MRI Patterns of Non-Enhancing T2-FLAIR Hyperintensity Lesions in Primary CNS Lymphoma

Hao Liu

The first Affiliated hospital of Zhengzhou University

Haiman Hou

The First Affiliated Hospital of Zhengzhou University

Xiaoge Liu

The First Affiliated Hospital of Zhengzhou University

Jie Bai

The First Affiliated Hospital of Zhengzhou University

Yong Zhang

The First Affiliated Hospital of Zhengzhou University

Jingliang Cheng (✉ chengjl-2008@163.com)

Zhengzhou University First Affiliated Hospital <https://orcid.org/0000-0003-0255-662X>

Research article

Keywords: primary central nervous system lymphoma, magnetic resonance imaging, T2- FLAIR sequences, non-enhancing T2-FLAIR hyperintensity lesions

Posted Date: August 26th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-52137/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose: The non-enhancing T2-FLAIR hyperintensity lesions at a distance from the enhancing tumor site at baseline have been observed of neoplastic nature in primary central nervous system lymphomas (PCNSL). Our aim was to explore the incidence, location, and morphology of the non-enhancing T2-FLAIR hyperintensity lesions in PCNSL.

Methods: We retrospectively reviewed patients diagnosed with immunocompetent PCNSL at our institution. We identified and evaluated the T2-FLAIR hyperintensity lesions without enhancement that markedly decrease or disappear in the MRI after treatment. MRI characteristics of PCNSL at initial presentation were analyzed and compared between patients with non-enhancing T2-FLAIR hyperintensity lesions and patients without these lesions.

Results: Among 89 patients, 10 patients (11.2%) were found to have non-enhancing T2-FLAIR hyperintensity lesions at a distance from the enhancing tumor site at baseline, that showed a markedly decrease or disappearance after treatment. The locations of these lesions were as follows: the juxtacortical and deep white matter in 7 lesions, periventricular white matter in 2 lesions, basal ganglia in 1 lesion, and infratentorial area in 1 lesion. Baseline MRI characteristics in patients with non-enhancing T2-FLAIR hyperintensity lesions exhibited a higher rate of multiple enhancing lesions ($P = 0.027$), and bilateral enhancing lesions ($P = 0.001$), compared to patients without non-enhancing T2-FLAIR hyperintensity lesions.

Conclusion: Non-enhancing T2-FLAIR hyperintensity lesions at a distance from the enhancing tumor lesions in patients with PCNSL, which indicated of neoplastic nature, was not rare. Those non-enhancing lesions should be incorporated in the initial evaluation of tumor burden and response in the follow up.

Introductions

Primary central nervous system lymphomas (PCNSL) are mainly diffuse large B-cell lymphomas (DLBCL) that restricted to the brain, meninges, and eye at the time of diagnosis [1,2]. It accounts for 6% of all intracranial malignant tumors and for 1-2% of all lymphomas [3]. Treatment for PCNSL has been advanced significantly with improved survival for this rare and aggressive lymphoma of the CNS after high-dose methotrexate-based chemotherapy. This is particularly true for younger patients and those with a good performance status. However, the 5-year survival proportion remains low [4].

Magnetic resonance imaging (MRI) with contrast enhancement is the most sensitive imaging modality when PCNSL is suspected. Typical characters in immunocompetent patients with PCNSL are intense and homogeneous enhancement with well-defined borders, usually localized in the periventricular areas [5-7]. Non-enhancing lesions in PCNSL are considered rare [8-11]. The most commonly used response criteria of treatment are those published by the International PCNSL Collaborative Group (IPCG), which include MRI findings [12]. MRI response criteria rely on the changes of contrast enhancement measures.

It has been observed that the non-enhancing T2-FLAIR hyperintensity lesions at a distance from the enhancing tumor site at baseline have the neoplastic nature [13]. However, the incidence, location, and shape of these non-enhancing T2-FLAIR hyperintensity lesions in PCNSL are still poorly characterized.

Materials And Methods

Patients

We retrospectively reviewed consecutive patients with all newly diagnosed immunocompetent PCNSL patients between 02/2009 and 09/2018 at our institution.

