Received:
26 October 2013

Revised:
1 February 2014

Accepted:
13 February 2014

doi: 10.1259/bjr.20130684

Cite this article as:

Partovi S, Karimi S, Lyo JK, Esmaeili A, Tan J, Deangelis LM. Multimodality imaging of primary CNS lymphoma in immunocompetent patients. Br J Radiol 2014;87:20130684.

PICTORIAL REVIEW

Multimodality imaging of primary CNS lymphoma in immunocompetent patients

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) belongs to the group of extranodal non-Hodgkin's lymphoma, and the management of the disease is radically different from other central nervous system neoplasms. Owing to its varied appearance on imaging, diagnosis of PCNSL can be challenging. The purpose of this pictorial review is to depict the brain findings of PCNSL during initial diagnosis in immunocompetent individuals. Multimodal imaging integrating advanced sequences can facilitate differentiation of PCNSL from other CNS neoplasms.

Primary central nervous system lymphoma (PCNSL) is a manifestation of extranodal non-Hodgkin's lymphoma, which accounts for 6% of all intracranial malignant tumours.¹ 90% of PCNSLs are histologically diffuse large B cell lymphomas, and the remaining 10% are poorly characterized low-grade, Burkitt's or T-cell lymphomas.² An increase in the incidence of PCNSL has been reported in immunocompromised and -competent individuals in the last decades, especially among the elderly. The reasons for this increase are largely speculative, but contributory factors might include the increasing incidence of acquired immunodeficiency syndrome, improvements in imaging approaches and increased utilization or success of stereotactic biopsy and tissue diagnosis. More recently, the incidence of PCNSL has been stable or slightly decreasing.³

Among immunocompetent individuals with PCNSL, the median age ranges between 53 and 57 years, with a male to female ratio of approximately 1.5:1.⁴ Symptoms at disease onset are typically focal neurological deficits, neuropsychiatric symptoms (including dementia and cognitive dysfunction), symptoms related to increased intracranial pressure (ataxia, headache and incontinence), seizures or ocular-related symptoms.⁵

The only known risk factor for developing PCNSL is congenital or acquired immunodeficiency.

Diagnostic work-up should start with contrast-enhanced MRI of the brain, which is the most sensitive imaging method to detect PCNSL. When contrast-enhanced MRI is not feasible because of contraindications such as pacemaker or claustrophobia (or if MRI is not available), contrast-enhanced CT can be performed.

Imaging may be complemented by CT or MRI of the spinal axis and by CT of the chest, abdomen and pelvis to assess for additional lesions (in particular, occult systemic manifestation that exists in 4–12% of PCNSL). To exclude occult systemic manifestations, bone marrow biopsy and testing are additionally recommended.^{6,7} Further diagnostic steps include cerebrospinal fluid (CSF) analysis and slit-lamp eye examination, especially when the patient complains of ocular symptoms. For definitive histopathological diagnosis, the patient should finally undergo stereotactic biopsy.

The purpose of this pictorial review is to depict the varied imaging presentations of PCNSL intracranially and intra-orbitally, based on patient scans acquired at Memorial

Figure 1. A 56-year-old male with confirmed diffuse large B-cell lymphoma of the central nervous system. Axial T_1 post-contrast image shows an enhancing right basal ganglia mass. Also, a periventricular lesion just adjacent to the right trigone at the edge of the corpus callosum can be appreciated.

Sloan-Kettering Cancer Center, New York, NY, in the last 8 years, with cases depicting both typical and interesting, as well as unusual, imaging variants of PCNSL.

PRIMARY CNS LYMPHOMA

Classical presentation

PCNSL classically appears iso- to hyperdense on CT and iso- to hypointense in T_1 and T_2 weighted MRI,^{8,9} with surrounding mild-to-moderate oedema. The oedema is hyperintense on long repetition time T_2 and fluid-attenuated inversion-recovery (FLAIR) sequences.¹⁰ Less frequently, lesions may have little to no oedema. The slightly hyperdense appearance on CT and the

Figure 2. A 90-year-old male with colon cancer presenting with word finding difficulties. Biopsy showed malignant T-cell primary central nervous system lymphoma. (a) Axial T_2 shows an expansive mass in the left thalamus. (b) T_1 post-contrast image shows no significant enhancement in the lesion.

