Author's response to reviews

**Title:** Proven invasive pulmonary mucormycosis successfully treated with amphotericin B and surgery in patients with acute myeloblastic leukemia: a case report

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**Author's response to reviews:** see over
Dear Sirs,

Please find enclosed the revised version of our manuscript No. 2207013329577703 entitled: “Proven invasive pulmonary mucormycosis in patient with acute myeloblastic leukemia successfully treated with amphotericin B and surgery” that we submitted for publication in The Journal of Medical Case Reports. First and foremost, we would like to express our sincere thanks to both of your referees for their constructive comments. We believe that their contribution has led to an improvement in the content and the style of the manuscript. Their remarks are addressed individually on the next pages.

We hope that these alterations will not cause you any inconvenience, and that you will consider the revised version of the manuscript more satisfactory than the previous one. We hope that this revised version of our manuscript is now appropriate for publication in the The Journal of Medical Case Reports.

Many thanks for your time and consideration.

Yours Sincerely,
Prof. dr Valentina Arsic Arsenijevic,
Institute of Microbiology and Immunology
Faculty of Medicine
University of Belgrade, Serbia

(i) Response to Editor:

1. Please include the ethnicity of the patient in the abstract
   We included ethnicity of the patient in the abstract (Caucasian man).

2. Please include the ethnicity of the patient in the case presentation section of the manuscript
   We included ethnicity of the patient in the case presentation section of the manuscript (Caucasian man).

3. Please remove the dates found in the Case presentation section
   We have removed the dates in Case presentation.

4. In keeping with journal style, please remove the sub-sections from the case presentation.
   We have removed sub-sections from the case presentation section.

5. Please format your title “Proven invasive pulmonary mucormycosis in patient with acute myeloblastic leukemia successfully treated with amphotericin B and surgery” to follow the structure: A presenting with B in C: a case report
We formatted it to “Proven invasive pulmonary mucormycosis successfully treated with amphotericin B and surgery in patients with acute myeloblastic leukemia: a case report.”

7. Please also highlight (with 'tracked changes'/colored/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.
We highlighted all changes that we have made in manuscript.

8. Please also ensure that your revised manuscript conforms to the journal style (http://www.jmedicalcasereports.com/info/instructions/). It is important that your files are correctly formatted.
We checked if our revised manuscript conforms to the journal style.

(ii) Response to Reviewer #1, Prof. dr Cornelia Lass-Floerl

1) Abstract
What is the role of testing anti-Aspergillus IgM antibodies for acute infection?
Which test system was applied?
We clarified it:
“Also, routinely commercial available serological ELISA tests for the screening of high risk patients for invasive fungal infections (IFI) were done: Galactomannan (GM) and Mannan (Biorad, France), as well as anti-Aspergillus IgG/IgM and anti-Candida IgG/IgM antibodies (Serion Virion, Germany).”

2) Please take care of the new nomenclature regarding zygomycosis and zygomycetes! Also, the term Absidia is no longer valid!!!
We insert the new nomenclature in introduction:
“(ii) Case presentation
Which early laboratory markers for IFI were applied? Anti-Aspergillus IgM or IgG? Which test -company? What is the rationale to apply antibody-based assays in AML?
We explained it:
“Also, routinely commercial available serological ELISA tests for the screening of high risk patients for invasive fungal infections (IFI) were done: Galactomannan (GM) and Mannan (Biorad, France), as well as anti-Aspergillus IgG/IgM and anti-Candida IgG/IgM antibodies (Serion Virion, Germany).”

4) What about direct microscopic examination?
We added new sentence:
“Direct microscopic examination has been done with bronchoaveolare lavage (BAL) sample and it was negative”.
5) Use amphotericin B rather than amphotericine B
   We have changed
term amphotericine B to amphotericin B

6) Why secondary prophylaxis with itraconazole?
   Does this drug cover Mucorales?
   We added new sentences:
   “...(only available anti-mold drug for outpatients in Serbia).” on page 5 line 3.
   “The drug of choice is AmB, as well as lobectomy according to recommendation of the Expert
   Medical Board [9], but also posaconazole and itraconazole have potent affectivity to Rhizopus
   oryzae [10].” on page 7 line 13.
   We changed the previous reference No. 10 with new one:
   “10. Shirazi F, Kontoyiaannis DP: Mitochondrial respiratory pathways inhibition in Rhizopus
   oryzae potentiates activity of Posaconazole and Itraconazole via apoptosis. Plos ONE 2013, 8(5):
   1-11.”

7) Discussion
   The authors do not discuss the possibility of a co-infection- why not? Why not thinking of an
   infection of Aspergillus and Mucorales?
   We added new sentences:
   The possibility of Aspergillus co-infection can’t be excluded, but the therapy with voriconazole
   resulted in progression of infiltration on chest CT, as well as the histology and mycology
   investigations on the lung and BAL samples were negative for Aspergillus.

