Myriad of MR imaging phenotypes of primary central nervous system lymphoma in a cohort of immunocompetent Indian patient population

Sankar Neelakantan, Sunitha P Kumaran, Sanjaya Viswamitra, Nandita Ghosal

Departments of Radiology and Pathology, Sri Sathya Sai Institute of Higher Medical Sciences, Bengaluru, Karnataka, India

Correspondence: Dr. Sunitha P Kumaran, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada. E-mail: sunitha.kumaran@uhn.ca; drsunitha27@gmail.com

Abstract

PCNSL (primary central nervous system lymphoma) is a chemosensitive and radiosensitive tumor, and early diagnosis has a significant impact on management. Unlike many other brain tumors, radical surgical excision of PCNSLs is not indicated because these lesions are highly infiltrative and even partial resection leads to a bad prognosis. The goal of this study is to highlight the unusual radiological presentation of PCNSLs and increase the awareness, familiarity, and global database of our observations that pose a challenge on management.

Key words: Atypical; MRI; primary central nervous system lymphoma; unusual

Introduction

Primary central nervous system lymphomas (PCNSLs) are the rare hematopoietic tumors accounting for 2–3% of all primary brain tumors and <1% of all non-Hodgkin’s lymphomas, and most are diffuse large B-cell lymphomas.[1] PCNSL is defined by disease which is restricted to the brain, leptomeninges, spinal cord, or eyes, without evidence of it outside the CNS (central nervous system) at primary diagnosis. The epidemiology, clinical presentation, and imaging findings vary depending on the immune status of the patient. Immunodeficiency either inherited or acquired is a major risk factor for the development of PCNSL, but a recent increase in incidence has been reported in immunocompetent individuals. Usual age of onset reported is between sixth and seventh decades of life, with earlier age of onset in immunocompromised individuals.[2] A few studies published from India have found that age of presentation is a decade earlier than that of the western population.[3]

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 available, CT scan can be used as an alternative, although it has lower sensitivity.[4] Treatment usually involves a combination of surgery, chemotherapy, and radiation therapy, with the specific approach depending on the extent and location of the disease.

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Cite this article as: Neelakantan S, Kumaran SP, Viswamitra S, Ghosal N. Myriad of MR imaging phenotypes of primary central nervous system lymphoma in a cohort of immunocompetent Indian patient population. Indian J Radiol Imaging 2018;28:296-304.
not feasible either due to contraindications (pacemaker or claustrophobia) or unavailability, contrast-enhanced CT can be performed. Imaging evaluation should precede steroid administration to avoid masking of imaging findings and/or biopsy results.\textsuperscript{[3,4]}

Imaging also includes screening of the spine, chest, abdomen, and pelvis to assess for additional lesions to rule out secondary lymphoma and occult systemic manifestation of PCNSL that exist in 4–12% cases.\textsuperscript{[4]}

Management strategies include obtaining a definitive histopathological diagnosis by stereotactic biopsy followed by radiotherapy and chemotherapy.

Restricted diffusion with low ADC (apparent diffusion coefficient) values are particularly useful in assessing response to chemotherapy, with increases in ADC values to above those of normal brain predictive of complete response.

**Classical MR findings in immunocompetent patients with primary central nervous system lymphoma\textsuperscript{[5,6]}**

- Solitary versus multiple lesions: Multifocal parenchymal lesions are less common than leptomeningeal disease, which account for two-thirds of cases. This could be explained due to its predilection for the periventricular and subcortical white matter regions and spread to ventricular or meningeal ependymal surfaces
- Location: Mostly periventricular and/or superficial central hemispheric
- Perilesional edema: Mild to moderate
- MR signals: Hypo- or isointense lesions on T1 weighted images and iso- or hypointense lesions on T2 weighted images, mostly hypointense to gray matter. This is due to its tumoral hypercellularity and high nuclear/cytoplasmic ratio
- Enhancement patterns: Homogenous enhancement of the lesion
- Functional imaging:
  - Diffusion weighted imaging (DWI): It measures the relative movement of water molecules within tissues and is considered a surrogate marker of tumor cellularity. CNS lymphomas being hypercellular tumors often show diffusion restriction
  - Diffusion tensor imaging: Essentially DTI measures diffusion of water molecules in six different directions. Differential cellularity of tumors affects fractional anisotropy values which is an objective measure for DTI. PCNSL has significantly lower FA values than glioblastoma multiforme, aiding in the differentiation of these lesions
  - Susceptibility weighted imaging (SWI): It is useful in ruling out tumoral bleed and/or calcifications. Hemorrhage or calcification within PCNSLs is quite a rare finding
  - Perfusion imaging: Typically, PCNSLs demonstrate decreased cerebral blood flow on color maps
  - Spectroscopy: It provides information regarding biochemical tissue composition. PCNSLs demonstrate elevated lipid peaks with high Cho/Cr ratios.

