Author’s response to reviews

Title: Survival of a case of Bacillus cereus meningitis with brain abscess presenting as immune reconstitution syndrome after febrile neutropenia – a case report and literature review

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Author’s response to reviews:

Response to Reviewer 1:

Page 5, line 9 - spelling mistake: immune reconstitution syndrome, not immune "reconstruction" syndrome

We modified as such, thank you.

Page 7, initial CSF result: What was the amount of RBC in the CSF? The reason for this is: could this be a traumatic tap, and hence yielded a positive PCR?

Thank you for your comment. There were no RBC detected in the CSF, excluding the possibility of a traumatic tap. We did not mention the traumatic tap issue in the manuscript, but if needed, we are ready to add the information to the manuscript.

Page 7, line 15 and 16: second CSF result - was culture or PCR sent off again? Has the treating team done investigations to rule out differential diagnosis or to confirm this is IRIS? I understand that the authors included some of these details under "discussion" section, but probably good to insert the details here in the body of the case report.

Thank you for your comment. Culture was made in every CSF sample and PCR was performed again in the fourth sample (day 19), when clinical symptoms worsened and it was negative. All other exams were made to rule out differential diagnosis. Therefore, we added the information.
“The CSF culture and PCR for B. cereus were both negative, and other diseases were excluded by the aforementioned examinations. Therefore, in concert with the increased leukocytes in peripheral blood and CSF, it was suggestive of immune reconstitution syndrome after B. cereus meningitis.”

Given that IRIS was postulated, was adjunctive therapy such as glucocorticoids considered or attempted?

We were prepared for glucocorticoids administration, but fortunately no severe neurological symptoms developed, though fever and meningisms became prominent. But if the pathogen had been as virulent as pneumococcus, we would have considered upfront administration.

“Glucocorticoid administration was considered, but not used because no severe neurological symptoms have developed.”

Page 10, line 1 and 2: Our case showed uncountable WBCs at the onset of meningitis and was complicated by brain abscesses. If authors can kindly clarify this sentence.

We intended to describe this case was one of the typical cases in terms of patient background or complications. To clarify this sentence, we modified as below.

“In comparison to the previous reports, our case shared common features, such as uncountable peripheral blood WBCs at the onset of meningitis or the complication of brain abscesses. While those are typical findings of neutropenia associated B. cereus meningitis, there are two particular features of this report.”

MRI images: Kindly add some descriptive texts to guide the readers.

According to your suggestion, we added the remarks (arrow heads and arrows) in the figure 1. And if acceptable, we would like to add another figure (figure 2), which can describe the lesions at day 32.

For all the CSF values and leukocytes, please insert reference range as well.

According to your suggestion, we inserted the reference range into the figure legend. The reference range of CSF-ADA is not shown, because the cut-off value for bacterial meningitis is not well defined.

Figure legend for Figure 1: Addition:
“The reference ranges are; Blood leukocytes 3,000-8,000/μL, CSF cells 0-5/μL, CSF protein 10-40 mg/dL, CSF glucose 50-80 mg/dL, and CSF sIL-2R, <50U/mL”

Overall commendable effort in reporting this case report. The table of 14 cases from the literature review is good, however how is the current case different from previous cases?

What is novel about this case? What would the authors want the readers to learn from the current case? It will be good if the authors can highlight certain elements of this case report to make it more novel and interesting.

Thank you for your advice. The point which is different from the previous reports are 1) new drugs and new antimicrobial combination strategy can cure this infection without sequelae, and 2) serial measurement of the markers have described the phenomenon which resembles IRIS in the central nervous systems. These are written in the discussion, but not in the conclusion. Therefore, we made a brief remarks on this.

P11L9: addition

“With serial measurement of inflammatory / immunological markers, our report described the phenomenon resembling immune reconstitution syndrome, and we also proved that contemporary antimicrobial regimens can cure this severe disease.”

Response to Reviewer 2:

Overall, an interesting case report with some worthwhile learning points.

A few relatively minor issues:

- Page 5 line 9 - reconstitution, not reconstruction

Thank you. We changed the phrase.

- Was B. cereus PCR repeated on the second CSF sample? May be useful in supporting diagnosis of IRIS (vs. persistent infection)

Thank you for comment. PCR was performed for the fourth sample (day 19), when clinical symptoms worsened and the result was negative. We added the information.

P7L16: Addition

“The CSF culture and PCR for B. cereus were both negative, and other diseases were excluded by the aforementioned examinations. Therefore, in concert with the increased leukocytes in
peripheral blood and CSF, it was suggestive of immune reconstitution syndrome after B. cereus meningitis.”

- Was toxo PCR done on either CSF sample (as a potential differential diagnosis - although I note TMP-SMX prophylaxis)

Thank you for comment. Toxo-PCR was not performed, because TMP-SMX was already administered.

- Is there any data on the use of combination antibiotic therapy in management? Any data supporting the use of linezolid specifically?

Thank you for comment. We did not find the data supporting the combination antibiotic therapy. It is probably because too small amount of B. cereus meningitis cases have been reported so far. The reason we selected linezolid are 1) its excellent penetration into the CNS and 2) the highest susceptibility among the agents for Bacillus sp. (Medicine 2019; 88: 279-283) and other gram positive bacteria.

It is regarded as one of the promising options in the treatment of meningitis (Expert Rev. Anti Infect. Ther. 2013; 11:1079–1095). Because not many cases have been reported after the emergence of linezolid, we believe this report is valuable on the point that it describes its clinical efficacy.

- Figure 1 is too busy - some useful information contained & imaging is good to include but current format is confusing

Thank you for pointing out. That’s what we have been worried about. We tried our best to change the layout, though we are not sure it works…

- Tables need headings

Thank you for pointing out. It has been missed during the submission process. We added the headings to the tables.

- Asterisks next to some figures in Table 2 - what do these refer to?

Thank you for pointing out. It has been missed during the submission process. We added the explanation. “* denotes the number of neutrophils”