Author’s response to reviews

Title: A case of allergic bronchopulmonary aspergillosis successfully treated with mepolizumab

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Dr. Terumi Midoro-Horiuti

Associate Editor

BMC Pulmonary Medicine

Dear Dr. Midoro-Horiuti:

We wish to re-submit our manuscript, “A case of allergic bronchopulmonary aspergillosis successfully treated with mepolizumab.” We thank you and the reviewers for your thoughtful suggestions and insights, and we believe that our manuscript has benefitted greatly from this input. Revisions in the manuscript are marked in red font, and point-by-point responses to the reviewers’ comments are provided below.
We want to thank the reviewers again for their thoughtful comments. We hope that our manuscript is now suitable for publication in BMC Pulmonary Medicine.

Sincerely,

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Responses to Reviewers’ Comments

Lokesh Guglani, MD (Reviewer 1):

1) Abstract, Line 13 - Replace the word "induces" with "causes"

Thank you for this suggestion. We have replaced “induces” with “causes” in the Abstract.

2) It is not clear from this case report as to when this patient was first diagnosed with asthma. Please specify, as it will be helpful to specify the chronology of events.
Thank you for the suggestion. We have added the following details to the Abstract: “(from 40 years of age)” (Line 18).

3) Abstract, Line 25 - The authors report recurrence but do not specify if it was recurrence of which symptoms.

Thank you for this suggestion. We have added the following details to the Abstract: “Peripheral eosinophilia and pulmonary infiltration” (now Lines 25-27).

4) Abstract, Line 33 - This sentence is confusing - was this patient receiving itraconazole for 3 years?

Thank you for the inquiry. Yes, that is correct. We have added the following details to the Abstract: “and itraconazole was added as an anti-fungal agent” (Line 30).

5) In 2017, prior to her "deterioration", was there any history of travel to areas where other fungal organisms are endemic? Was there any history of specific environmental exposures that could have induced specific hypersensitivity?

Thank you for this inquiry. There was no history of travel to any areas where other fungal organisms are endemic, nor were there specific environmental exposures that risked inducing the observed hypersensitivity.

6) Case Presentation, Line 36 - The patient presented first with a history of fever for 2 weeks - this is quite unusual for ABPA. One other condition that comes to mind that can occur in patients with asthma and cause a similar presentation with prolonged fever is Acute Eosinophilic
Pneumonia. Did the authors ever consider this in the differential diagnosis for this patient? The treatment for eosinophilic pneumonia is also steroids and most patients show rapid improvement in their symptoms, pulmonary infiltrates and mucoid impaction after steroid therapy.

Thank you for this inquiry. We have added the following sentences to the Discussion in order to address your question (Page 6, Lines 45-Page 7, Line 36):

“Our patient was diagnosed with ABPA because the observed clinical, radiologic, and laboratory findings met essential criteria for ABPA that were proposed in 2013, which include: 1) predisposing conditions: asthma or cystic fibrosis; 2) obligatory criteria: total baseline serum IgE >1000 IU/mL, as well as positive immediate hypersensitivity skin test or elevated specific IgE to A. fumigatus; 3) supportive criteria: eosinophilia >500 cells/µL, serum precipitating or IgG antibodies to A. fumigatus, and consistent radiologic opacities [1]. The radiologic features include transient (consolidation, nodules, and tram-track or gloved-finger appearance) or permanent (bronchiectasis or fibrosis) pulmonary opacities. Although persistent fever, which was seen in our case, is not a common symptom of ABPA, fever is included as one of the symptoms of ABPA [1, 3]. Differential diagnoses in our case included eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis. The predominant patterns of CT findings in acute eosinophilic pneumonia are consolidation and/or ground-glass opacity, frequently accompanied by interlobular septal thickening [4]. Positive IgE against A. fumigatus and mucoid impaction (as documented by imaging and bronchoscopy) suggested ABPA, rather than acute eosinophilic pneumonia, in our case. The absence of extrathoracic manifestation and negative ANCA excluded the possibility of eosinophilic granulomatosis with polyangiitis.”

7) Case Presentation, Line 39 - The authors have called her asthma as "Severe", but have not provided adequate details about her asthma history. When was she first diagnosed? What was her baseline lung function? What asthma specific therapies was she receiving prior to her presentation?
Thank you for this inquiry. We have added the following details to the Case presentation section to address your question (Page 4, Lines 36-49):

“A 64-year-old woman was diagnosed with bronchial asthma at 40 years of age. Initially, her symptoms were mild and controlled with a moderate dose of inhaled corticosteroid (ICS) and a short-acting beta-agonist. She reported a medical history of eosinophilic rhinitis. At 60 years of age, she experienced frequent wheezing exertion; spirometry revealed forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of 62.6%, FEV1 of 0.92 L, and peak expiratory flow of 202 L/min.”

8) Page 6, Line 3 - Bronchoscopy was done for this patient but the authors have provided minimal details of the procedure and the results. What was the result of the BAL cultures? Did she grow Aspergillus on BAL fungal cultures? Which lobe/lung segment was the BAL performed in?

