Author’s response to reviews

Title: Primary central nervous system small lymphocytic lymphoma in the bilateral ventricles: two case reports

Authors:

Rongjing Guo (guorongjing533@126.com)
Xiaolong Zhang (long7878521@163.com)
Chunxiao Niu (409433694@qq.com)
Yibin Xi (xiyibin@fmmu.edu.cn)
Hong Yin (yinhong@fmmu.edu.cn)
Hong Lin (tdneuroa@fmmu.edu.cn)
ting chang (changting1981@163.com)

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Author’s response to reviews:

Dear editors,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate the editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript, entitled "Primary central nervous system small lymphocytic lymphoma in bilateral ventricles: two case reports" (NURL-D-19-00262R1). We have studied reviewer’s comments carefully and have made revision accordingly. A point-to-point set of responses to the four reviewers is included below, with R1.2 referring to Reviewer #1, comment #2.

akira tenpaku (Reviewer 1): I think this manuscript is very interesting and useful for readers of BMC Neurology. Additional explanations would be useful to get further understanding of the readers. I recommend that authors should explain the following 4 points.

R1.1 How about the diffusion-weighted image (DWI) in MRI?
Response: Yes, these two patients completed DWI MRI scan. The lesions showed no diffusion restriction on DWI and now we have added the description on DWI in details in the revised manuscript.

R1.2 How to perform the biopsy on patient 1? Stereotactic biopsy or open biopsy? And which direction approach was done?

Response: Open biopsy was performed on patient 1, using the transcallosal approach.

R1.3 How many dose of methotrexate was administered to the patients?

Response: We have added the dosage in the revised manuscript. Patient 1 was administered 7g of methotrexate in the department of Hematology of our hospital, and Patient 2 was given 8g methotrexate in the department of Hematology of No.309 of the Chinese PLA hospital.

R1.4 The overall survival periods or observation periods without disease reprogression should be described.

Response: Patient 1 was followed up for more than one year (from Feb 2018 to May 2019) without disease reprogression and the patient 2 was followed up from Nov 2017 to May 2019 without disease reprogression. We have described the follow-up periods in the revised manuscript.

Mingyang Li (Reviewer 3): Major issue:

R3.1 The language of the manuscript is far from formal article and needs to be improved.

Response: Thank you very much for your advice. The revised manuscript was critically read and modified by professionals on English writings. We hope that this re-edited manuscript would reach the publishable English standard.

R3.2 There are some undiscussed results and irrevalent outcomes and the clinical prospect of these two cases is not well discussed in the whole essay.

Response: Thank you for your helpful suggestion. We rewrote the discussion and have added more descriptions on the clinical prospect of these two cases.

Frédéric London (Reviewer 4): The authors present 2 interesting cases of primary CNS small lymphocytic lymphoma revealed by intraventricular lesions. The cases are unusual in that the lesions are confined to the ventricular system, an extremely rare location. The cases are well illustrated. However, the manuscript needs revision to be suitable for publication.
R4.1 Abstract. It is stated that the "CSF cytology and flow cytometry revealed malignant CD-19 positive clonal population." However, CSF flow cytometry is only described for patient 1. Was this analysis performed in patient 2? If not, it should be mentioned in the text.

Response: Thank you very much for your suggestion. Indeed CSF flow cytometry was not performed in patient 2, and this mistake was corrected in the revised manuscript.

R4.2 Introduction: "Small lymphocytic lymphoma (SLL) as a low-grade NHL is different from DLBCL in that its indolent and less aggressive features with good prognosis." Are there any papers to demonstrate it? Please provide a reference. What is the long-term prognosis of this subtype of lymphoma in comparison to high grade PCNSL?

