Author's response to reviews

Title: Concurrent Pulmonary Mucormycosis and Mycobacterium tuberculosis infection

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Author's response to reviews: see over
Dear Prof. Kidd

Re: Concurrent Pulmonary Mucormycosis and Mycobacterium tuberculosis infection
We would be grateful if you could consider the above article for publication in the Journal of Medical Case Reports. We have revised the manuscript with reference to the comments made by the two reviewers. Please find below our response to the reviewers comments

Yours sincerely,

Dr Ian Clifton.

Reviewer 1
General
Patel et al's case report is unique, but not (primarily) for the reason (concurrent infection) they choose to highlight the case. This report may serve to better characterize a unique syndrome; please see Mayo Clinic Proceed 1999;74:698-701; in particular see Figure 3. The endobronchial presentation should be the focus of the paper and concurrent infection a secondary item.

Revisions necessary for publication
Refocus the paper as listed above. Also, address the concept of respiratory colonization; see Clin Infect Dis 2000;30:851-6.
Response: We thank the review for their comments. We have added a section reporting the endobronchial findings of mucormycosis (See page 3 paragraph 3)
Was a bronchial or lung biopsy obtained? This should be stated.
Response: We thank the review for their comments. A biopsy of the necrotic tissue was obtained which demonstrated numerous fungal hyphae with a morphological appearance of zygomycetes within necrotic areas of tissue (Page 2 paragraph 2).
Was the fungus identified? This should be stated.
Response: We thank the review for their comments. The fungus was only identified on the basis of the histological appearance (Page 2 paragraph 2).
Was susceptibility performed for the fungal isolate? It is very likely that the isolate may have been resistant in vitro to itraconazole. This should be discussed. Also, like voriconazole, there is an interaction with itraconazole.
Response: We thank the review for their comments. No susceptibility testing was performed as the fungus was not able to be isolated from specimens taken for culture (Page 2 paragraph 2). We have commented that oral azoles have little activity against zygomycetes; however there are anecdotal reports of successful treatment (See page 4 paragraph 1).
The figure does not demonstrate "foreign" material; it is the interaction of host with fungus (ie necrotic ulcer).

Response: We thank the review for their comments. We have changes the phrase “foreign material” to “necrotic ulcer”.

Reviewer 2

General

The authors are presenting an interesting case of pulmonary mucormycosis and concurrent tuberculosis infection in a patient with no identified risk factors. The manuscript lacks some useful information for the case.

1. It does not mention some of the risk factors associated with these infections even if the patient has none of them. The authors did not mention the HIV status of the patient (mucormycosis has been reported in AIDS patients), his past PPD status, exposure history, his travel history and possible risk factors associated with his severe ischemic heart disease such as diabetes. Were all the risk factors ruled out? If so, we would like to know how.

Response: We thank the review for their comments.

2. Mucormycosis infection has been reported in a patient with no "apparent" risk factors. The authors did not cite couple of cases of pulmonary mucormycosis in normal hosts. One case of solitary pulmonary nodule caused by phycomycosis in a patient without obvious predisposing factors was published in 1980 in Thorax (1) and one case of isolated pulmonary mucormycosis in an apparently normal host was published in 1995 in Journal of National Medical Association (2). Other forms of mucormycosis infection have occurred in children. A case of isolated hepatic mucormycosis in an immunocompetent child was published in the American Journal of Gastroenterology (3) in 1996. (Please see references at the end of this section). The authors referred to 2 cases of concurrent TB and mucormycosis (references 6 and 7), which were published in Japanese literature.

Response: We thank the review for their comments. We have added a comment regarding the rare occurrence of pulmonary mucormycosis in patients without recognised risk factors (See page 2 paragraph 3).

2. On the section of making the diagnosis, the appropriate tests were used. Was the team able to grow the fungus? Would it be possible to see the histology slide instead of the bronchoscopy picture?

Response: We thank the review for their comments. We were not able to grow the fungus from any samples taken for culture (See page 2 paragraph 2). We feel that the bronchoscopy findings are particularly interesting as it is unusual to see endobronchial black necrotic material. We have tried to refocus the paper as suggested by reviewer 1 emphasising the endobronchial appearance and the similarity to that described by Collins et al[1].

3. On the other hand the management of the patient did not follow the standard guidelines for treatment of mucormycosis for the oral treatment part. It is not acceptable to state that voriconazole is the antifungal of choice to treat this infection. In fact some patients developed mucormycosis infection while on voriconazole.

Response: We thank the review for their comments. The patient received three weeks of intravenous liposomal amphotericin. We have removed the section regarding voriconazole been the oral treatment of choice for mucormycosis.

(4). It is very well known that azoles have no activity against mucormycosis with the exception of the newly introduced posaconazole that seems to be promising. The
use of inappropriate treatment for such a serious (deadly) infection in a patient who had a good outcome put in question the accuracy of the diagnosis and does not add any teaching points to the manuscript. The patient could have had a response to TB treatment with symptoms resolution (assuming it was sensitive) but not to mucormycosis treatment.

Response: We thank the review for their comments. The patient received three weeks of intravenous liposomal amphotericin. We are aware that oral azoles have little activity against mucormycosis, however there are anecdotal reports of azoles having some benefit[2-4]. We have added a section regarding this and also the potential benefit of posaconazole.

Overall, it is a well-written case discussing 2 concurrent infections in an unusual combination. The history is missing some useful information and the management of the patient described as aggressive was inappropriate.

Response: We thank the review for their comments. We have removed the term aggressive in relation to the medical management of this patient.


Revisions necessary for publication
To summarize the elements mentioned in the previous sections, authors need to document (include or exclude) the risk factors associated with this disease.

-Please provide the following information if possible:
  Patient HIV status, travel/exposure history, HbA1c level.

The patient had no history of diabetes mellitus and random blood glucose was normal. HIV testing was not performed. The patient had recently travelled to the United Kingdom from India.

-Is it possible to add the histology slide?

We feel that the bronchoscopy findings are particularly interesting as it is unusual to see endobronchial black necrotic material. We have tried to refocus the paper as suggested by reviewer 1 emphasising the endobronchial appearance.

-Delete the following statement in page 3 line 17-18: “The use of voriconazole, the anti-fungal agent of choice, was precluded due to its interaction with rifampicin”.

Response: We thank the review for their comments. We have removed this sentence and added more discussion of the role of antifungal treatment in to the conclusion (See Page 4 paragraph 1). The patient had no history of diabetes mellitus and random blood glucose was normal. HIV testing was not performed.

-Page 3 lines 19-20-21 is confusing, needs to be explained clearly i.e. what were the concerns?

Response: We thank the reviewer for their comments. We have clarified that the concern on CT scan was with regard to lack of resolution of the multiple nodules (Page 2 paragraph 4).
-Page 4 lines 21-22-23 are irrelevant to this case. “While sputum cultures are often negative, BAL is more sensitive and can be helpful, in patients with haematological disorders where biopsies are contraindicated due to the presence of thrombocytopaenia”.
Response: We thank the review for their comments. We have removed this sentence.
-In the treatment section page 5 lines 1-2, add the appropriate medical treatment as a teaching point.
Response: We thank the review for their comments. We have added discussion of the role of antifungal treatment in to the conclusion (Page 4 paragraph 1).
Revise What next?: and resubmit

Quality of written English: Needs some language corrections before being published

Reference List