Figure 3. An 80-year-old male with diffuse large B-cell lymphoma. Axial T_1 post-contrast image shows enhancing masses in the frontal lobes.

slight hypointensity on T_2 imaging are attributed to the dense cellularity of the lymphomatous deposits. After gadolinium contrast administration, the mass often exhibits intense enhancement visible on both CT and MRI.¹¹ According to our experience, lymphomatous lesions can usually be differentiated from metastases based on their more pliable and infiltrative borders, which appear to conform to and follow more the underlying brain anatomy, as opposed to brain metastases that often have spherical discrete borders and push adjacent anatomy. Nevertheless, atypical imaging findings are frequent in PCNSL,^{11,12} including a diffuse or patchy enhancement or

Figure 4. A 55-year-old female with progressive cognitive changes. Biopsy revealed diffuse large B-cell lymphoma. Sagittal T_1 post-contrast scan showing multifocal enhancement of the right frontal and temporal lobe white matter.

Figure 5. A 65-year-old female with diffuse large B-cell lymphoma. Axial T_1 post-contrast image shows an enhancing mass in the anterior corpus callosum.

non-enhancement, which is often indistinguishable from other non-metastatic processes such as demyelinating disease. Multimodal and advanced imaging techniques, such as perfusion-weighted MRI, diffusion-weighted (DWI) MR sequences in conjunction with apparent diffusion coefficient (ADC) maps and 2-deoxy-2- 18 Fluorodeoxyglucose positron emission tomography (FDP-PET), can facilitate diagnosis in difficult cases.

Contrast enhancement

Although intense homogeneous enhancement is usual within the lymphomatous mass, enhancement patterns are often variable for

Figure 6. A 72-year-old male with memory loss and confusion due to diffuse large B-cell lymphoma. Coronal T_1 post-contrast image shows an enhancing mass around the right occipital horn.

Figure 7. A 58-year-old male with headaches and vertigo. Biopsy showed diffuse large B-cell lymphoma. Sagittal T_1 post-contrast image shows an enhancing mass within or along the fourth ventricle causing obstructive hydrocephalus.

PCNSL, with lesions exhibiting heterogeneous or mild enhancement, or even non-enhancement (Figures 1 and 2). In a study that analysed 100 PCNSL patients, 85% of the lesions showed intense enhancement, 10% moderate enhancement and 1% no significant enhancement.¹³ Non-enhancing PCNSL is often difficult to diagnose without biopsy, and a wide variety of other aetiologies must be entertained, such as demyelination (acute disseminated encephalomyelitis or multiple sclerosis), chronic white matter microvascular changes, gliosis or encephalomalacia, encephalitis and migraines, among other possibilities, with these considerations

Figure 8. A 60-year-old female with mild headaches and clumsiness resulting from primary central nervous system lymphoma. Sagittal T_1 post-contrast image demonstrating a mass along the superficial left parietal cortex, which abuts the overlying dura and mimics an extra-axial mass. During surgery, parts of the mass were found to be stuck to the pia surface.

Figure 9. A 74-year-old male with seizures and high-grade diffuse large B-cell lymphoma with systemic manifestation. Coronal T_1 post-contrast image shows diffuse folial enhancement sugar-coating appearance of leptomeningeal disease.

necessarily influenced by clinical presentation and laboratory tests. The presence of focal volume loss within the lesion, however, would favour a non-lymphomatous (or chronic) process, as active PCNSL should result in some degree of expansion or mass effect. Ring enhancement has also been observed in immunodeficient subjects, and is rare in immunocompetent persons with PCNSL.¹⁴ In an immunocompetent patient, ring enhancement may suggest a centrally necrotic high-grade glioma or metastasis, or an abscess in the proper clinical setting. PCNSL can involve the entire craniospinal axis including the brain, leptomeninges, spinal cord and eyes. Within the brain, PCNSL is most often found in the frontal lobes (Figure 3), as infiltrative white matter disease (Figure 4), or in deep structures such as the basal ganglia and corpus callosum (Figure 5); it may also infiltrate the periventricular regions (Figures 6 and 7). In a study analysing 100 cases of PCNSL, the most common localizations were the cerebral hemispheres (38%), in particular the frontal lobes, followed by basal ganglia/thalamus (16%), corpus callosum (14%) and ventricular regions (12%), with the cerebellum as the least likely location (9%).¹³

PCNSL involving the corpus callosum can infiltrate trans-callosally, appearing as a symmetric "butterfly lesion".¹⁵ The

Figure 10. An 82-year-old female with decreased vision and swelling of left eye. Biopsy showed malignant marginal zone type orbital lymphoma. (a) Axial T_1 non-contrast image showing an expansive mass in the left orbit and infiltrating the orbital apex, with proptosis. (b) Coronal T_1 post-contrast image shows that the mass enhances.