PCNSL can occur in the immunocompetent and in the immunocompromised patients, but the cause and behavior of PCNSL differ based on the affected population.\textsuperscript{[7]} [Table 1] Immunocompromised patients are at a risk for developing PCNSL which is usually secondary to HIV, organ transplantation, or congenital immunodeficiency syndromes. In this subgroup, PCNSL arises from Epstein–Barr virus (EBV) infection of B-lymphocytes. In contrast, there is no well-established cause for PCNSL in immunocompetent patient. No association has been found between the disease and EBV or the human herpes viruses in immune competent population.\textsuperscript{[7]} It is still a mystery on how these neoplasms develop and grow in the CNS, as B-lymphocytes have no known role in the normal brain.\textsuperscript{[7]}

The main difference with reference to imaging between immunocompetent and immunocompromised patients is the enhancement pattern of the lesions; rest of the findings overlap.\textsuperscript{[5]}

**Rare subtypes of primary central nervous system lymphoma**

- Lymphomatosis cerebri: Rare variant of PCNSL with poor prognosis. They pose a diagnostic challenge as they present late and mimic more common tumors. The radiological findings may be similar with those of the gliomatosis cerebri, T1 hypointense, and T2 hyperintense confluent lesions in bilateral periventricular deep white matters, basal ganglia, diencephalon, and brainstem\textsuperscript{[8]}
- Primary intravascular lymphoma: Rare variant of PCNSL, generally diagnosed at autopsy. MRI features mimic ischemic disease/encephalopathy. Initial contrast enhancement followed by progressive tissue loss is noted\textsuperscript{[9]}
- Neurolymphomatosis: It is a rare and polymorphic form of PCNSL clinically presenting as cranial/peripheral neuropathy. MR imaging features are altered signals, thickening and enhancement of the involved nerve roots\textsuperscript{[9]}
- Primary intraocular lymphoma: It is an uncommon subset of PCNSL which initially presents with ocular involvement with or without simultaneous CNS involvement. MR imaging is to rule out CNS involvement.

| Table 1: PCNSL Lymphoma-Characteristic findings in immunocompetent and immunocompromised group |
|-----------------------------------------------|-------------------------------------|-------------------------------------|
| Characteristic findings                      | Immunocompetent                   | Immunocompromised                   |
| Mean age of presentation                     | 60 years                           | 30 years                            |
| Multiple lesions (%)                         | 30-50                              | 63-81                               |
| Necrotic change                              | Rare                               | Common                              |
| Post-contrast enhancement on imaging         | Homogenous                         | Heterogeneous                       |

Indian Journal of Radiology and Imaging / Volume 28 / Issue 3 / July - September 2018
involvement, diagnosis is made by vitrectomy/vitreous biopsy[11]

- Primary dural lymphoma: Rare subset of PCNSL which is more indolent and has a better prognosis compared to parenchymal PCNSL. MR imaging reveals single or multiple extra-axial masses which show diffuse post-contrast enhancement[12]
- Primary spinal lymphoma: Can be epidural/intraduillary in location

This study is aimed at reviewing atypical MRI features of PCNSL in immunocompetent patients that can cause diagnostic challenges in this relatively uncommon malignancy and also illustrate various imaging appearances that may potentially aid in the differentiation of primary CNS lymphoma from other more common brain tumors.

