Author’s response to reviews

Title: Invasive Pseudomembranous Upper Airway and Tracheal Aspergillosis Refractory to Systemic Antifungal Therapy and Serial Surgical Debridement in an Immunocompetent Patient

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Author’s response to reviews:

Dear Editors, BMC Infectious Diseases

We thank you for the opportunity to submit this revised draft of our case report entitled, “Invasive Pseudomembranous Upper Airway and Tracheal Aspergillosis Refractory to Systemic Antifungal Therapy and Serial Surgical Debridement in an Immunocompetent Patient” for your consideration.

We appreciate the valuable feedback provided by your editorial staff and reviewers and have incorporated many of your suggestions into this revised manuscript.

As requested, here is a point-by-point response to the reviewers’ comments and concerns:

Technical Comments:
None noted
Reviewer Comments:

Comment 1. Title: I suggest to remove the expression 'first case' - it is not needed to make the case interesting, and the remainder of the title is self-explanatory.

Response:

The title has been modified to omit ‘first case’ and now reads, “Invasive Pseudomembranous Upper Airway and Tracheal Aspergillosis Refractory to Systemic Antifungal Therapy and Serial Surgical Debridement in an Immunocompetent Patient.”

Comment 2. Abstract: The abstract is way too long - the essential points can be made in 50% of its present volume - the text of the background section would just be fine. If sections are needed, pl. shorten accordingly.

Response:

In our review of the submission guidelines for BMC Infectious Diseases case reports, abstracts are required to include separate sections for Background, Case Presentation, and Conclusions. As such, we have maintained this format within the Abstract section of the manuscript. To facilitate brevity, we have removed the final two sentences from the Background section of the abstract. The total word count in this section is now 206 words (previously 286 words, per guidelines 350 words max).

Comment 3. Introduction: The last sentence of the introduction may be removed.

Response:

The ‘Background’ section (p. 4) has been updated to reflect this change.
Comment 4. Case report, line 51: Were there any other abnormal findings on chest CT initially or during the course of her illness? I would wish to have a representative section of both CTs in the report for documentation, or at least a representative chest x-ray to exclude the presence of lower airway involvement.

Response:

The patient’s initial chest CT did not demonstrate any abnormal parenchymal findings suggestive of lower respiratory tract involvement. We have modified the Case Report section (p.5; line 12-14) to make this important negative finding more explicit within the text. The reviewer also rightly pointed out the importance of demonstrating disease isolation to the upper airways for the duration of her disease course. Serial chest x-rays were obtained during the patient’s disease course, all of which were negative for lung parenchymal involvement. To make this clear, we have added a sentence to the Case Report section commenting on these negative x-ray findings (p. 7; line 6-8). This is also addressed in the Discussion section of the text (p. 11; line 1-3). Although the reviewer requested representative imaging as a possible additional figure, we feel that this would likely be superfluous as such a figure would simply be a series of radiographically normal chest x-rays (i.e no pertinent positive findings). If the editors feel that it should be included, we will be happy to include an additional figure.

Comment 5. Case report, line 80: In my opinion, this patient would need a more detailed work up by Immunology for defects in T-cell function, immune signaling and defects in mucosal immunity; this is clearly justified by the extent and duration of her illness.

Response:

Early in her prolonged disease course, the patient underwent a workup for primary immunodeficiency. Per the 2015 Practice Guidelines published by the American Academy of Allergy, Asthma, and Immunology (AAAAI), this entails screening tests to assess humoral immunity, cellular immunity, phagocytic function, and complement. As stated in the ‘Case Report’ (lines 11-13; p. 6) the conventional screening tests for each of these immunological components were found to be normal. The AAAAI Practice Guidelines further recommend that in patients with abnormal screening results further advanced immunological testing should be pursued. In the case of this patient, a further workup was not done given her normal screening studies. Furthermore, if this is a case of primary immunodeficiency it would be odd for a first presentation so late in life as well as to have only a single disease manifestation as observed in this case. However, the reviewer’s suggestion for further T cell function studies is well taken and we have added this to the discussion section suggesting that other providers encountering a similar patient presentation should consider further functional assays (line 11-21; p.8).
Comment 6. Case report, throughout: I am also not sure about the role of corticosteroids for maintaining the infection. It seems that the patient was most of the time on inhaled steroids +/- steroid rinses, which also are risk factors to develop oropharyngeal candidiasis. Please clarify the exact supportive treatment of the patient.

Response:

While generally not appropriate for invasive aspergillosis, per the current treatment guidelines for aspergillosis published by the Infectious Diseases Society of America (IDSA), the use of topical/mucosal corticosteroids in combination with antifungals has a well defined role in allergic fungal rhinosinusitis.

As stated in the Case Report (line 14-16; p.6), topical amphotericin B and budesonide rinses were started as an ancillary therapy only after persistence of infectious symptoms in spite of systemic antifungals and mechanical debridement. As commented on in the text, the patient initially responded well to this combination of therapies and for that reason was continued on antifungal-steroid rinses for symptom control. However the authors agree that there is no well-defined role for topical steroids in this disease and that there is likely as much a potential for harm as there is for benefit. A comment has been added to the Discussion section to directly address this concern (line 3-8; p.11).

Dosing of amphotericin B (100 mcg/ml) and budesonide (10 mcg/ml) irrigation solution has been added to the text as requested (line 15; p.6).

Comment 7. Case report, line 94: What were the doses of voriconazole, and what was the exact exposure to the drug? Pl. clarify.

Response:

The Case Report has been updated with the exact dosing of voriconazole at different stages of the patient’s treatment course (line 3, line 16, line 27; p. 6).

Comment 8. Discussion, line 190: Pl. see point 4.

Response:

Please see response to Comment 4 above.

Comment 9. Conclusions, line 209: pl. see comment 5.
Response:

Please see response to Comment 5 above.

We look forward to hearing from you soon and would be pleased to address any further questions or comments that you may have.

Sincerely,

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