI in the same patient also shows the adjacent high signal edema (within rectangle).
Fig. 5: T1 weighted axial MRI shows a case of secondary CNS lymphoma with right parietal extra axial mass, dural enhancement (diamond) # and associated edema (star). Pathology H&E slide shows abnormal lymphocytic infiltration of the dura.
Fig. 6: Axial T1 contrast enhanced MRI at level of upper pons shows abnormal enhancement of the cisternal segment of the right trigeminal cranial nerve consistent with leptomeningeal secondary CNS lymphoma. (between arrows)

Fig. 7: Axial T1 contrast enhanced MRI at level of mid pons shows bilateral enhancement of VII and VIII cranial nerves in keeping with leptomeningeal involvement by lymphoma. (arrows)
Fig. 8: T1 post contrast: ill-defined feathery and punctate areas of enhancement in right centrum semiovale suspicious for angiocentric intravascular lymphoma

Fig. 9: Abnormal centrum semiovale and thalamocapsular FLAIR hyperintensity in the same patient with histologically confirmed angiocentric intravascular lymphoma
Fig. 10: H&E slide shows abnormal perivascular lymphocytes in keeping with diagnosis of angiocentric intravascular lymphoma.
**Fig. 11:** (from left to right): Hyperdense mass on non contrast CT. MRI, shows contrast enhancement, perilesional oedema and diffusion restriction. (circled)

**Fig. 12:** (From left to right): High Power H&E: Polymorphic infiltrate composed of small lymphocytes, eosinophils and enlarged malignant cells (arrows), some of which are binucleate with prominent nucleoli. CD3: CD3 is a T Cell immunocytochemical marker which highlights a large number of reactive T cells. CD 30: The malignant cells are positive for CD30.
**Fig. 13:** Axial T1 post contrast MRI showing ring enhancing lesions in centrum semiovale and left caudate nucleus. Histologically these lesions were lymphoma.

**Fig. 14:** Ring enhancing lesions in same distribution were biopsy proven cerebral toxoplasmosis.
Fig. 15: (From left to right): NC CT shows hyperdense mass involving corpus callosum. Biopsy showed this to be CNS lymphoma. (diamond). T1 post contrast showing glioblastoma multiforme in the corpus callosum of another patient (star).
Fig. 16: (From left to right): T2 and FLAIR MRI again showing glioblastoma multiforme in the corpus callosum. (star)
Fig. 17: Multivoxel MR Spectroscopy shows raised choline and decreased NAA in keeping with an aggressive process such as lymphoma. High choline is a marker of increased cell turnover and NAA is a marker of neuronal integrity.
Conclusion

The variety of imaging appearances of central nervous system lymphoma has been reviewed. The valuable role of MRI at present and into the future to assist in establishing an accurate sub diagnosis of this heterogenous clinical entity has been highlighted. This is particularly well illustrated by a rare case angiocentric intravascular lymphoma with pathological correlation.

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