Response: Thank you very much for your helpful advice. As we all known low-grade PCNSL is extremely rare, and the limited data on low-grade PCNSL derive from a few case reports and case series. The largest cohort come from Jahnke and colleagues’s1 reports. Their retrospective study characterized the clinical picture, course, and outcome of low-grade PCNSL compared with those with high-grade PCNSL. Among their cohort, 20 cases of low-grade small lymphocytic lymphoma were included. Their long-term results disclosed relatively indolent clinical course and the long survival of low-grade PCNSL compared with high-grade PCNSL, suggesting a better prognosis for low-grade PCNSL. We added this relevant references in the revised manuscript. Based on our follow-up results, these 2 patients were symptoms-free and progression-free for more than 1 year, which was consistent with Jahnke and colleagues’s report.

R4.3 Case presentation. The clinical description is poor. The authors link the headache to the brain lesions. A better description of headache should therefore be provided.

Response: Thank you very much for your advice. More information was described about headache in the revised manuscript including the location, property, intensity and exacerbating or relieving factors.

R4.4 More information is needed regarding the neurological examination of the 2 patients. No information regarding cognition is provided in the case presentation.

Response: We agree with reviewer that the description about clinical information on 2 patients is little. In the revised manuscript, we provided detailed information about the medical history and neurological examination of the patients.

R4.5 CSF: please specify the reference cute off values of the laboratory for the different analyzes

Response: Thank you for your helpful advice. The revised manuscript included the reference cut-off values of the laboratory.

R4.6 Why does the treatment differ between the 2 patients?
Response: Owing to the rarity of low-grade PCNSL and the limited data on low-grade PCNSL derive from a few case reports and pathological series, currently, no standard therapy is available for low-grade PCNSL. Most doctors adopted regimens recommended for systemic low-grade lymphoma including local irradiation and high-dosage methotrexate-based chemotherapy. Besides, 2 patients in our report were treated in different hospitals and received different treatment regimens.

R4.7 Please explain the abbreviations of H&E, Cho peak, NAA, NAA/Cr.

Response: Thank you very much for your advice. In the revised manuscript, we give the full name of these abbreviations. H&E means Hematoxylin-Eosin. Cho peak means Choline peak and NAA is the abbreviation of N-acetyl aspartate. NAA/Cr represents the ratio of N-acetyl aspartate/Creatine.

R4.8 Discussion. The authors state that the prognosis of the 2 patients was good. I wonder what argument this statement is based on, because they did not provide any information about follow-up except that the headache resolved after treatment. When was the last follow-up? Is there a follow-up MRI available after treatment? How have the lesions evolved after treatment?

Response: We are very sorry for not providing the detailed information about the prognosis of these two patients. In the revised manuscript, we described the detailed info on follow-up clinical symptoms, CSF studies, MRI results and observation periods of the patients after treatment. Patient 1 was treated with chemotherapy in a total of 5 cycles from Feb to July 2018. She had complete resolution of the headache after the last chemotherapy. Simultaneously follow-up CSF studies showed 4 white cells (normal range, <4*10^6/L) and slightly elevated CSF protein (623.4mg/L, normal range 80-430 mg/L). Simultaneously follow-up MRI showed the lesions were similar in location, size and shape compared with prechemotherapy. Thereafter she was outpatient followed and performed cranial MRI every three months. The last follow-up was performed in May 2019. The patient described no clinical symptoms and there was no significant change in the lesions showed in MRI compared with prechemotherapy. The overall follow-up period was more than one year. Patient 2 was not treated in our hospital and his follow-up CSF studies and MRI results were not available. His symptom was evaluated through telephone follow-up and the last follow-up was performed in May 2019. He showed free from symptoms and progression.

R4.9 Discussion. "This image characteristic might be due to the obstruction of pulp vein". What do the authors mean? Obstruction by what? What do 'pulp vein' mean?

Response: We are very sorry for our obscure description. Brain MRI of both patients demonstrated bilateral thalamic hyperintensity on T2WI. However, the lesions in bilateral thalamus did not present contrast enhancement. Whereas the lesions in the bilateral ventricles presented homogeneous enhancement. We presumed that the lesions in the bilateral ventricles obstructed the drainage of the Galen vein, and consequently contributed to bilateral thalamic
swelling and hyperintensity. Because Galen vein, consisted of the internal cerebral veins and basal veins, drains the deep white matter, the corpus callosum, the basal ganglia, and the upper brainstem. In addition, we observed enlarged vein in thalamus on SWI. Based on these neuroimage characteristics, we speculated bilateral thalamic swelling and hyperintensity was attributed to the obstruction of drainage vein other than the spread of tumor. We have rewritten the discussion section for clearer.

