Author’s response to reviews

Title: Subarachnoid small vein occlusion due to inflammatory fibrosis—a possible mechanism for cerebellar infarction in cryptococcal meningoencephalitis: a case report

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Author’s response to reviews:

Dear Dr. Richard:

Thank you very much for having considered our manuscript. I am very pleased to see the favorable comments of all the Reviewers. Review 1, 2, and 3 raised 3, 9, and 5 comments, respectively. I fundamentally agree with all these comments and incorporated them the Revise version. Red indicates the parts that I changed according to Review 1, blue for Reviewer 2, and green for Reviewer 3. According to these changes, I added some sentences to make the context clear. The native medical profession and I linguistically checked the manuscript once again, and I changed or deleted very small parts. They are very trivial points (some words or a single sentence) and thus I did not indicate them to avoid complexity. Otherwise, I did not touch the original manuscript.

I hope that you would evaluate this Revision version positively.

Sincerely,

Yoshiteru Shimoda, MD, PhD
Response to Reviewers

Red indicates the parts that I have changed according to the Reviewer 1’s advices. Blue indicates the parts that I have changed according to Reviewer 2’s suggestions, and green indicates the parts revised according to Reviewer 3’s suggestions. Some of the corrections are overlapping.

To the Review 1

Thank you very much for your advice. I agree with all the points and have incorporated them to the R1 version (red color).

1. the quality of written English is inappropriate for publication in a peer-reviewed scientific journal unless it is extensively edited

Answer: We have submitted the manuscript to a professional English editing company named “Enago,” which is recommended by Springer and Elsevier.

2. The introduction is very lacking and does not set forth an appropriate transition into the actual case
3. Cerebral venous thrombosis has been extensively described in meningitis, and I do not see how this case report will contribute to any further of what is already known.

Answer to 2 and 3: Thank you for your critical advice. We agree that the cases of venous sinus thrombosis have been reported in the past; however, the pathology involved in our case was different from venous thrombosis. In our case, the pathology suggested a mechanical process that compressed the small veins in the subarachnoid space and led to congestion in the venules of the parenchyma. To avoid reader misunderstanding, we have made revisions to the title, abstract, background and throughout the entire manuscript. These revisions are shown in red.

To Reviewer 2

Thank you very much for your good advices. I agree with all nine points and have incorporated them to the R1 version (blue color).

1. It should be mentioned in the manuscript that small arteries occlusion may have also contributed to the clinical picture (in addition to the venous pathology).

Answer: Thank you for your critical advice. We mentioned the occlusion of small arteries as a cause of infarction at the discussion part. Please check at page 11, line 6-8.

2. Venous thrombosis secondary to cryptococcal meningitis is rare, but has been described before. Please refer to other reports regarding this issue (for example: "A rare cause of cerebral venous thrombosis: cryptococcal meningoencephalitis" by Senadim S et al. PMID 27025504)

Answer: Thank you for your advice. We believe that the main pathophysiology of this case is different from sinus occlusion (as described in the cited reference) because the venous sinuses were patent (confirmed by MRI). We have added a new figure to support the same. In contrast, in our case, vein occlusion was mainly demonstrated in the small veins. We agree that this issue is important and have referred to page 11, line 13.
3. Did this patient have an MR-venography? If so, and if this test was normal, then consider indicating in the title and in the manuscript that the damage was caused in the "small veins" (as opposed to large cerebral venous sinuses).

Answer: Thank you for your advice. We totally agree with this point.

We have now added Figure 2, which depicts a reconstruction of Gd-enhanced MRI to show the patency of the venous sinus. According to this data, we decided that the main reason for the observed cerebellar edema was the subarachnoid small vein occlusion. We have added more information in the figure legend and some sentences in the main document on page 6, line 10 and 11. We have also changed the title.

4. Description of some pertinent parameters in the CSF is needed:

   a. Was LP performed, and what was the opening pressure? - If LP was not applicable due to posterior fossa edema please note it in the text.

   b. Other CSF parameters (cell count, protein, glucose).

Answer: Thank you for your advice. We added the following sentences at page 7, line 3-5.

"Lumbar puncture to collect cerebral spinal fluid (CSF) was not performed until this time because of the risk of cerebral herniation. CSF from continuous ventricular drainage demonstrated mild inflammation (cell count, 36 /mm3; protein, 16 mg/dl; glucose, 113 mg/dl)."

