Author’s response to reviews

Title: Eosinophilic Pneumonia Associated with Daptomycin: A Rare Case and Literature Review

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Author’s response to reviews: see over
Dear Dr. Kidd,

We have carefully examined all the questions and suggestions that were raised by the referees regarding the manuscript that we recently submitted for consideration to the *Journal of Medical Case Reports*, entitled "Eosinophilic Pneumonia Associated with Daptomycin: A Rare Case and Literature Review".

Regarding the manuscript content we have proceeded in some elucidatory changes (highlighted in yellow in the manuscript):
In the background segment of the manuscript, in the first paragraph, we added the website with the, constantly updated, list of drugs suspected of causing lung disease. In the same segment, in the last paragraph, we pinpointed that our patient did not develop severe respiratory failure during the eosinophilic pneumonia condition.

In the case presentation segment, in the second paragraph, we added further information concerning the patient's past medical history. In the same segment we added the chest radiographic images upon the patient's hospital admission with symptoms of heart failure and after improvement of the latter, respectively (paragraphs 3, 4). Furthermore, in the fourth paragraph, we further demonstrated arterial blood gases analysis and added information on the supplemental oxygen administration and chest computed tomography that was carried out. In the same paragraph, we highlighted the pleuritic fluid analysis after thoracocentesis of the pleural effusion, and we clarified the exact therapeutic regimen of the patient after daptomycin's withdrawal.

In the discussion segment, in the first paragraph, we added supplementary information with regards to the pathophysiology of eosinophilic pneumonia. In the same paragraph we quoted supplemental arguments, illustrating the criteria of Salomon and Schwartz for eosinophilic pneumonia that our patient fulfilled and additional information with respect to the differential diagnosis upon patient's clinical presentation and laboratory findings.

Please find in the next pages specific replies to the comments of each referee.

I would be more than willing to respond, should you have any questions regarding the aforementioned changes and comments.
Sincerely,

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Response to referee #1

1. A high resolution computed tomography was performed upon the patient's clinical symptoms. Furthermore, since the blood cultures were negative, the differential diagnosis had to involve autoimmune disorders especially small vesels vasculitis that may cause endocarditis with pulmonary lessions. For this reason we considered it important to assess autoimmune markers.

2. A research for reported cases of eosinophilic pneumonia due to daptomycin administration was performed by using a standard MEDLINE search, the PUBMED database. During that time five cases had been reported:

3. The authors agree with the reviewer that ampicillin could have been the cause for the eosinophilic pneumonia observed in this patient. However, the ampicillin was not withdrawn from the therapeutic regimen as initially reported erroneously in the submitted manuscript. Since ampicillin was continued and the condition of the patient
improved the eosinophilic pneumonia could not have been attributed to ampicillin. Furthermore, the Solomon and Schwarz criteria regarding diagnosis of eosinophilic pneumonia are clearly stated in this manuscript. According to these criteria, respiratory deficiency defined as acute lung injury or acute respiratory distress syndrome enhances the possibility for eosinophilic pneumonia. In our case respiratory failure with acute lung injury was noted, without however the need for mechanical or non-mechanical ventilation treatment.

4. Further information with respect to the pathophysiology of eosinophilic pneumonia was added to the discussion section of the manuscript. The website www.pneumotox.com was cited as well.

5. The missing dates in two of the manuscript's references were added.
Response to referee #2

1. Arterial blood gases analysis upon the patient's clinical symptoms during the
development of eosinophilic pneumonia were added to the case presentation segment
of the manuscript.
Response to referee #3

1. The authors agree with the reviewer that ampicillin could have been the cause for the eosinophilic pneumonia observed in this patient. However, the ampicillin was not withdrawn from the therapeutic regimen as initially reported erroneously in the submitted manuscript. Since ampicillin was continued and the condition of the patient improved the eosinophilic pneumonia could not have been attributed to ampicillin.
1. After initial treatment for congestive heart failure symptoms along with the significant improvement of clinical signs and symptoms, there was also a significant resolution of radiographic findings (figure 1b.) In addition, all blood cultures, serology and BAL fluid examination were negative for parasitic or fungal infections.

2. The patient had no history of allergies or recent travels and he was not a smoker.

3. A diagnostic thoracentesis was performed to the patient in order to evaluate bilateral pleural effusions. Pleural fluid analysis revealed a transudate with 6700 nucleated cells (70% lymphocytes, 15% eosinophils, 15% neutrophils). In addition, the 480 nucleated cells in BAL fluid analysis are comparable to the corresponding number of inflammatory cells in the case reported by Hayes et al. This may be attributed to the anti-inflammatory effect of the inhaled corticosteroids that were given to the patient before the bronchoscopy procedure.