Eligibility criteria of this study included: (1) complete and available patient chart; (2) histologically confirmed diffuse large Bcell lymphoma confined to the brain at initial diagnosis, without evidence of non-CNS involvement; (3) had MRI images including at least T2-FLAIR, T2WI, T1WI, and T1WI with contrast-enhancement at baseline and follow up; (4) age over 18 years old; (5) patients didn't receive corticosteroid treatment before baseline MRI. Patients with poor images quality were excluded. The study was approved by the ethics committee of the First Affiliated Hospital of ZhengZhou University (No. 2019-KY-231)

Neuroimaging Assessment

Evaluation of MRI images were performed at baseline, before histological diagnosis and initiation of corticosteroid treatment, and at the time of following up after treatment. The MRI parameters included at least T1WI, T1WI with gadolinium injection, T2WI, and T2-FLAIR sequences. All MRI images were reviewed by two radiologists blinded to individual patient outcomes. Disagreements were resolved with consensus.

MRI analysis of non-enhancing T2-FLAIR hyperintensity lesions of PCNSL

Initially, white matter hyperintensities in axial T2-FLAIR sequences of cerebral MRI were evaluated in all patients at the baseline and following up. Then, we identified the white matter hyperintensity lesions without enhancement that markedly decrease or disappear in the following-up MRI. The information including number, anatomical site, shape of those lesions was recorded. The location of lesions was divided into periventricular white matter, deep white matter, juxtacortical white matter, internal capsule, and infratentorial white matter. Infratentorial localization was defined as lesions in the brainstem and/or the cerebellum.

MRI analysis of enhancing lesions of PCNSL

The following characteristics including number, lateralization, anatomical location, and contrast enhancement pattern of the PCNSL at initial presentation on MRI were analyzed and documented. Lateralization was based on the Talairach atlas; deep lesions were defined as lesions in periventricular regions, basal ganglia, brainstem, and/or cerebellum according to previous study [14]. Infratentorial

localization was defined as lesions in the brainstem and/or the cerebellum. Enhancement pattern included homogeneous and heterogeneous enhancement. MRI characteristics of PCNSL at initial presentation were compared between patients with non-enhancing T2-FLAIR hyperintensity lesions and patients without these lesions.

Statistical Analysis

Clinical characteristics and imaging profiles are reported as means $\pm$ standard deviations for continuous variables. Categorical variables are reported as proportions. The independent samples Mann–Whitney U-test was used to compare continuous variables. Fisher's exact test was used to compare dichotomous variables. Significance was set at $P < 0.05$. All statistical analyses were performed using SPSS, Version 25.0 (IBM Corp., Armonk, NY, USA)

Results

Patient Characteristics

At the time of analysis, a total of 89 patients were included in this neuroimaging study. The mean age of patients was 54.7 ± 12.3 years, and 33.7% were male. 20 (22.5%) received stereotactic biopsy and 69 (77.5%) patients underwent surgical resection. Then all patients were given methotrexate-based chemotherapy. Demographics and baseline MRI characteristics of patients were detailed in Table 1.

Characteristics of non-enhancing T2-FLAIR hyperintensity lesions

Ten patients (11.2%) were found to have non-enhancing T2-FLAIR hyperintensity lesions at a distance from the enhancing tumor site at baseline, and these lesions showed a markedly decrease or disappearance after treatment. Total 11 lesions were confirmed in these 10 patients. One lesion markedly decreased, and ten lesions disappeared after treatment. The mean age of those patients was 53.9 ± 11.2 years, and 4 (40%) were male.

Among these lesions, seven (63.7%) lesions located in the juxtacortical and deep white matter. Two (18.2%) lesions involved periventricular white matter. One (9.1%) lesion located in the basal ganglia, and one (9.1%) lesion located in the infratentorial area. Those lesions showed large volume, and irregular shape (Fig1, 2). Four lesions located in the right hemisphere, and the other seven lesions located in the left hemisphere.

Comparison of baseline demographics and MRI characteristics between patients with non-enhancing T2-FLAIR hyperintensity lesions and patients without non-enhancing T2-FLAIR hyperintensity lesions

Demographic information and MRI characteristics in patients with or without non non-enhancing T2-FLAIR hyperintensity lesions were detailed in Table 2. Age and gender showed no significant difference between two groups. Patients with non-enhancing T2-FLAIR hyperintensity lesions ($n = 10$) exhibited a higher rate of multiple enhancing lesions (60.0% vs 24.1%, $P = 0.027$), and a higher rate of multiple

enhancing lesions (70.0% vs 19.0%, $P = 0.001$), compared to patients without non-enhancing T2-FLAIR hyperintensity lesions ($n = 79$). There were no significant differences in other radiological parameters including location, enhancement pattern between these two groups.