**Materials and Methods**

A retrospective review of brain tumors in the pathology archives of our institution, from 2009 to 2017, revealed 40 cases of PCNSL out of which only 31 cases fitted into the criteria of our study. Only immunocompetent patients without history of acquired immunodeficiency syndrome or any other congenital immunodeficiency disorders were included in the study. None of these patients had any associated intracranial diseases. This study was approved by the review board and ethics committee of our institution. All patients underwent plain and contrast MRI on 1.5 T (GE and Aera Siemens). MR images were acquired at a slice thickness of 8 mm. Axial SE T1WI and T2WI were performed before contrast medium administration. Subsequently, gadolinium-DTPA (diethylenetriaminepenta-acetic acid) enhanced SE T1WI images were obtained. CT scans (128 slice GE) were performed only in two patients where PNS (paranasal sinuses) were involved. Screening of the chest, abdomen, and pelvis by CT was done in all the cases to rule out secondary lymphoma.

All scans were reviewed on the basis of location, signal on T2, pattern of contrast enhancement, diffusion with ADC maps, and susceptibility/gradient imaging. Perfusion
Results

PCNSL often has a characteristic appearance on both CT and MR imaging [Figure 1]. This is due to its hypercellular nature with high nuclear/cytoplasmic ratio causing disruption of the blood–brain barrier, and its predilection for the periventricular and superficial locations, often in contact with ventricular or meningeal surfaces (5,6). In our study, 51.6% of PCNSLs in immunocompetent population showed classical MRI findings in terms of location and signal characteristics like that of a single lesion in usual periventricular location or a butterfly lesion involving anterior callosum which is hypointense on T2W images (increased cellularity), showing homogenous enhancement with contrast, presence of restricted diffusion and no blooming on susceptibility weighted images/gradient images with presence of a lipid peak on MR spectroscopy.

- Solitary versus multiple lesions: Of the total number of PCNSLs in immunocompetent population (n = 31), 51.6% (n = 16) had typical MRI characteristics. All these lesions were solitary [Figure 1]. Some of them had more than one lesion [Figure 2]. In the 48.3% of atypical group (n = 15), 33.3% (n = 5) had multiple lesions (more than two) [Figures 3].

- Location: Of the 51.6% of PCNSLs which had classic MRI appearance, the lesion which was single; was located in corpus callosum, basal ganglia, frontal and parietal locations. In our study, 58% showed atypicality with...
respect to its location. Lesions were also noted to involve multiple locations (more than two) in each patient of the atypical group.

In the 15 cases of atypical group of the total \( n = 31 \) PCNSLs, all the lesions were present in unusual locations like cortical and subcortical \( (n = 3) \) [Figures 2 and 4], hypothalamus and vermis \( (n = 2) \) [Figures 3 and 5], meningeal \( (n = 2) \) [Figure 6], dural based \( (n = 2) \) [Figure 7], PNS \( (n = 2) \) [Figure 5], intraventricular location \( (n = 3) \) [Figures 8 and 9], hypothalamus and midbrain \( (n = 1) \) [Figure 10], thalamopeduncular location \( (n = 2) \) [Figure 11] and cerebellum \( (n = 2) \) [Figure 12].

- **MR signals**: About 13.3% of the cases of the total 48.3% atypical group showed unusual MRI characteristics. Lesions \( (n = 2) \) were hyper intense on T2W images and had associated peripheral restriction on DW images [Figures 2 and 12].

- **Enhancement patterns**:
  - The contrast enhancement varied in atypical PCNSL group (48.3%). Of the 48.3%, 13.3% showed peripheral rim enhancement \( (n = 2) \) [Figures 2 and 12], 13.3% revealed mixed leptomeningeal-pachymeningeal enhancement \( (n = 2) \) [Figure 6], and 13.3% had

Associated cerebellar folia enhancement ($n = 2$) [Figure 12] in the lesions located in cerebellum. There was cranial nerve enhancement in one case 6.6% ($n = 1$) [Figure 5]. In one case ($n = 1$), there was no enhancement in one of the lesions located in cerebellum which was hypo intense on T2 W image [Figure 11].

**Functional imaging:**
- DWI: Peripheral restriction on diffusion was noted in 13.3% ($n = 2$), of the atypical PCNSL group (48.3%). In these two cases, the lesions were presumed to be necrotic as evident on T1W, T2W images [Figures 2 and 12]. In one case ($n = 1$), there was no restricted diffusion noted in one of the lesions located in cerebellum which was hypo intense on T2 W image [Figure 11], although the larger lesion in the same patient showed restricted diffusion. However, the ADC ratio in this lesion was 1.05.
- SWI: Blooming on a gradient image was noted in 6.6% ($n = 1$) of the 48.3% atypical PCNSL group which could suggest bleed/calcification [Figure 4]. Perfusion imaging done in few cases ($n = 5$) showed reduced cerebral blood volume (CBV). The low CBV in lymphoma could be due to the angiocentric growth pattern and the resultant intensity time curve is characteristic for a lymphoma. Multivoxel MR spectroscopy performed in limited cases ($n = 6$) revealed increased choline, reduced N-acetyl aspartate (NAA) and a lipid peak at 1.2 ppm.