Figure 11. A 76-year-old male with confusion. Cerebrospinal fluid sampling showed cells highly suspicious for lymphoma of the central nervous system. Coronal T_1 post-contrast image shows infiltration and expansive enhancement of the bilateral pre-chiasmatic optic nerves.

appearance might be similar to a transcallosal high-grade glioma or an unusual appearance of a tumefactive demyelinating process. Corpus callosum involvement would be unusual for a metastasis. PCNSL might also mimic an extra-axial mass (Figure 8) when it abuts the dural surface.

PCNSL can present with solitary or multifocal lesions and, according to the literature, PCNSL presents with a solitary lesion in one-third of cases and is multifocal in the other two-thirds of cases (with up to ten lesions often present).^{13,16}

Leptomeningeal dissemination (Figure 9) occurs in 16–41% of PCNSL at initial diagnosis¹⁶ and may be detected as nodular and asymmetric sulcal or folial enhancement. It can be confirmed with CSF sampling because non-lymphomatous processes can look identical (including other neoplasms and granulomatous or infectious processes) with cross-sectional imaging. Leptomeningeal deposits are preferentially located caudally, such as in the posterior fossa or along the lower spinal cord and cauda equina, presumably due to gravity effects. Early leptomeningeal disease might present with only sulcal hyperintensity on FLAIR sequences; although in the absence of nodular enhancement, this finding is not specific and might also be seen with subarachnoid haemorrhage or infection (and often this is an artefact). Especially in cases where the leptomeningeal enhancement is diffuse and non-nodular, other considerations including anaesthesia-related vascularity, infection and vascular congestion should be considered.

PCNSL can present as orbital/ocular involvement (Figure 10), although these findings might often not be discernible on MRI

Figure 12. A 47-year-old female with seizures who has diffuse large B-cell lymphoma. (a) Sagittal T_1 pre-contrast and (b) sagittal T_1 post-contrast scans show an enhancing haemorrhagic mass with pre-contrast T_1 hyperintense signal haemorrhage within the lesion. (c) Axial T_2 sequence shows low intensity of the haemorrhage and high signal of surrounding oedema.

or CT scan, especially when located within the globes without a sufficiently large soft tissue component. Such cases might be more amenable to ophthalmologic examination. Patients with ocular involvement might complain of blurred vision and seeing “floaters”, diminished visual acuity and painful red eyes. At initial diagnosis, uveitis is a relatively specific sign of ocular involvement and is observed in 10–20% of patients. Ocular involvement by PCNSL might be seen on imaging as vitreous or optic nerve infiltration (Figure 11) and is frequently bilateral; it may be present in 20% of newly diagnosed PCNSL.¹⁶

Rare findings

PCNSL presenting with haemorrhage is rare (Figure 12), although a few cases with haemorrhagic PCNSL have been described.^{14,17} Cyst formation and calcifications are other exceedingly rare manifestations at initial diagnosis, although reports exist describing these features in PCNSL.¹⁰ However, these findings should raise suspicion for other disease processes as well.

Primary dural lymphoma

Primary dural lymphoma is a rare type of PCNSL, which arises from the meninges or spinal dura.¹⁸ One study analysed their own PCNSL patient collective and found that 2.4% of all PCNSLs were

primary dural lymphomas.¹⁹ This tumour entity typically occurs in middle-aged females and presents with symptoms such as headaches, cranial nerve involvement or meningeal reactions.²⁰ Histologically, primary dural lymphomas are marginal zone B-cell lymphomas, which are low-grade indolent non-Hodgkin's lymphomas.²¹ Imaging has an important role in primary dural lymphoma. The typical MRI and CT appearance is an extra-axial mass attached to the dura, which enhances diffusely after contrast administration. The most common localizations are the cerebral convexities.²² Oedema and invasion into the brain parenchyma help to differentiate this malignancy from meningioma. Whole-body CT in conjunction with bone marrow biopsy has been suggested to assess the neurological and systemic extent of the disease.¹⁹ After treatment, frequent follow up with MRI or CT is required owing to the high risk of systemic relapse. The usual treatment in primary dural lymphoma is surgical resection followed by adjuvant radio-chemotherapy. The tumour seems to have a favourable prognosis in comparison with PCNSL from the brain parenchyma.¹⁹

Intravascular lymphoma

Intravascular lymphoma is a very rare type of lymphoma with cell proliferations within the vascular lumen. This tumour is most commonly localized in the CNS or skin. Histologically, it

Figure 13. (a) Fractional anisotropy and (b) coloured fractional anisotropy map of the same patient show lack of anisotropy of the tumour.

