Author’s response to reviews

Title: Diffuse leptomeningeal gliomatosis initially presenting with intraventricular hemorrhage: a case report and literature review

Authors:

Min Zhu (zhumin1@126.com)
Junjun Zheng (zjj259@163.com)
Yuanzhao Zhu (846366855@qq.com)
Hui Wan (ncwanhui@sina.com)
Yuchen Wu (wuyuchen52@163.com)
Daojun Hong (hongdaojun@hotmail.com)

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Dear editors:

We are glad to have an opportunity to submit the revised manuscript. We appreciated the good suggestions raised by reviewers and editors, and carefully read and analyzed the comments. The article was revised according to these comments. We gave point-by-point response to the concerns.

We want to emphasize that it is an interesting case that primary diffuse leptomeningeal gliomatosis (PDLG) initially presented with intraventricular hemorrhage which might be caused by astrocytomas infiltrating into pial vessels. The title changed as “Diffuse leptomeningeal gliomatosis initially presenting with intraventricular hemorrhage: a case report and literature review”. We prepare this manuscript as case report. The content of this manuscript has not been published or submitted for publication elsewhere. The patient’s wife signed the informed consent according to the Declaration of Helsinki. As for the disclosure: The authors report no conflicts of interest.

Best wishes,

Yours sincerely,

Dr. Daojun Hong

Department of Neurology

The first affiliated hospital of Nanchang University

Yong Wai Zheng Street 17#, Nanchang, 330006, P.R.China

Telephone: 86-791-8869-2511; Email: hongdaojun@hotmail.com
Answers to the comments are the followings.

Professor Joseph Burns

Question 1
The authors claim that this would be the first published case of LMG presenting as ICH. By their search methods this is true. However, it would actually be the second case, the first being: Clinical Reasoning: a 52-year-old man with spells of altered consciousness and severe headaches. Burrus TM, Burns JD, Huston J 3rd, Lanzino G, Rabinstein AA, Uhm JH. Neurology. 2009 May 26;72(21):e105-10.

Reply:
The article written by Burrus TM. et al. is interesting and helpful to us. We carefully read it. Burrus TM et al. in 2009 described a case diagnosed as hemorrhagic glioblastoma of the frontal lobe adherent to the underlying dura with leptomeningeal metastases. However, intraventricular hemorrhage was first described in our patient with diffuse leptomeningeal lesions. We revised the description in the new manuscript.

Question 2
The paper is fairly well-written, but certainly needs extensive English language editing by a native speaker before being ready for publication.

Reply:
We carefully checked on grammatical usage of the article. The revised manuscript was edited by native English speaker.

Question 3
What was the patient’s blood pressure on admission? Did he have a history of hypertension? The hemorrhage seen in this patient is really intraventricular, and primary IVH without a history of trauma, hypertension, and no aneurysm or AVM would have been early indicators that something unusual was occurring.

Reply:
Yes, primary IVH without a history of trauma, hypertension, and no aneurysm or AVM would
have been early indicators that something unusual was occurring. In our patient, no history of hypertension was reported. He was admitted to our hospital with right paresis, headache and vomiting for one hour. On admission, his blood pressure was 130/80mmHg. Cerebral CT angiography underwent on day 2 after admission revealed no aneurysm and vascular malformation. Unfortunately, after ruling out aneurysm and vascular malformation, physician made a misdiagnosis as simple cerebral hemorrhage at the early stage of disease course. It was one of our aims to write the article to learn a clinical lesson. We made modification in the revised version.

**Question 4**

Line 74: what specifically was the initial treatment for decreasing ICP and vasospasm? Were corticosteroids used? If so, how much and for how long? Application and withdrawal of steroids could explain the waxing/waning course.

**Reply:**

We only used mannitol to decrease ICP and nimodipine to anti-vasospasm for 10 days. We did not use corticosteroids at the early stage of disease course. We revised the description in the new version.

**Question 5**

Line 79: the lesion referred to in the right temporal horn is actually at the right temporal tip.

**Reply:**

Yes. It is actually at the right temporal tip and it was corrected in revised manuscript. Thank you very much.

**Question 6**

What occurred between acquisition of the scans showing nodular enhancing lesions and deterioration on day 15? What was the working differential diagnosis at that time? What diagnostic tests were done and what therapy was administered?

**Reply:**

It was a great mistake to neglect the nodular enhancing lesions by the patient’s physician at the early stage of disease course. The patient was treated as a simple intraventricular hemorrhage by
mannitol and nimodipine. In fact, the clinical condition of this patient gradually improved in accordance with the outcome of cerebral hemorrhage during the first stage of clinical course. However, the patient’s condition suddenly became worse when the ruptured blood completely disappeared. A nodular mass with high density were found on the surface of right pons when physicians retrospectively analyzed the first cerebral CT. The lesions were clearer in the enhanced CT image performed at the next day of the first CT.

