Author’s response to reviews

Title: Autoimmune Pulmonary Alveolar Proteinosis Developed During Immunosuppressive Treatment in Polymyositis with Interstitial Lung Disease: a case report

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Dr. Tamara Hughes
Editor in Chief
BMC Pulmonary Medicine

Dear Dr. Tamara Hughes,

We are grateful for the opportunity to revise our paper PULM-D-20-00035 entitled "Autoimmune
Pulmonary Alveolar Proteinosis Developed During Immunosuppressive Treatment in Polymyositis with Interstitial Lung Disease: a case report,” and the helpful comments of your reviewers.

We attach a revised version showing the tracked changes and, separately, list our point-by-point responses. We feel that the comments have allowed us to improve the paper and hope you convey our gratitude to the reviewers.

We look forward to hearing a favorable response from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.

Yours sincerely,

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Response to Editor’s comment

We here reply to the comments from the reviewer as follows.
The corrections are highlighted in bold in the revised manuscript so that you can refer to them quickly.

Reviewer 1
Dear Dr. Effrosyni Manali,

C1:
To further ameliorate their work, the authors are kindly advised to provide the microbiological results of the BAL and to comment in the discussion the role that infections might play in the development of the disease in an immunocompromised patient.

R1:
We detected no bacteria, fungi, or acid-fast bacilli in BALF. We added the results of infectious disease tests in the case presentation and discussion, as pointed out (Page 5, line 71, page 6, line 100, and page 10, line 162).

Reviewer 2
Dear Dr. Cormac McCarthy

C1:
Case presentation: When the patient first presented, she had GGO in her lungs and although she did not have cytological findings in keeping with PAP how do we know she did not have aPAP then, was GM-Ab checked at this time? Perhaps she had aPAP in a mild form there. Histology can be patchy and is non diagnostics in ~25% of confirmed aPAP cases, cytology is even weaker finding.

R1:
We make a diagnosis of PAP based on histopathologic findings of specimens obtained by open lung biopsy or transbronchial biopsy or on cytologic results in BAL samples (AJRCCM 2008 177:752).
When the patient with PAP has GMAb, he or she should be APAP. Even if they have the Ab but no histopathologic findings of PAP above mentioned, we do not diagnose them as PAP because the disease is currently considered a pathological abnormality. Very rarely, we find a patient diagnosed as other lung diseases with GMAb positive (ERJ Open Res. 2020 Jan 27;6(1). pii: 00259-2019). It is possible, however, as the reviewer’s comment that BAL could not detect a mild PAP anywhere in the lung. We revised the statement in the discussion (Page 8, line 122-127).

C2:
Page 4 line 45: "Pulmonary alveolar proteinosis (PAP) is a rare diffuse lung disease", please change this to say is a rare syndrome as PAP comprises many diseases, of which aPAP is one, please check this for consistency throughout the manuscript.

R2:
We changed the expression of a rare diffuse lung disease to a rare syndrome (Page 4, line 45).

C3:
Page 4 Line 54-55: "Only a few cases can be found in registry studies and case reports", please also refer to the association recently described in Juvenile Idiopathic Arthritis. (Schulert et al Arthritis Rheumatol , 71 (11), 1943-1954 Nov 2019)

R3:
Schulert et al. reported 18 patients with juvenile idiopathic arthritis-associated lung disease with pathologically mixed features of PAP and endogenous lipoid pneumonia. Those cases in the report, however, did not show elevated levels of GM-Ab and could not be asserted as APAP as we report here. We revised the sentences in the discussion quoting this report (Page 10, Line 168-175).

C4:
PSL is not a standard abbreviation for prednisolone and is not helpful to the reader, please spell out prednisolone throughout the manuscript instead of abbreviating.

R4:
Prednisolone is an active drug itself, but prednisone is a pro-drug which is activated to prednisolone inside the liver. Thus, prednisone cannot be prescribed to patients with liver dysfunctions. Prednisone is only given orally, but prednisolone can be more convenient, given orally, for injection, or for topical application. Besides, prednisone is less effective than prednisolone. We, Japanese doctors, prefer prednisolone to prednisone (BMC Pulm Med, 2015). All PSL abbreviations used in the manuscript have been changed to prednisolone (Page 5, line 75, Page 5, line 77, Page 5, line 81, and Page 7, line 110).

C5:
Page 7 Line 104: Please reference which method was used or a reference for the cut-offs for GM-CSF antibody level, as different cut-offs apply with different methods.

R5:
We added two references, both of which used the same method to decide the cut-offs for the GM-CSF antibody level (Page 7, Line 107).

C6:
Discussion: Please refer to the recent Schulert report regarding JIA and also comment on the lack of HLA association reported by Anderson et al, PLOS One 2019.

R6:  
We revised the statement in the discussion, citing both documents (Page 10, line 168-175).

C7:  
Discussion: Please also refer to the fact that GMAb was not checked in 2004 and she may have had aPAP then.

R7:  
We added a sentence that GMAb was not checked in 2004 (Page 5, line 72).

As we stated in the R1 response, we could not make a diagnosis of PAP (not APAP) at the development of myositis-ILD, but it is possible that BAL only could not detect a mild PAP anywhere in the lung. We, however, think it is unlikely that she had APAP with myositis because of the following reasons. First, her BALF looked clear, with no pathological findings suggesting PAP. Second, her ILD improved in response to corticosteroid treatment. We previously reported that corticosteroid therapy might fail to ameliorate APAP but deteriorate the disease (BMC Pulm Med, 2015). We revised the statement in the discussion (Page 8, line 122-128).