Author's response to reviews

Title: Marked Improvement in Autoimmune Pulmonary Alveolar Proteinosis with Severe Hypoxemia in a Patient Treated with Ambroxol.

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Author's response to reviews: see over
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Dear Journal of Medical Case Reports

We thank the editor and referees for fruitful suggestions, We have revised the manuscript on the basis of the Referee's comments. We look forward to a publication of our manuscript in Journal of Medical Case Reports.

Sincerely

Nao Oda MD, Koji Tamai MD, Yujiro Suzuki MD, Harukazu Yoshimatsu MD, Hirofumi Matsuoka MD, Yusuke Matsumoto MD, Nobuhiko Okada MD.

Our responses to the referees’ reports are as follows:

**Referee: 1**

Thank you for reviewing our manuscript. Our responses are as follows.

1. In the introduction section the phrase “The pathogenesis of PAP involves abnormal metabolism of surfactant resulting from dysfunction of granulocyte-macrophage colony-stimulating factor (GM-CSF)” is not correct. Please rephrase.

Reply
Thanks for pointing out that. We recognize that neutralizing GM-CSF auto antibodies blocked its binding to GM-CSF receptors on cell, which leads to inhibition of signaling, thereby inhibiting surfactant mature.( J Exp Med
My description is incorrect, so I rephrase as below. (Page2 Line26)

The pathogenesis of autoimmune PAP involves neutralizing antibody that directly bound granulocyte-macrophage colony-stimulating factor (GM-CSF) and blocked its binding to GM-CSF receptors on cells, which leads to inhibition of signaling, thereby inhibiting surfactant mature (J Exp Med 190:875–880, 1999).

2. In the introduction section the phrase “Oral ambroxol should be considered for patients with PAP, even in those with severe respiratory compromise” should be omitted. It is more of a conclusion than an introduction.

Reply

Thanks for your comments. As you indicated, that sentence should be described in the discussion section. I deleted the sentence from Introduction section and described in Discussion section. (Page5 Line2)

Though WLL or inhaled GM-CSF therapy remains the first line therapy, oral ambroxol could be tried for PAP in the case of WLL and inhaled GM-CSF therapy not being feasible due to a various reasons, even in patients with severe respiratory compromise, because it is a simple treatment and with few side effects.

3. In the case presentation section what is the difference between %FEV1 of 105.2%; and FEV1% of 84.2% ? Please explain.

Reply

Thanks for your question.

%FEV1 is defined as FEV1(L)/FEV1 predicted(L) which is calculated by sex, age, height, which is more to be described as FEV1% predicted. FEV1% is a parameter which is calculated as FEV1(L)/FVC(L).
Moreover, I made a mistake of the FEV1% predicted data. The correct pulmonary function data is “FEV1% predicted of 76.0%; and FEV1% of 84.2%”. There are no more mistakes. I’m very sorry for my error. (Page3 Line14)

Pulmonary function tests on admission revealed a vital capacity (VC) of 1.49 L; %VC of 68.6%; forced expiratory volume in 1 second (FEV1) of 1.17 L; FEV1% predicted of 76.0%; and FEV1% of 84.2%.

4. In the discussion section the phrase “Dysfunction of GM-CSF, which plays a critical role in the surfactant system, is considered to play a primary role in the pathogenesis of PAP” is again misleading. The authors seem to confuse the three etiologic forms of PAP (congenital, secondary, autoimmune). Please explain where you are referring to and accordingly describe the pathogenesis of each one should you find it necessary.

Reply
Thank you for your comment. As you indicated, I confused about three etiologic forms of PAP.

The secondary PAP is found in association with pulmonary infection, hematologic malignancies, and inhalation of dust, mineral and metal particles. (J Exp.Med. 190: 875-880, 1999) Secondary PAP is likely related to a relative deficiency of GM-CSF and related macrophage dysfunction, thereby compromising surfactant clearance. (Respirology 18: 82-91, 2013) The causes of congenital PAP is genetic abnormalities of GM-CSF or its receptors. (J Clin Invest 100: 2211-2217, 1997)
Autoimmune PAP, more than 90% cases of PAP, is caused by neutralizing auto antibody that directly bound GM-CSF and blocked its binding to GM-CSF receptors on cells. (J Exp Med 190:875–880, 1999)
Since this case report is about autoimmune PAP, we explain about pathogenesis of autoimmune PAP as below.(Page4 Line4)
The majority of PAP is autoimmune PAP. Dranoff et al. found that absence of local GM-CSF dependent activation of macrophage in the lungs was involved in surfactant clearance (Science 264: 713–716, 1994). Autoimmune PAP is now considered to be occurred by the neutralizing antibody, which inhibits GM-CSF binding for receptors (J Exp Med 190:875–880, 1999). That leads to a defect of alveolar macrophages and abnormal surfactant metabolism, resulting in intra-alveolar accumulation of surfactant.