Discussion

The aim of this study was to analyze the prevalence and characters of non-enhancing T2-FLAIR hyperintensity lesions of neoplasia nature in PCNSL patients. Better understanding of the pattern and mechanism of non-enhancing T2-FLAIR hyperintensity lesions is vital for early detection and accurate evaluation of the true burden of disease, potentially guiding the management.

Of 89 PCNSL patients, we observed that 10 (11.2%) patients had non-enhancing T2-FLAIR hyperintensity lesions at a distance from the enhancing lesions that markedly decrease or disappear. This dynamic change indicated that these white matter non-enhancing T2-FLAIR hyperintensity lesions had neoplastic nature. It has been reported that the prevalence of this phenomenon was about 23% [13]. In our research, the most frequently involved locations of non-enhancing T2-FLAIR hyperintensity lesions were deep and juxtacortical white matter. We found that patients with non-enhancing T2-FLAIR hyperintensity lesions exhibited significantly more multiple enhancing tumor lesions ($p = 0.027$) and bilateral enhancing lesions ($p = 0.001$) compared to the patients without non-enhancing T2-FLAIR hyperintensity lesions. The underlying mechanism of this phenomenon is still unknown. The consideration of PCNSL as a whole brain disease might contribute to this [15].

Pathology reveals that PCNSL is highly proliferative tumor cells in an angiocentric growth pattern, in which lymphoma cells accumulate around small and medium-sized blood vessels [16]. During the angiotropic invasive growth of tumor, tumor cells arrange themselves centripetally around the Virchow–Robin space and show a sleeve-like infiltration pattern. When those lesions grow larger, this will lead to disruption of the blood-brain barrier and enable their detection by virtue of pathological contrast enhancement. We thought the non-enhancing lesions might be the early phase of lymphoma, while they have not yet disrupted the blood-brain barrier. Routine contrast enhanced MRI only reflects the damage of the blood brain barrier, but not the degree of tumor angiogenesis. It is important to keep in mind that contrast enhancement is a surrogate for disruption of blood-brain barrier, which does not exhibit the true extent of tumor in the central nerve system. Very few PCNSL cases have been reported that do not have contrast enhancement [9,11]. Most of those cases exhibited a diffuse brain infiltration with lymphoma cells. Those diseases include lymphomatosis cerebri and intravascular lymphoma (IVL), a rare variant of aggressive (usually B cell) non-Hodgkin's lymphoma with selective growth of neoplastic cells within blood vessel lumina.

Recognizing the features of non-enhancing T2-FLAIR hyperintensity lesions that of neoplastic nature is key for early detection. However, it is challenging to distinguish the non-enhancing lymphomatous infiltration from non-specific white matter hyperintensities lesion, which can be caused by diverse etiologies, including migraine, stroke, dementia, and healthy aging [17-19]. We observed that most of non-

enhancing T2-FLAIR hyperintensity lesions of tumor nature mostly located in deep and juxtacortical white matter, with relatively large volume and irregular shape. Those characters might be helpful to differentiate non-enhancing white matter high signal lesions of tumor nature from other diseases. MRI spectroscopy and PET scan should be investigated as complementary tools. However, there is no specific diagnostic method, and the most important is the follow up.

More importantly, knowing the features of non-enhancing T2-FLAIR hyperintensity lesions that of neoplastic nature is key for accurate evaluation of tumor burden. This might provide potential insight into the mechanisms of PCNSL pathogenesis, as well as help develop appropriate strategies of treatment. It is generally appreciated that the radiographic appearance of the tumor underestimates the disease extent [15]. Our result was consistent with this. However, non-enhancing lesions have not been taken into consideration in the current IPCG response criteria [12]. According to IPCG criteria, lack of contrast-enhancing lesions in the absence of other lymphoma manifestations is regarded as complete response in PCNSL. Non-enhancing T2-FLAIR hyperintensity lesions that of neoplastic nature should be incorporated in refined criteria defining response and progression in PCNSL. Previous research has reported that the non-enhancing high signal could become the relapsing site of tumor during the follow up [13], though we did not find this. Perhaps it is because of the small sample size in our study.

