Author’s response to reviews

Title: Clinical challenge: Fatal mucormycotic osteomyelitis caused by Rhizopus microsporus despite aggressive multimodal treatment

Authors:

Norbert Harrasser (norbert.harrasser@mri.tum.de)
Ingo J Banke (ingo.banke@mri.tum.de)
Matthias Hauschild (Matthias.Hauschild@tum.de)
Ulrich Lenze (Ulrich.Lenze@mri.tum.de)
Peter M Prodinger (p_prodinger@hotmail.com)
Andreas Toepfer (toepfer@tum.de)
Christian Peschel (christian.peschel@mri.tum.de)
Rüdiger von Eisenhart-Rothe (r.eisenhart-rothe@tum.de)
Ingo Ringshausen (i.ringshausen@lrz.tu-muenchen.de)
Mareike Verbeek (Mareike.Verbeek@lrz.tu-muenchen.de)

Version: 2 Date: 12 July 2014

Author’s response to reviews:

Dear Sherly Ramos,

thank you for your kind letter of July 05, 2014 outlining importance and originality of our manuscript (referee 1 and 2) and including valuable suggestions and improvements predominantly addressing style / format and not scientific content / figures of our manuscript “Clinical challenge: Fatal mucormycotic osteomyelitis caused by Rhizopus microsporus despite aggressive multimodal treatment” (MS: 1524137118130464).

Please find enclosed our revised manuscript incorporating all of the valuable suggestions and criticism raised by Referee 2 (changes in manuscript appear in bold). Our point by point response to each concern is attached.

Furthermore according to editorial requirement and Referee 2 the whole manuscript has been extensively copyedited by a native British English speaker (English teacher) to improve the style of written English. Finally according to editorial requirement “Authors’s contribution” has been reviewed critically for criteria of authorship with respective corrections.

Referee 1 accepted our manuscript without asking for changes.

We submit a revised version of our manuscript and Figures 1 and 2 in their originally submitted form (both figures were not criticized) for publication in BMC Infectious Disease. Since we have carefully addressed all of the concerns of the Reviewers, we hope this manuscript is now acceptable for publication in BMC Infectious Disease.

We are looking forward to hearing from you. Please do not hesitate to contact me
Referee 2

1. “Correction needed in spelling (several places in the manuscript). Incorrect: Rhizopus microspores
   - Correct: Rhizopus microsporus“

   Throughout the whole manuscript “Rhizopus microspores“ was replaced by “Rhizopus microsporus“. (p 3, l 59; p 13, l 263)

2. “Line 34: Would give % incidences of sinus, pulmonary, skin, and rhino
cerebral disease.“

   % incidences are now given in the text: “…rhinocerebral (39%) or pulmonary (24%), seldom to cutaneous (19%) or disseminated disease (23%) in predisposed individuals”. (p 3, ll 64-65)

3. “Please define “comprehensive osteomyelitis““

   The confusing term „comprehensive“ was replaced by “extensive”. (p 2, l. 51)

4. “Lines 64-67: Please revise sentence to provide more clarity. Line 66-67 are not clear in context of the previous lines, 64-65.“

   We agree with the reviewer and have rewritten the respective sentences to:
   “Previously reported risk factors for mucormycosis are prolonged neutropenia, immunosuppression, iron overload and prolonged hyperglycemia or manifest diabetes. Patients treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) often suffer from a combination of these risk factors [1].“ (p. 3, ll. 68-70)

5. “Lines 102-104: Please clarify. You say “Computed tomography (CT scan)
   revealed bilateral infiltrations referring to atypical pneumonia. Thus lumbar discitis was ruled out by magnetic resonance imaging (MRI).” In the context of presentation with respiratory failure, what lead to suspicion and investigation of lumbar discitis?“

   We are thankful for this highly valuable point of critique raised by the reviewer. Accordingly the paragraph has been rewritten to: “Computed tomography (CT) scan revealed bilateral infiltrations referring to atypical pneumonia and regional osteopaenia with mild focal bone lysis at the level of the lumbar spine. Lumbar spondylodiscitis was ruled out by magnetic resonance tomography imaging (MRI).” (page 5, ll 108-112)

destruction”“.  