Figure 14. (a) Plasma volume and (b) K-trans or permeability maps from dynamic contrast-enhanced perfusion imaging demonstrate increased perfusion and permeability of the tumour.

Figure 15. (a) Non-contrast CT of a patient with primary central nervous system lymphoma demonstrates an iso- to slightly hyperdense mass in the medial left temporal lobe extending to the corpus callosum with surrounding oedema. (b) Revealing avid enhancement. (c) The tumour is hypointense in the T_2 weighted MRI image owing to high cellularity and (d) with homogeneous intense enhancement on the contrast-enhanced T_1 weighted MR image. (e) The tumour is hyperintense in the diffusion-weighted image and (g) the exponential map with (f) decreased signal on the apparent diffusion map.

is a subtype of diffuse large B-cell lymphoma, and malignant cells can be found in the intravascular space.²³ Masses in the CNS can be also found in this lymphoma subtype.^{24,25} These

Figure 16. (a) Axial contrast T_1 weighted image and (b) T_2 weighted image 3 weeks after the start of systemic treatment demonstrate marked decrease in the enhancing mass with resolution of oedema and mass effect. Note that the residual abnormality no longer demonstrates low signal intensity (compare with Figure 15c).

mass lesions show histopathological features of extravascular B-cell lymphoma with a minor intravascular component.²⁶ The symptoms range from ischaemia and infarction to hepatomegaly and splenomegaly as extracerebral manifestation. The variety of symptoms and histological appearance can make the diagnosis challenging.^{27–29} The differentiation to PCNSL might be difficult when intravascular lymphoma occurs with CNS mass lesions. Imaging can help to detect the CNS mass lesions in CT or MRI.³⁰ In one study,²⁶ radiographic findings were described as low-density lesion on native CT with ring or homogenous enhancement in contrast to CT or MRI. White matter lesions mimicking an infarct in cross-sectional imaging were suggested as a typical sign of intravascular lymphoma.²⁶ In the few cases there are, reports existing about this exceedingly rare disease entity show a rather poor outcome, despite systemic chemotherapy.²⁶

DISCUSSION

PCNSL might present with a variety of imaging findings and should always be associated with some degree of expansion or mass effect and not volume loss. Imaging is important for timely and accurate diagnosis and for determining the proper management.⁴ Unlike for other brain neoplasms, such as high-grade gliomas that undergo neurosurgical resection, stereotactic biopsy is often obtained for histopathological confirmation of

Figure 17. ^{18}F Fluorodeoxyglucose (FDG)-positron emission tomography image reveals marked FDG avidity owing to high metabolic activity of the tumour.

the diagnosis of PCNSL. Prior to stereotactic biopsy, steroids should be withheld, since the lymphotoxicity of steroids can lead to the disappearance of the lesion within a few days, making tissue diagnosis more difficult. Steroid response of a brain lesion is not diagnostic for PCNSL, as many brain lesions that may mimic PCNSL on imaging can improve after steroid administration, such as neurosarcoidosis and multiple sclerosis.³¹ Unusual manifestations of PCNSL may make its diagnosis with conventional MRI and CT difficult, and thus special sequences and post-processing techniques may be

obtained for further information to at least narrow the differential diagnosis (Figures 13 and 14). Furthermore, cross-sectional imaging might be of benefit for treatment response assessment (Figures 15 and 16).

On perfusion imaging, there is usually lower perfusion in PCNSL than other brain tumours such as high-grade gliomas, meningiomas and metastases. The low perfusion in combination with the strong enhancement in PCNSL is explained by the low induction of neovascularization and destruction of the blood–brain barrier. DWI with ADC maps is already commonly performed in routine protocols owing to its short scan time and usefulness in problem solving, and restricted diffusion with a low intensity on the ADC map is typical for PCNSL.³² In quantitative analysis, it has been demonstrated that the ADC values of lymphomas are significantly lower than astrocytomas of different grades,^{32,33} and this may be related to the dense cellularity or small cell size of the lymphomatous deposits. FDP-PET reveals strong tracer accumulation in PCNSL reflecting hypermetabolism of the cells (Figure 17).

After diagnosis and therapy induction, follow up with contrast-enhanced brain MRI is recommended to re-evaluate the PCNSL lesions and to assess for decrease in size or disappearance of the lesion. In our institution, follow up MRI is performed every 3 months for 2 years after treatment and every 6 months for the next 3 years.⁷

Our experience with PCNSL is that multimodal imaging, including MRI with advanced sequences, PET and CT, supports reliable differentiation of lymphomas from other CNS neoplasms and non-neoplastic processes and is an important aid in determining proper management.

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