R4.10 The authors conclude that lesions enhancing homogeneously in bilateral ventricles is a typical MRI presentation of SLL, but low grade PCNS lymphoma frequently show absent/moderate and heterogeneous/irregular post contrast enhancement in comparison to high grade PCNSL (even though significant overlap may be observed). Can the authors comment?

Response: We completely agree with the reviewer that low grade PCNSL frequently show absent/moderate and heterogeneous/irregular post contrast enhancement in comparison to high grade PCNSL. However, we observed homogeneous contrast enhancement in our patients and the diagnoses of SLL primarily in the CNS were confirmed through pathological results. It is interesting that these two cases demonstrated identical neuroimage findings. Thus we speculated such neuroimaging features might be representative of SLL primarily in bilateral ventricles.

R4.11 The authors claim that this is the first report of primary CNS SLL involving the ventricles. Has intraventricular involvement been reported with other types of PCNS lymphoma? Is there any other (non tumoral) differential diagnosis that should be considered in case of homogeneously enhancing intraventricular lesions? Adding this information would enhance the discussion.

Response: Thank you very much for your helpful suggestion. The classic location of PCNSL is supratentorial and has a predilection to involve the periventricular white matter. Basal ganglia are involved in 13% to 20% of patients. Indeed, other less typical location have been reported, such as intraventricular mass emanating from the choroid plexus, exclusive leptomeningeal disease or Meckel’s cave infiltration. In addition, the hypothalamus, brainstem, cerebellum pituitary talk, and spinal cord also can been involved. PCNSL in ventricles often cause mass effect and asymmetric obstructing hydrocephalus. Unlike high grade PCNSL and other common ventricular neoplasms, the lesions in our patients presented homogeneous contrast enhancement and did not cause mass effect and asymmetric obstructing hydrocephalus. The differential diagnosis should be done between low grade PCNSL and other non tumoral disorders located in ventricles such as toxoplasmosis, subacute infarction, and tumefactive demyelinating. This content has been added in the discussion.

R4.12 I am not sure that the radiological presentation is typical of primary CNS SLL lymphoma in comparison to other subtype of PCNSL. Therefore the conclusion should be that the presence of homogeneously enhancing intraventricular lesions should raised the hypothesis of primary CNS lymphoma (not only SLL).
Response: We completely agree with this valuable suggestion by the reviewer. As I mentioned in question 9, unlike high-grade PCNSL and other common ventricular neoplasms, the lesions in our patients did not cause mass effect and asymmetric obstructing hydrocephalus. It is interesting that these two cases demonstrated identical neuroimaging findings. Thus we speculated such neuroimaging features might be representative of SLL primarily in bilateral ventricles.

R4.13 The last part of the discussion is repetitive and should be revised for clarity.

Response: Thank you very much for your advice. We have deleted repetitive content and rewritten the last part of the discussion for clearer and more concise.

R4.14 Overall, the manuscript requires significant editing for grammar and syntax. The text is especially difficult to follow at times. There are several grammar and spelling mistakes. E.g (not exhaustive list): abstract: our reports alerts…, sympotoms ; introduction: …delay…, which would like to alert….in mind ; case presentation: multiplemyeloma ; immune-negtive ; 2rd ; discussion: the case like this,…

Response: Thank you very much for your advice. The revised manuscript was critically read and modified by professionals on English writings. We hope that this re-edited manuscript would reach the publishable English standard.

1. Reference


Thank you and best regards.

Corresponding author:

Name: Ting Chang

E-mail: changting1981@163.com
Tel: +86-29-84777741
Fax: +86-29-83552982 Address: Department of Neurology, Tangdu Hospital, the Air Force Medical University, 569 Xinsi Road, Xi’an 710038, Shaanxi Province, P.R.China