**Question 7**
Line 98: what was the serum glucose at the time of the first lumbar puncture?

**Reply:**
The concomitant blood glucose was 4.7mmol/L and it was added in the revised manuscript.

**Question 8**
Line 102: was flow cytometry on the CSF performed?

**Reply:**
No, flow cytometry on the CSF was not performed. We only counted the cell numbers and types by CSF cytology. We revised the descriptions in the manuscript.

**Question 9**
Which tumor biomarkers were sent? Also, were these from serum or CSF?

**Reply:**
Tumor biomarkers were included AFP, CEA, CA199, CA125, CA153, CA724, PSA, NSE and Cyfra21-1. But only serum biomarkers were examined. We revised the descriptions in manuscript.

**Question 10**
What occurred between days 15-34? What was the patient’s condition? Did he really suddenly deteriorate, or did he slowly deteriorate with sudden acceleration of his worsening on day 34? What was the differential diagnosis during this time? What diagnostic tests were done and what therapy was administered? Again, details of the use of corticosteroids is important in understanding the case?
When the patient suffered from severe headache and recurrent vomiting on day 15 after admission, cerebral CT and MRI were performed immediately. Basing on the clinical features and radiological changes, several possible disorders such as primary tuberculous meningoencephalitis, fungal infections, meningal neoplasm, metastases, and vasculitis were taken into consideration. So a series of examinations were further carried out, including thoracic-abdominal CT, PET, CSF tests, multiple blood tests, and so on. After tuberculous meningoencephalitis and fungal infections were excluded, intravenous dexamethasone (20mg for 7 days and then 10mg for 3 days) was started on day 20 after admission, but the patient’s situation showed no signs of improvement and gradually worsened daily. In the literatures, some cases were also treated with corticosteroids (Riva M. Neurol Sci. 2005; 26:129-34). We revised the description in manuscript.

Question 11
Why did the team taking care of the patient wait until day 46 to biopsy the patient? Clearly the CT with contrast and MRI, performed much earlier in the course, indicated that something much more than primary intraventricular hemorrhage was occurring.

Reply:
Unfortunately, due to the misdiagnosis, the biopsy was not considered by physician at the initial 15 days after admission. Physician was aware of the importance of the biopsy to definitive diagnosis after the clinical condition began to a sudden turn for deterioration with intracranial hypertension and cerebral hernia. However, the patient’s guardian (his wife) had not signed the informed content until day 46 after admission.

Question 12
Lines 116-120: this information should be supplied earlier in a brief single paragraph methods section.

Reply:
We revised the descriptions in the manuscript. We wrote this manuscript basing on the progression of disease. Actually, the complete pathological results were reported after patient died from cerebral hernia.
Question 13
What was the proximal cause of the patient’s death? Disease progression with intractable intracranial hypertension? A new hemorrhage? Complications of the biopsy?

Reply:
The patient’s situation got gradually worse and worse daily at the late stage of disease course. The cerebral CT was not performed after needle biopsy. Therefore, it is difficult to make clear to the cause of death. However, we inferred the intractable intracranial hypertension as the possible cause of the patient’s death. (1) When patient died, he gradually fell into deep coma. Bilateral pupils gradually got dilation (5mm, no reactive to light), and then breathing stop. (2) If a new hemorrhage, it maybe with sudden acceleration of his worsening, and the patient maybe present with sudden vomiting and coma. (3) The needle biopsy lesion located in the left frontal lobe, and obvious hemorrhage was not observed in the specimen. If complications of the biopsy (puncture bleeding), the left pupil will get dilation firstly, and sudden aggravation should be observed. We revised the description in manuscript.
Professor Rimas Lukas

Question 1
This work requires significant English language editing.

Reply:
We carefully checked on grammatical usage of the article. The revised manuscript was edited by native English speaker.

Question 2
This manuscripts concepts can be condensed and the work can be markedly truncated with ~1page of text and ~1page of Figures.

Reply:
We condensed some descriptions and truncated some content in the new manuscript (total page number decreased to 15 pages from 16 pages). In addition, we truncated the figure 2 as an additional file. However, the case was difficult to diagnose initially, and gave us a great lesson. We made detailed descriptions about the clinical course. Combined with literature review, we illustrated some new findings. In addition, BMC neurology is an electronic journal, and no limits to word counting. Therefore, we preferred to present with complete and detailed clinical case.

Question 3
A more definitive reference for incidence of intracranial hemorrhage in gliomas (large autopsy series? large imaging series) would be preferable to the current reference.

Reply:
We searched in Pubmed and found some references. We modified the descriptions in the revised manuscript.

Question 4
Lines 133-137 imply that a definitive diagnosis of PDLG can possibly be made radiographically.
This is not correct and the sentiment should be clarified.

Reply:
Thank you for pointing out the mistake. We revised the description in manuscript.

**Question 5**

If tissue is available it would be worthwhile to look for and comment on the presence or absence of IDH mutation (at least the most common R132H IDH1 mutation) as no one has reported on this in PDLG to my knowledge.

**Reply:**

Thank you for the good idea. IDH mutations were closely associated with gliomas. Unfortunately, there were not enough tissues to complete this work.