5. If no prominent meningeal enhancement and/or nodules were found in the brain MR imaging, then indicate this in more emphasized manner in the manuscript, since this is an important negative finding in the context of cryptococcal meningitis.

Answer: I agree. We have inserted the following sentence in page 6, line 8, 9.

" Brain magnetic resonance imaging (MRI) did not reveal any prominent meningeal gadolinium enhancement or nodule "
6. In the conclusion part, I suggest considering to change part of the sentence to a more general conclusion: "In this case, the temporal change in perifocal edema and ischemic lesions suggested an etiology different from a simple arterial infarction"

Answer: Thank you for your advice.
We have modified the sentence at page 13, line 3-5. Please check.

7. Please change the term "atheromatous" to "arterial".

Answer: We have changed the term atheromatous to arterial at 3 parts. Page3, line 9, page 11, line 2, and page 19, line 3.

8. Include an insert of greater magnification in figure 3-A to demonstrate more clearly the inflammatory infiltration of the subarachnoid space.

Answer: Thank you for your advice. We have replaced figure3A and B for greater magnification to demonstrate the inflammation and fibrosis more clearly.

9. Add marks to indicate the parenchyma and the subarachnoid space in figure-3C.

Answer: Thank you for your advice. I have added marks to indicate the parenchyma and the subarachnoid space in figure 4C.

To Reviewer 3

Thank you very much for your good advice. I agree with all the points and have incorporated them to the R1 version (green color).

1. Cryptococcal infection in patient without known immunosuppression is always surprising especially when presenting as vascular incident. However we can argue that this gentleman was
far from healthy as there was a history of chronic infection and liver failure. Authors should mention that in abstract. In the body of text they should mention social situation, drug history etc. which can be relevant.

Answer: Thank you for your advice. We have inserted the patient’s information at page 3, line 8 in the abstract. In addition, we added the drug and medical history at page 6, line 4, 5.

2. Only problem I have with this case report originates from the emphasis authors put on venous origin of "stroke-like" presentation in this patient. They mentioned normal angiogram but it seems that formal venogram or at least venous phase of angiogram was not studied/done.

Answer: We have now added Figure 2, which confirms that the main venous sinuses were patent. In addition to the pathological findings, this data suggests that small veins, and not the large veins, might be occluded and led to massive edema.

3. I still would accept it; however in figure's legend authors mentioned "proliferation of endothelial cells was observed inside the inner cavity of small arteries (arrows in D, F), which implies the slow progression of arterial occlusion". Is this not a direct contradiction to title putting emphasis on venous occlusion? Was not this responsible for "slow stroke" presentation?

Answer: Thank you for your advice. I agree that the DWI high lesion observed upon initial MRI was due to the arterial occlusion. In contrast, the range of atypical edema in the left cerebellar hemisphere upon initial presentation could not be explained by arterial occlusion alone. We have now added this information on page 11, line 6–12.

4. Granuloma was found in biopsy sample, why authors suspected venous ischaemia as primary cause for lesion. Authors admit that fungi, granuloma swelling and fibrous tissue could lead to secondary venous compression and mention that "oedema was caused rather by infection rather then infarction".

These are all slightly contradictory statements. If I am not mistaken authors work with assumption that pathogenesis occurred in this order (many of the below naturally occurred
almost simultaneously): haematogenic infection spread - granuloma/fibrosis - venous occlusion - venous stroke - oedema (oedema of both granuloma and ischemia).

I would rather vote for: haematogenic infection spread - granuloma/fibrosis - endothelial proliferation/small arteries occlusion - ischemia - oedema (oedema of both granuloma and ischemia) - secondary venous occlusion.

This conclusion seems more logical and backed by pathological findings. I would be happier if case report is changed according to my comments but if there is anything I misunderstood please let me know.

Answer: Thank you for these critical points. We agree that although part of the edema might have originated from the small arterial occlusion, we could not explain that the massive edema noticed upon initial MRI (Fig1) purely arose from arterial occlusion. Small arterial occlusion was not frequently observed in the specimen. We think that the edema mainly arose from the occlusion of small veins in the subarachnoid space which may have been induced by fibrosis/granulation. We have changed part of the discussion on page 11, line 9–12 to avoid misunderstanding.

5. Is fibroid tissue (collagen) greenish/bluish in Masson's staining? Please add to legend, will be useful for clinicians without proper histology knowledge.

Answer: Thank you for your appropriate advice. We have added "which appears as green. " at page 20, line 11 in the figure legend.