Thank you for this inquiry. We have added the following details to the Case presentation section to address your question: “the differential specimen count obtained by bronchial washing from the right middle lobe was composed of 27% eosinophils. Notably, the bronchial washing culture yielded no bacteria or fungus” (Page 5, Lines 19-22).

9) Page 6, Line 10 - Before discussing the diagnosis of ABPA, the authors need to add a list of differential diagnoses for this patient here. What are the points against this being labeled as recurrence of eosinophilic pneumonia?

Thank you for this inquiry. Please see our response to point #6 above.
10) Page 6, Line 39 - For the acute "deterioration" in 2017, the authors have provided very limited information about her presenting symptoms. Was there a recurrence of fever at this time? What other symptoms did she have at that time?

Thank you for this inquiry. We have added the following details to the Case presentation section to address your question:

“She complained of wheezing, productive cough, and dyspnea on effort” (Page 5, Lines 53-56).

11) Page 8, Line 23, Discussion Section - Please discuss the role of Interleukin-5 (IL-5) specifically in the pathogenesis of ABPA. There are multiple reports that implicate Th2 cytokines (IL-4, IL-5 and IL-13) in the pathogenesis of ABPA.

Thank you for this suggestion. We have added the following details to the Discussion section:

“The increased secretion of interleukin-4 and interleukin-5 from peripheral cells from patients with ABPA suggests that TH2 inflammation contributes to the pathogenesis of ABPA [14]” (Page 8, Lines 52-58).

Lori D. Wilson (Reviewer 2):

1. Specifically, in both the Abstract and body of the manuscript, improvements in FEV1 were mentioned. In some places, the absolute value of the FEV1 was only given and did not indicate either a percent predicted or the FEV1/FVC ratio. Since the absolute FEV1 is a size, age and gender dependent variable it is meaningless unless references to its predicated value or % of FVC. In several locations the FEV1/FEV was list as a percent. Was this an error? Again this is unclear. An FEV1/FVC ratio of 66.9 is much different than an FEV1 percent predicted of 66.9%.
We are very sorry for our mistake. We have replaced “FEV” with “FVC” in all relevant locations.

2. Additionally, eosinophil counts are provided as measures of improvement but do not clearly indicate if the cells are from peripheral blood or bronchial washing. All cell counts should identify the source of cells for future clinical referencing.

Thank you for this suggestion. We have added “peripheral” to our descriptions of cell sources.

3. Some reference as to the clinical significance of an improvement in FEV1/FEV (or is it FEV1/FVC) of 66.9 to 69.2 and an FEV1 of 1.01 L to 1.25 L or 1.28L would also be very helpful.

Thank you for this suggestion. We have added the following details to the Discussion section:

“The improvement of lung function in our case appears to be dramatic, compared with the study of patients with severe eosinophilic asthma, in which the mean increase in FEV1 was 100 mL after mepolizumab therapy [10]” (Page 9, Lines 26-36).

4. More detail regarding the specific areas of improvement in the Asthma Control Test would also be helpful. What do scores of 18 and 24 indicate, i.e. moderate/poor control?

Thank you for this inquiry. We have added the following details to the Discussion section:

“An ACT score of ≤19 indicates uncontrolled asthma and a 3-point change in ACT score is clinically significant [16]” (Page 9, Lines 23-26).
5. Any more detailed information regarding precautions or positive outcomes when transitioning from omalizumab to mepolizumab would enhance the overall quality of the manuscript. Are there any IgE precautions with mepolizumab to be aware of?

Thank you for this inquiry. We have added the following details to the Discussion section to answer your question:

“A post hoc analysis showed that mepolizumab was effective for patients, regardless of prior history of omalizumab use; moreover, most patients in the prior omalizumab use subgroup reported that omalizumab was ineffective [12]. Total IgE level at the start of therapy does not affect the efficacy or adverse effects of mepolizumab, and mepolizumab is recommended as one of the therapeutic options in cases of severe eosinophilic asthma with total IgE >1,500 IU/mL [13]” (Page 8, Lines 33-48).

Keiko Wakehara (Reviewer 3):

1. Authors used "forced expiratory volume in 1 second (FEV1)/FEV" many times in the manuscript. Do they mean "forced expiratory volume in 1 second (FEV1)/FVC"? Please check them.

We are very sorry for our mistake. We have replaced “FEV” with “FVC” in all relevant locations.

2. Authors did not use Omalizumab for this patient because of the high level of total IgE. Did mepolizumab reduce total IgE level of this patient?
Thank you for this inquiry. We have added the following details to the Case presentation section to answer your question:

“The serum level of IgE did not change after mepolizumab” (Page 6, Lines 22-24).

3. As authors mentioned, the report of ABPA treated with mepolizumab alone is not found yet. However, the report of ABPA treated with omalizumab and mepolizumab was published in J Allergy Clin Immunol Pract. 2017, 5(4): 1137. Can you comment about it?

Thank you for this inquiry. As mentioned, a case of ABPA that was treated with omalizumab and mepolizumab has been reported. We consider our case report to be important and interesting because our case shows that a single dose of mepolizumab alone can induce dramatic improvement. Thus, we have added the following details to the Discussion section:

“The synergistic effects of omalizumab and mepolizumab have been reported in a patient with severe and steroid-dependent ABPA [15]” (Page 9, Lines 10-13).