Our study has several limitations. First, it is an observational, retrospective cohort study, which may generate some biases due to confounding factors. Second, the sample size is relatively small in our study. Third, MRI scans were obtained in different type of scanner and imaging parameters, but all 3 T scanner. There was no systematic difference in diagnostic imaging qualities which influence the assessment.

Conclusions

The present study found that 11.2% of patients with PCNSL display non-contrast enhancing lesions at a distance from the enhancing tumor lesions. The remarkably decrease or disappearance of these white matter lesions after treatment indicated their neoplastic nature. Those lesions should be incorporated in initial diagnosis, and evaluation of response and progression in the follow up. However, further prospective studies are needed to investigate the underlying mechanism and clinical consequences of those lesions in PCNSL patients.

Abbreviations

PCNSL: primary central nervous system lymphomas; DLBCL: diffuse large B-cell lymphomas; MRI: Magnetic resonance imaging; IPCG: International PCNSL Collaborative Group; IVL: intravascular lymphoma

Declarations

Acknowledgements

NO

Author Contributions

H. Liu, H.-M. Hou, and J.-L. Cheng conceived and designed this study; H. Liu, J. Bai and X.-G. Liu were involved in the collection of the data; H.-M. Hou and Y. Zhang analyzed the data; H. Liu and H.-M. Hou wrote the manuscript. All authors critically reviewed the results and the manuscript.

Funding

None

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee of the First Affiliated Hospital of ZhengZhou University (No. 2019-KY-231). Because our study is retrospective, and we collected and analyzed the data of enrolled patients by reviewing their electronic medical records. The information of enrolled patients is anonymous. The collection, analysis and publication of the data will not infringe enrolled patients' health, safety and privacy. Informed consent was obtained orally from the included patients by telephone.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹MRI Department, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China

²Neurology Department, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China

References

1. Korfel A, Schlegel U (2013) Diagnosis and treatment of primary CNS lymphoma. *Nature reviews Neurology* 9 (6):317-327. doi:10.1038/nrneurol.2013.83
2. Grommes C, DeAngelis LM (2017) Primary CNS Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 35 (21):2410-2418. doi:10.1200/JCO.2017.72.7602
3. Villano JL, Koshy M, Shaikh H et al (2011) Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *British journal of cancer* 105 (9):1414-1418. doi:10.1038/bjc.2011.357
4. Ostrom QT, Gittleman H, de Blank PM et al (2016) American Brain Tumor Association Adolescent and Young Adult Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro-oncology* 18 Suppl 1:i1-i50. doi:10.1093/neuonc/nov297
5. Sutherland T, Yap K, Liew E et al (2012) Primary central nervous system lymphoma in immunocompetent patients: a retrospective review of MRI features. *Journal of medical imaging and radiation oncology* 56 (3):295-301. doi:10.1111/j.1754-9485.2012.02366.x
6. Brandao LA, Castillo M (2016) Lymphomas-Part 1. *Neuroimaging clinics of North America* 26 (4):511-536. doi:10.1016/j.nic.2016.06.004
7. Zhang D, Hu LB, Henning TD et al (2010) MRI findings of primary CNS lymphoma in 26 immunocompetent patients. *Korean journal of radiology* 11 (3):269-277. doi:10.3348/kjr.2010.11.3.269
8. Bathla G, Hegde A (2016) Lymphomatous involvement of the central nervous system. *Clinical radiology* 71 (6):602-609. doi:10.1016/j.crad.2016.02.006
9. Lachenmayer ML, Blasius E, Niehusmann P et al (2011) Non-enhancing primary CNS lymphoma. *Journal of neuro-oncology* 101 (2):343-344. doi:10.1007/s11060-010-0258-x
10. Fischer L, Koch A, Schlegel U et al (2011) Non-enhancing relapse of a primary CNS lymphoma with multiple diffusion-restricted lesions. *Journal of neuro-oncology* 102 (1):163-166. doi:10.1007/s11060-010-0287-5
11. Kuker W, Nagele T, Korfel A et al (2005) Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. *Journal of neuro-oncology* 72 (2):169-177. doi:10.1007/s11060-004-3390-7
12. Abrey LE, Batchelor TT, Ferreri AJ et al (2005) Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 23 (22):5034-5043. doi:10.1200/jco.2005.13.524
13. Tabouret E, Houillier C, Martin-Duverneuil N et al (2017) Patterns of response and relapse in primary CNS lymphomas after first-line chemotherapy: imaging analysis of the ANOCEF-GOELAMS prospective randomized trial. *Neuro-oncology* 19 (3):422-429. doi:10.1093/neuonc/now238
14. Ferreri AJ, Blay JY, Reni M et al (2003) Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *Journal of clinical oncology : official*