   Accordingly the respective sentence has been rewritten to “…extensive bone and soft tissue destruction…” (p 2, l 46; p 5, ll 126)

7. “Line 126: Please specify which aspect of the thigh got worse?“

   The following information is now given: “…the properties of the wound at the
level of the proximal aspect of the thigh got worse with increasing wound secretion and shading of the surrounding skin.“ (p 6, ll 137-138)

8. “Were blood cultures performed? If so, what were the results?“
The following information is now given: "No relevant bacterial, viral or fungal cause could be identified by bronchoalveolar lavage and multiple blood culture collections during the stay on the ICU." (p 5, l 114)

9. “Was cardiac echocardiography performed? If so, what were the results?“
The following sentence has been added: “Cardiac echocardiography was performed and culture-negative endocarditis could be ruled out.“ (p 5, ll 114-116)

10. “You mention fungal markers were done. What were these fungal markers and their results?“
Despite extensive search we could not find the term “fungal markers“ in our manuscript. However the following sentences in detail describe our performed detection methods: "As the detection of mucorales-specific antigens so far has not become generally accepted for diagnostic purposes because of its relatively low sensitivity [3], currently the most effective method for mucorales-detection is PCR [2]. The internal transcribed fungal spacer (ITS) region (18S rRNA and 28S rRNA) is sequenced and the isolates are identified by e.g. Basic Local Alignment Search Tool (BLAST®). In our case we were able to identify RM by a combination of phenotypic methods (Fig. 2b-d) and genetic sequencing.” (p 9, ll 209-216)

11. “Avoid use of trade names for medications. Would review manuscript and change to generic names.“
Throughout the whole manuscript trade names for medications have been replaced by generic names: “…antithymocyte globuline…” (p 4, ll 93), “…co-trimoxazole…” (p 4, l 102)

12. “Generic names do not need to capitalized. Would review and change.“
Throughout the whole manuscript generic names now appear not capitalized: “acyclovir, co-trimoxazole and posaconazole (p 4, ll 102-103), amphotericin B (p 5, l 129), liposomal amphotericin B (p 6, l 134), posaconazole (p 6, l 135), liposomal amphotericin B and posaconazole (p 9, l 223), posaconazole (p 9, l 227).

13. “The manuscript contains very useful information and the figures are extremely useful in particular. The write up however needs extensive revision with orderly presentation of findings in the case write up as well as discussion. For example: Page 7-8, the discussion starts with zygomycetes introduction as a class which is appropriate but then goes to rhizopus microsporus, back to order mucorales. Would introduce in discussion the class, the order and then talk about genus and then species (i.e. Rhizopus microsporus).“
We are highly thankful for this valuable point of critique raised by the reviewer in order to improve our manuscript for the interested reader. The manuscript has
been rewritten accordingly with orderly presentation in background (p 3, ll 56-61) and discussion (p 7, l 164-165), strictly following the classification of fungi correctly suggested by the reviewer. In consequence the term "zygomycosis" has been replaced by "mucormycosis" throughout the whole manuscript for better reading. (p. 1, l 7; p 2, l 30 and 34; p 7, l 160; p 11, l 241-242)

14. “As described in detail below, goal and hypothesis have been stated clear in the respective paragraphs of Introduction and Discussion. Level of interest: An article of importance in its field. Quality of written English: Not suitable for publication unless extensively edited.”

As stated above the whole manuscript has been extensively copyedited by a native British English speaker (English teacher) to improve the style of written English (p 2 ll 29-41, p 2 l 44, p 2 ll 49-50, p 3 l 78, p 4 ll 81-83, p 5 ll 87-88, p 5 l 91, p 4 ll 96-97, p 4 ll 104-106, p 5 ll 130-131, p 6 ll 132-133, p 6 ll 137-138, p 6 l 141, p 6 l 148, p 7 l 151+153+154+156+160+168+174, p 8 ll 177-178+182+183+185+188+191+200, p 10 l 228+230+233+236-237, p 11 l 245+248+249+250).