Incidental findings: There was an associated right PCA (posterior cerebral artery) territory subacute infarct in one case of lymphoma at parafalcine location [Figure 7] among the atypical group.

Figure 7 (A-G): History – A 48-year-old immunocompetent man presented with history of headache for 1 month. History of left sided limb weakness progressive in nature in the past 3 months. On MRI, there was an extra axial dural-based lesion along the right parafalcine location isointense on T1 (A), hypointense on T2 (B) that showed homogenous enhancement on post contrast study (C) and restricted diffusion on diffusion weighted and apparent diffusion coefficient images (D and E). There is resultant subfalcine herniation to the left side due to the mass effect. Subacute infarct noted in the right PCA territory seen as hyperintensity on FLAIR image (F) with gyral enhancement (arrow) on post-contrast T1 W image (G)

Figure 8 (A-D): History – 13-year-old immunocompetent girl presented with a history of headache associated with nausea and vomiting for 3 months. MRI showed a midline posterior fossa lesion that involved the fourth ventricle which was isointense on T1 W (A), hypo intense on T2 W (B) images, hyper intense on FLAIR (C) with homogenous enhancement on post-contrast study (D). Diffusion and advanced sequences were not done because of the patient’s inability to hold still
Discussion

In this retrospective study, we evaluated the MRI findings of 31 histologically confirmed cases of PCNSL in immunocompetent patients, divided them into typical and atypical groups based on the location and MRI characteristics, and focused to review the spectrum of atypical MRI features in this cohort.

The average age of presentation was 42.12 years with a male preponderance of 58.0% which is relatively less as compared to previous data by Slone et al.[13] There was no significant difference for mean age between solitary and multifocal lymphomas which is similar to the study by Zhang et al.[5] There was male predominance consistent with previous reported data.[14,15]

In our study, 33.3% (n = 5) had multiple lesions out of 48.3% (one case showing six lesions) in the atypical category which is concordant with the study done by Zhang et al.[5] and Ali Fazeli et al.[16] In our study, 48.3% showed atypicality with respect to its location as opposed to the usual periventricular location or a butterfly lesion involving anterior callosum. Zhang et al.[5] reported 24% of the lesions in the posterior fossa. About 13.3% cases (n = 2) in the atypical group showed unusual MRI characteristics where the lesion was hyperintense on T2W images with peripheral restriction on DW images. The reason for this appearance is presumed to be due to the central necrosis within the lesion. Necrosis is usually noted in immunocompromised patients and is very rarely encountered in PCNSL in immunocompetent patient population. Mansour et al.[7] did not observe necrosis in his study group.

We observed variable contrast enhancement in the atypical PCNSL group (48.3%). These include peripheral rim enhancement in 13.3%, mixed leptomeningeal and pachymeningeal enhancement in dural-based lesions in 13.3%, cerebellar folia enhancement in 13.3%, and cranial nerve enhancement (7–8th nerve complex) in 6.6% of patients in atypical category. Variable contrast enhancement is also reported by Zhang et al.[5] in his study.

Heterogeneous/Peripheral restriction on diffusion was noted in 13.3% (n = 2), of the atypical PCNSL group (48.3%). However, the ADC ratio was 0.9 and 1.1 in these lesions. CNS lymphoma being a high cellular tumor would demonstrate a relative decrease in ADC values. Mansour et al.[7] in their study reported that mean normalized ADC

Hemorrhage and calcification are very rare in immunocompetent population with PCNSL. Edema which is a common feature of PCNSL was present in all the cases (n = 31) in our study. Edema was proportional to the size of the lesion. Lesions more than 4–5 cm showed moderate-to-severe edema, whereas smaller lesions revealed mild-to-moderate edema.