- journal of the American Society of Clinical Oncology 21 (2):266-272. doi:10.1200/jco.2003.09.139
15. Lai R, Rosenblum MK, DeAngelis LM (2002) Primary CNS lymphoma: a whole-brain disease? Neurology 59 (10):1557-1562. doi:10.1212/01.wnl.0000034256.20173.ea
16. Camilleri-Broët S, Martin A, Moreau A et al (1998) Primary central nervous system lymphomas in 72 immunocompetent patients: pathologic findings and clinical correlations. Groupe Ouest Est d'étude des Leucénies et Autres Maladies du Sang (GOELAMS). American journal of clinical pathology 110 (5):607-612. doi:10.1093/ajcp/110.5.607
17. Trauninger A, Leél-Ossy E, Kamson DO et al (2011) Risk factors of migraine-related brain white matter hyperintensities: an investigation of 186 patients. The journal of headache and pain 12 (1):97-103. doi:10.1007/s10194-011-0299-3
18. Wiszniewska M, Devuyst G, Bogousslavsky J et al (2000) What is the significance of leukoaraiosis in patients with acute ischemic stroke? Archives of neurology 57 (7):967-973. doi:10.1001/archneur.57.7.96719. Gootjes L, Teipel SJ, Zebuhr Y et al (2004) Regional distribution of white matter hyperintensities in vascular dementia, Alzheimer's disease and healthy aging. Dementia and geriatric cognitive disorders 18 (2):180-188. doi:10.1159/000079199

Tables

Table 1. Patient demographics and baseline MR imaging characteristics

Clinical and Baseline Neuroimaging Characteristics	Values
Age(years)	54.7 ±12.3
Male	30(33.7%)
Number of enhancing lesion(s)	
≤2	64(71.9%)
Diffuse (> 2)	25(28.1%)
Lateralization	
Left	26(29.2%)
Right	29(32.6%)
Bilateral	22(24.7%)
Midline	12(13.5%)
location	
Deep [#]	62(69.7%)
Superficial	17(19.1%)
deep and Superficial	10(11.2%)
Infratentorial lesions	18(20.2%)
Enhancement type	
Homogeneous	72(81.9%)
Heterogeneous	17(19.1%)
Treatment	
Biopsy +chemotherapy	20(22.5%)
Surgery + chemotherapy	69(77.5%)

[#]Deep includes corpus callosum, basal ganglia, brainstem and/or cerebellum

Table 2. Comparison of baseline demographics and MRI characteristics between patients with non-enhancing T2-FLAIR hypersignal lesions and patients without non-enhancing T2-FLAIR hyperintensity lesions

Baseline Characteristics	Patients with non-enhancing T2-FLAIR hyperintensity lesions (n=10)	Patients without non-enhancing T2-FLAIR hyperintensity lesions (n=79)	P
Age(years)	53.9±11.2	54.8±12.5	0.837
Male	4(40.0%)	26(32.9%)	0.728
Number of enhanced lesion(s)			
≤ 2	4	60	0.027*
Multiple (> 2)	6	19	
Lateralization			
Left	1	25	0.001*
Right	0	29	
Bilateral	7	15	
Midline	2	10	
location			
Deep [#]	7	55	0.583
Superficial	1	16	
Deep and Superficial	2	8	
Enhancement type			
Homogeneous	9	63	0.680
Heterogeneous	1	16	

*mean significant differences

[#] Deep includes corpus callosum, basal ganglia, brainstem and/or cerebellum

Figures

Figure 1

Male, 43 years old a, b, c Axial T2-FLAIR images showed patchy irregular high signal lesions in left deep white matter and juxtacortical white matter (white arrow). d, e, f Those lesions were not enhanced on axial T1-weighted images with contrast enhancement. g, h, i After treatment in the follow-up, axial T2-FLAIR images revealed that the previous high signal lesions disappeared

Figure 2

Female, 40 years old a, b Axial T2-FLAIR images showed irregular high signal lesions in left periventricular white matter (white arrow). c, d Those lesions were not enhanced on axial T1-weighted images with contrast enhancement. e, f After treatment in the follow-up, axial T2-FLAIR images revealed that the previous high signal lesions disappeared