Author's response to reviews

Title: Pleural Effusion as the Initial Clinical Presentation in Disseminated Cryptococcosis and Fungaemia: An Unusual Manifestation and a Literature Review

Authors:

Mayun Chen (chenmayun@126.com)
Xiaomi Wang (910966090@qq.com)
Xianjuan Yu (185819484@qq.com)
Caijun Dai (851230705@qq.com)
Dunshun Chen (chendunshun@sina.com)
Chang Yu (wzmcy@126.com)
Xiaomei Xu (xuxiaomei248@163.com)
Dan Yao (zdyadn@163.com)
Li Yang (taiyang2630@163.com)
Yuping Li (wzliyp@163.com)
Liangxing Wang (wzyxywlx@163.com)
Xiaoying Huang (zjwzhxy@126.com)

Version: 4 Date: 7 August 2015

Author’s response to reviews: see over
Dear Reviewers,

Thank you for your letter and for your comments concerning our manuscript, entitled “Pleural Effusion as the Initial Clinical Presentation in Disseminated Cryptococcosis and Fungaemia: An Unusual Manifestation and a Literature Review” (MS ID: 8385500691584000). These comments were all valuable and very helpful for revising and improving our paper, as well as for providing important guidance to our research.

We have read the comments carefully and have made corrections that we hope will meet with approval. The revised portions are marked in red in the revised manuscript. The main corrections in the paper and our response to your comments are as follows:

1. Response to the reviewer Joshua Rhein’s comments:

   Major Compulsory Revisions

   (1) Major revision 1:
   
   Comment: The dates indicated in the text have no meaning to the reader as date of admission is not indicated. I recommend that the authors count in days rather than using dates, with the day 1 being the date of admission. In general, the timeline is somewhat confusing, and would go back and clarify throughout. This is important as the timing of things could give some insight into possible immune reconstitution inflammatory syndrome (patient was immunosuppressed then given
rhG-CSF which could have stimulated immune system resulting in hyperinflammatory syndrome).

Response: We count in days in the paper.

(2) Major revision 2:
Comment: There is overall too much repetition of the case presentation in the discussion section. Do not need to go over the entire history of the case in the discussion. Recommend revising, deleting repetitious material, and instead focus on diagnosis (done well), misdiagnosis of TB (done well), treatment (discussed little), and potential reasons why this was an unusual presentation (not discussed at all).
Response: We deleted repetitious material, and added a discussion of treatment from lines 248 to 278. We also added a discussion of the potential reasons why this was an unusual presentation from lines 218 to 225.

(3) Major revision 3:
1) Comment: Why did you choose the treatment you did? The 3-drug combination (ampho, flucytosine, and voriconazole) for extended duration of 8 weeks is a little unusual and outside of many international guidelines. Are the guidelines different in China? Would
be an interesting discussion.

**Response:** We added a discussion of why we chose the treatment that we did from lines 248 to 278.

2) Comment: Why the unusual presentation? Is this a function of being a transplant patient (vs HIV-associated cryptococcosis)? Was he perhaps receiving too much immunosuppression? Did rhG-CSF contribute to the pathology of his presentation or perhaps the rapid deterioration of the patient? My guess is that it absolutely did, and would give for an interesting discussion.

**Response:** We added a discussion in response to your questions “Why the unusual presentation? Is this a function of being a transplant patient (vs HIV-associated cryptococcosis)? Was he perhaps receiving too much immunosuppression?” from lines 218 to 225. We also answered your question “Did rhG-CSF contribute to the pathology of his presentation or perhaps the rapid deterioration of the patient?” from lines 279 to 299.

**Minor Essential Revisions**

(1) Minor revision 1:

Comment: Please italicize 'C. neoformans' throughout.

**Response:** We italicized “*C. neoformans*” throughout the text.
(2) Minor revision 2:

Comment: Suggest placing sentence starting on line 35 further down in abstract, before the sentence that starts out as ‘Cryptococcus spores were found...’ on line 41.

Response: We moved the sentence starting originally on line 35 to line 43.

(3) Minor revision 3:

Comment: Need to define acronym RICU on line 40 as this is the first occurrence in the manuscript.

Response: We defined the acronym “RICU” as “respiratory intensive care unit” on line 42, as this is the first occurrence in the manuscript.

(4) Minor revision 4:

Comment: Delete 'spores' in line 41 of abstract and where it appears again in the discussion. Cryptococcus appears as budding yeast in the CSF, not spores, so the statement is inaccurate.

Response: We deleted “spores” originally on line 41 of the abstract and where it appeared again in the discussion.

(5) Minor revision 5:
Comment: Delete the sentence in line 43 as this is a complete repetition of the sentence that appeared earlier in the paragraph.

Response: We deleted the sentence originally on line 43, as this was a repetition of a sentence that appeared earlier in the paragraph.

(6) Comment: Indent new paragraphs in text.

Response: We indented new paragraphs in the text.

(7) Comment: Regarding the medication sulperazone in line 94. This may be a common antibiotic in China, but it is not used in much of the world, and readers might not be familiar with it. Suggest changing brand name to ‘cefoperazone + sulbactam’, which will help readers identify it as a broad-spectrum antibiotic.

Response: The term “sulperazone,” which was originally on line 94 (now line 93), was replaced with “cefoperazone + sulbactam.”

(8) Comment: Remove urine from the sentence in line 233. It is unusual to make a diagnosis of cryptococcosis by antigen found in urine.

Response: We removed “urine” from the sentence on line 233 (now line 227).

Discretionary Revisions
1) Comment: Delete words ‘the initial’ in line 38.

Response: We deleted the words “the initial” originally on line 38.

2) Comment: Delete comma in line 74.

Response: We deleted the comma on line 74 (now line 72).

3) Comment: Delete word ‘repeatedly’ in line 87.

Response: We deleted the word “repeatedly” on line 87 (now line 86).

4) Comment: Change ‘presented’ to ‘present’ in line 99.

Response: We changed “presented” to “present” on line 99 (now line 98).

5) Comment: Change word ‘transferred’ to ‘obtained and sent’ in line 134.

Response: We changed the word “transferred” to “obtained and sent” on line 134 (now line 135).

6) Comment: Insert word ‘opening’ between cerebrospinal and pressure in line 141.

Response: We inserted the word “opening” between “cerebrospinal” and “pressure” on line 141 (now line 142).

7) Comment: Change word ‘dehydration’ to ‘intravenous hydration’ in line 143.

Response: We changed the word “dehydration” to “intravenous hydration” on line 143 (now line 145).

8) Comment: Change word ‘target’ to ‘targeted’ in line 191.
**Response:** We change the word “target” to “targeted” on line 191 (now line 195).

2. Response to the reviewer Nelesh Govende’s comments:

Discretionary Revisions

Comment: The authors recommend using a cryptococcal antigen test in serum or CSF. CrAg testing of pleural fluid could also be recommended though there are limited data evaluating this. The case report could be improved structurally and linguistically by careful editing.

**Response:** We added information on cryptococcosis diagnosis, including CrAg testing of pleural fluid, on line 228.

The structure of the case report was improved, and the language of the text was edited carefully.

Best regards,

Yours sincerely,

Prof. Xiaoying Huang

Corresponding author

Email: zjwzhxy@126.com