5. In the discussion section the phrase “Oral ambroxol should be tried for PAP, even in patients with severe respiratory compromise, because it is a simple treatment, unlike WLL or inhaled GM-CSF” is not supported by current evidence. Oral ambroxol could, and not should, be tried in PAP and the treatments of WLL and iGM-CSF have many studies to support their use. The authors need to rephrase this and make it clear that ambroxol is not comparable or equivalent to WLL or iGM-CSF in the treatment of PAP.

Reply
Thank you for the important comment.
As you indicated, WLL and inhaled GM-CSF are the only evidence-based therapy. It is too much to say that Ambroxol should be tried on PAP. But we feel worthy trying Ambroxol as alternative therapy if WLL and inhaled GM-CSF therapy are not feasible for various reasons, as in the described patient. I rephrased the sentence as below. (Page5 Line2)

Though WLL or inhaled GM-CSF therapy remains the first line therapy, oral ambroxol could be tried for PAP in the case of WLL and inhaled GM-CSF therapy not being feasible due to a various reasons, even in patients with severe respiratory compromise, because it is a simple treatment and with few side effects.

6. It is imperative that the authors make at least a speculation on how ambroxol works in PAP.
Reply
Thank you for your comment. PAP is characterized by accumulation of surfactant and phospholipids in the pulmonary alveoli. That is due to impaired ability of surfactant clearance. The main pharmacodynamic effects of ambroxol are surfactant stimulation, mucokinetic activity, and some secretagogue activity (Eur J Respir Dis 153:255–262, 1987). Ambroxol may stimulate type II pneumocytes that is related to chemico-physical and functional changes in alveolar macrophages, probably through an improvement in surfactant secretion and uptake system (Lung 165: 333-340, 1987). We hypothesized that this may leads to improvement of PAP, but these are largely speculative. We entered our comments in discussion section. (Page4 Line35)

Ambroxol may stimulate type II pneumocytes that is related to chemico-physical and functional changes in alveolar macrophages, probably through an improvement in surfactant secretion and uptake system (Lung 165: 333-340, 1987). We hypothesized that this may leads to improvement of PAP.

Please let me know if there are further comments and questions.

Referee: 2

Thank you for reviewing our manuscript. Our responses are as follows.

1) "Here, we report a case of autoimmune PAP with chronic severe hypoxemia, which was cured by oral administration of ambroxol". The word cured should be replaced with a milder expression (e.g. responded to) as it can lead to misleading conclusions.

Reply
Thank you for your comment. I also think the word “cure” may be misleading. I changed the word “cured” to “responded to”. (Page2 Line34)
Here, we report a case of autoimmune PAP with chronic severe hypoxemia, which was responded to oral administration of ambroxol.

2) "Chest radiographs (CXR) showed bilateral ground glass opacities". Ground glass opacities is a descriptive term regarding High Resolution Computed Tomography and it should be avoided in the description of a Chest X Ray. The term "bilateral infiltrates in the mid and lower lung zones" is preferable.

Reply
Thank you for pointing it out. It is inadequate sentence. I replaced the text as your advice. (Page3 Line9)

Chest radiographs (CXR) showed bilateral infiltrates in the mild and lower lung zones (Fig. 1A) and chest CT showed bilateral ground glass opacities with thickened interlobular septa, an appearance termed the “crazy-paving” pattern (Fig. 2A).

3) "The patient has continued ambroxol treatment without disease progression". Could you specify the exact time range that the patient is in stable condition with ambroxol therapy.

Reply
Thank you for your comment. The patient has continued taking oral ambroxol for 17 months without exacerbation until now. I described as below in the Case presentation section. (Page3 Line35)

The patient has continued ambroxol treatment for 17 months without disease progression.

4) "Oral ambroxol should be tried for PAP, even in patients with severe respiratory compromise, because it is a simple treatment, unlike WLL or inhaled GM-CSF"
This comment can be misleading as the evidence of ambroxol efficacy regarding
PAP remains scarce. This comment implies superiority of ambroxol vs WLL/GM-CSF therapy and should be rephrased. According to current evidence (as already included in the manuscript), first line therapy is WLL and inhaled GM-CSF. Ambroxol therapy can be tried as a last resort alternative in cases that WLL or GM-CSF therapy is not feasible for various reasons, as in the described patient.

Reply
Thank you for your comment. As you noted, there is no evidence that Ambroxol is as worthy as WLL or inhaled GM-CSF on PAP. But it could be the alternative therapy if WLL and inhaled GM-CSF therapy are not feasible for various reasons, as in the described patient. I rephrased the sentence as below. (Page5 Line2)

Though WLL or inhaled GM-CSF therapy remains the first line therapy, oral ambroxol could be tried for PAP in the case of WLL and inhaled GM-CSF therapy not being feasible due to a various reasons, even in patients with severe respiratory compromise, because it is a simple treatment and with few side effects.

Please let me know if there are further comments and questions.