The limitations in our study are as follows: CT brain was not done in all the cases to compare and compliment the MR imaging characteristics. Perfusion imaging and MR spectroscopy which would have increased the diagnostic efficacy were not studied in all the cases. Since post-biopsy, all the patients were referred to a tertiary oncology institute, we could not follow-up and do further

Figure 11 (A-I): History – A 52-year-old immunocompetent female presented with headache since one and half month; right hemiparesis with deviated angle of mouth to left side for 20 days. On MRI, there was a left thalampopeduncular lesion isointense on T1W (A), hypointense on T2W (B) images with homogenous enhancement on post-contrast study (D) and restricted diffusion on diffusion weighted and apparent diffusion coefficient images (ADC) images (E, F). Another non-enhancing lesion noted in the left cerebellum (arrow) adjacent to fourth ventricle on post-contrast study (G). This was hyperintense on T2W (C), FLAIR (not shown in the figure), and showed no restricted diffusion on diffusion weighted and apparent diffusion coefficient images (H and I)

Figure 12 (A-H): History – A 50-year-old immunocompetent man presented with history of headache associated with vomiting since a month. History of gait unsteadiness for 1 month, right > left. MRI revealed a lesion, in the right cerebellum which is isointense on T1W (A), hypointense on T2 W (B) images with homogenous enhancement of the lesion and adjacent cerebellar folia on post-contrast study (C). There is another lesion (arrow) in the right inferior cerebellar region with central hypo intensity on T1 W (E), hyperintensity on T2 W (F) images and showed a thick, irregular rim-enhancement and non-enhancing central necrosis (G) with restricted diffusion in the periphery on diffusion weighted images (D and H) [and apparent diffusion coefficient not shown in the figure].

values (ADC$_{wm}$/ADC$_{wm}$) for all lesions measured (including the non-diffusion-restricted ones) was 1.4. The ADC ratio range reported was between 0.91 and 3.00.[7] Blooming on a gradient image was noted in 6.6% of the 48.3% atypical PCNSL group. It is suggestive of bleed/calcification. Mansour et al.[7] in their study of CNS lymphomas in immunocompetent patients observed hemorrhage in 2 of the 36 lesions, which were hyperintense on T1 and found no calcification in any of the lesions. Ali Fazeli et al.[16] and Zhang et al.[5] also observed insignificant number of cystic changes and hemorrhage within tumor in their study. Hemorrhage in lymphomas is noted in immunocompromised group treated and presence of calcification with the lesion is noted in patients who are treated with radiation or antineoplastic agents.[11] Hemorrhage and calcification are very rare in immunocompetent population with PCNSL.

Edema which is a common feature of PCNSL was present in all the cases (n = 31) in our study. Edema was proportional to the size of the lesion. Lesions more than 4–5 cm showed moderate-to-severe edema, whereas smaller lesions revealed mild-to-moderate edema.

The limitations in our study are as follows: CT brain was not done in all the cases to compare and compliment the MR imaging characteristics. Perfusion imaging and MR spectroscopy which would have increased the diagnostic efficacy were not studied in all the cases. Since post-biopsy, all the patients were referred to a tertiary oncology institute, we could not follow-up and do further
To summarize our study with what has been described in the literature for PCNSL in immunocompetent patient population, PCNSLs mostly present in the 5th or 6th decade and they can present as a solitary lesion or can be multifocal. Lesions are typically located in the frontal lobe, corpus callosum, or the basal ganglia and may appear as a "butterfly lesion." However, they can also be present in various locations in the brain. On pre-contrast MR images, tumors usually appear hypo- or isointense on T1WI and T2WI and commonly show homogenous enhancement. Again, enhancement is variable especially if the lesions are multifocal and occur in unusual locations. Although calcifications, necrosis, and hemorrhage are rare findings, they can still be encountered on imaging. New imaging techniques (MRS, PWI, and DWI with ADC values) become important when the characteristic imaging features on conventional imaging are absent.

Conclusion

Although rare, PCNSLs in immunocompetent patients may have a multitude of MR imaging findings, and knowledge of these should aid in classifying tumors as PCNSLs, which in turn helps to avoid steroid administration/excision instead of a stereotactic biopsy as the next step in management. Along with the obvious lesion, it is important to look for associated MR imaging findings, such as sub-ependymal enhancement, enhancing nodules in unusual locations, cranial nerve enhancement, cerebellar folia enhancement, and/or meningeal enhancement, which aid in the diagnosis.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References