   The statement on the drug posaconazole is wrong!
   We moved the sentence:
   “In vitro data with posaconazole ate encouraging, but this has not yet been studied in clinical
   trials”.

   The conclusion on antibody-detection is somewhat strange! How could the authors detect cross-
   resistance?
   We added new sentences:
   “In the present context we speculate that the high levels of anti-Aspergillus IgM Ab may attribute
   to cross-reactivity with fungal antigens from Mucoraceae family. It is well known that IgM Ab
   has potential cross-reactivity between different virus families, several parasites and spiroheta
   proteins and those facts affect some laboratory tests. In spite of that, there are little data about
   cross-reactivity between different fungal families and further investigation should improve this”.

   Quality of written English: Needs some language corrections before being published
   Manuscript is now checked my native English speaker.
(iii) Response to Reviewer #2 Prof. dr Hugo Bonatti

1.) All doses of applied drugs must be given;
Doses of drugs are included now in abstract and manuscript; we have highlighted it.

2.) The paper should be revised by a native English speaker
Manuscript is now checked my native English speaker PhD Dr Marija Jankovíc.

Abstract
Doses of drugs,
Doses of drugs are included now in abstract and manuscript; we have highlighted it.

2nd paragraph: delete reporting by pathologist;
We have deleted that part of sentence.

Last sentence what method was used to identify Rhizopus;
We add new sentences:
“…and the mycology culture of the lung tissue sample revealed Rhizopus oryzae;”

3rd paragraph: move "Patient remained in complete....to 2nd paragraph;
We moved the sentence
“Patient remained in complete remission for more than one year” from 3rd to 2nd paragraph.

Make your conclusion sentence more precise;
We changed conclusion:
“As a rare disease IMM is not well understood by the medical community. This fact suggests improvement of education about prevention, diagnosis and treatment of IMM.”

Introduction
Add amongst others to last sentence
We added:
“…which include amongst others Mucoraceae family with genuum: Rhizopus, Mucor, Rhizomucor, Lichtemia and Apophysomyces.”

Case presentation
Use chest X-ray; use intravenously instead of parenteral; use bone marrow biopsy instead of myelogram; use English terms....superior vena cava, inferior vena cava, azygos vein;
We included all this English terms in manuscript instead of previous.

Was the patient discharged after 1st hospitalization on antifungals?
We added:
“On day 44 of hospitalization, patient was discharged with normal blood count”;

Do not use by a mycology expert...you can say retesting in a reference laboratory instead; use chest CT-scan
We included new term in sentence:
“Histology examination of the specimen was done, as well as the revision of the earlier samples with well trained mycologist in the reference laboratory and the diagnosis was switched to the pulmonary IMM.”

During third hospitalization: state of shock? Was this hemorrhagic or septic shock?
We changed it in manuscript as followed
“On day 13, hemoptysia, hypotension and septic shock were developed.”

Next sentence just state...The patient was successfully resuscitated.
The statement ....as a treatment of pulmonary IMM according to.....should be moved to discussion;
We have moved it to discussion as followed sentence
“The drug of choice is AmB, as well as lobectomy according to recommendation of the Expert Medical Board [9], but also posaconazole and itraconazole have potent affectivity to Rhizopus oryzae [10].”

Not sure where the discussion starts...I assume the first sentence is IMM has emerged as the third most common.....please change headers;
We changed start of discussion and it is now started with sentence
“IMM has emerged as the third most common IFI in patients with hematological malignity and the second most frequent lethal invasive mold infection in those patients”.

Sentence....The early, adequate and multidisciplinary...... is unclear: please rephrase;
We changed it as followed
“Beside the fact that the diagnostics of IMM is difficult with a lack of typical symptoms, signs of disease and specific early laboratory biomarkers, in our case the proven diagnosis was established by conventional methods and contributed to proper therapy and favorable outcome [8]”.

Sentence: The revision of histology slides.....please rephrase....maybe....requires a well trained mycologist with a well equipped laboratory;
We changed that sentence as followed
“However, the progression of pulmonary infiltration, development of thrombotic masses in the pulmonary arteria, multiple nodules changes in the lung and pleural effusion despite of voriconazole treatment led to revision of IPA diagnosis made by well trained mycologist who established the proven IMM.”

References are acceptable.....you could briefly comment on other cases of IMM where combined surgical and antifungal therapy was successful; figures are good;
In order to support usage of itraconazol as secondary prophylaxis we changed the reference no 10

Quality of written English: Needs some language corrections before being published.
Manuscript is now checked my native English speaker.