

Dear Editors and Reviewers:

Thank you for your letter and for the reviewer's comments concerning our manuscript entitled "Manifestation of severe pneumonia in anti-PL-7 Antisynthetase syndrome and B cell lymphoma: a case report" (ID:65435). Those comments are very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in highlight in the paper. The main corrections in the paper and the responds to the reviewer's comments are as following:

Responds to the reviewer's comments:

Reviewer #1:

1. Response to comment: "and was used to drinking more than 30ml daily for 20 years."

Drinking what ?

Response : Drinking liqueur. It has been modified in this paper.

2. Response to comment: "The PCT concentration was 0.19ng/ml (normal range: 0-0.5ng/ml)." what is PCT?

Response : We are very sorry we don't describe clearly. PCT is short for Procalcitonin.

3. Response to comment: Authors have used acronyms in abundance, more than what is warranted or necessary.

Response : We are very sorry for our mistake. It has been deleted in this paper appropriately.

4. Response to comment: "Sputum culture results showed 7 respiratory viruses" authors should provide more details on that.

Response : I'm very sorry that we didn't express it clearly. 7 respiratory viral RNA in Sputum (including influenzavirus, respiratory syncytial virus, parainfluenza virus) and blood capsular polysaccharide antigen of cryptococcus neoformans were negative.

5. Response to comment: "chest CT revealed bilateral gradual consolidation not only in the upper lobes but also in the inferior lobes" what does that mean? Consolidation was present even before, do the authors mean resolution of the consolidation?

Response : I'm very sorry that we didn't express it clearly. It means chest radiography worsened and consolidation increased. It has been modified in this paper.

6. Response to comment: Did the authors test for elevated creatinine kinase and/or aldolase?

Response :I'm very sorry that we didn't express it.Creatinine kinase is normal.

7.Response to comment:Information on lung biopsy?

Response :The patient was in critical condition and could not tolerate lung biopsy.

8.Response to comment:What was the reason for continuation of antibiotics despite lack of improvement from antimicrobial therapy?

Response :First, because the patient's condition was still progressing and CRP,PCT was increased. Second, the results of NGS showed the presence of Acinetobacter baumannii (30 series) and enterobacter cloacae (5 series), We can't exclude these as the pathogen of pneumonia although its detection series number were relatively low.

9.Response to comment:Information about echocardiography? Did the patient also have pulmonary hypertension?

Response :I'm very sorry that we didn't express it.The result of echocardiography was normal and there was no indication of pulmonary hypertension. It has been modified in this paper.

10.Response to comment:The title “Pneumonia” in a patient with anti-synthetase syndrome and B cell lymphoma does not fit since there is “No evidence” that the patient had pneumonia to start with. It might all be a manifestation of either underlying lymphoma or anti-synthetase syndrome associated ILD. I would suggest changing the title to “Acute respiratory failure in a patient with newly diagnosed anti-PL27 antisynthetase syndrome and B cell lymphoma” since there is virtually no evidence of pneumonia.

Response :Thank you very much for your suggestion. We will consider changing the title.

11.Response to comment:Also the work up seems incomplete without lung biopsy, histopathology and echo findings.

Response :The patient was in critical condition and could not tolerate lung biopsy. However,the patient accepted bone marrow biopsy and deltoid muscle biopsy and had a clear diagnosis.

12.Response to comment:Authors need to discuss the role of steroids in patients with respiratory failure who do not improve despite the trial of antibiotics such as this case. What does the evidence say for that?

Response :Thank you very much for your suggestion. It has been added in this paper.

13. Response to comment: Another point to discuss is whether the anti-synthetase syndrome was a paraneoplastic manifestation of the underlying malignancy. “ In our study, we highlight an important consideration of differential diagnosis in patients with severe pneumonia.” This is NOT a study; this is an isolated case. Needs to be rephrased.

Response : Thank you very much for your suggestion. It has been modified in this paper.

14. Response to comment: “Besides, the acute exudative lesions in the lung was the principal cause of respiratory failure and death of this patient.” Not sure what the authors mean by “exudative lesions”? Exudate is a biochemical finding assessed on the pleural fluid and not on imaging. I strongly suggest authors to seek expert opinion from a Pulmonologist for scientific approval of the content.

Response : Thank you very much for your suggestion. We should use “ acute lung injury” more accurately.

Reviewer #2:

1. Response to comment: Line 10 : “It is, however, rare to observe severe pneumonia as the first clinical manifestation in ASS patients, associated with B cell lymphoma.” The association between SSA and interstitial pneumonia is frequent and it is, moreover, a prognostic factor. In the SSA, lung damage is very common compared with others myopathies. The clinical course is generally more rapid and more severe. The association with lymphoma is rare.

Response : I'm very sorry that we didn't express it clearly. It has been modified in this paper.

2. Response to comment: Line 15 : “A chest computer tomography (CT) radiograph revealed bilateral diffuse ground-glass infiltrates in both upper fields, left lingual lobe and right middle lobe. Initially, the patient was diagnosed with severe community-acquired pneumonia and respiratory failure.” This is not the classic radiological appearance of bacterial community-acquired pneumonia. In times of pandemic; no test for SARS-CoV-2 is described (such as PCR, antigen or serology). Especially that there are associations between Covid-19 and ASS.

Response : Combined with the history, the patient developed fever and pulmonary infiltration in the community, We first diagnosed community-acquired pneumonia.

3. Response to comment: Line 18 : why use of broad spectrum antibiotics as first line empiric antibiotherapy for a community acquired pneumonia ? Are there any risks factors for carrying multi-resistant bacteria ? Line 33 : about the mechanic's hand ?

Response : I'm very sorry that we didn't express it clearly. It has been modified in this paper.

4. Response to comment: Line 42 : "Previous studies have shown frequent involvement of the lungs, but not muscular involvement while the other symptoms associated with ASS such as Raynaud's phenomenon were rare" With the anti-PL7 ? Muscle involvement seems to be the rule in dermatomyositis. The diagnosis is sometimes difficult: negative CPK, negative myogenic damage on electromyography, need to monitor troponins I

Response : Yes, these are the characteristics of anti-PL7 ASS. It has been modified in this paper.

5. Response to comment: Line 65 : "Chest CT showed bilateral diffuse ground-glass infiltrates in both upper fields, left lingual lobe and right middle lobe (Figure 1C). At first the patient was diagnosed with severe community-acquired pneumonia with respiratory failure. He was put under ceftizoxime antibiotics, which was changed to meropenem (1g every 8 hours) plus moxifloxacin (0.4g daily), and fluconazole injections (200mg daily)." Same remark as line 18 ; why using Meropenem as this stage ? Why using Fluconazole (with small dosage) ?

Response : We use meropenem because 1) the patient's condition progressed after empirical anti-infective treatment with the high levels of PCT and CRP. 2) The patients may have high risk factors of aeruginosa/acinetobacter infection such as structural lung disease and diabetic. 3) We considered to cover hospital acquired pneumonia related pathogens due to the patient with long hospital stay. We use low doses of fluconazole to prevent fungal infections due to the usage of high-doses glucocorticoid.

6. Response to comment: Line 78 : "the CK or CK-MB were within the normal range" : How to explain that these values are negative despite the final diagnosis of ASS ?

Response : CK-MB may be more closely related to myocardial injury. CK has high specificity and low sensitive in PM/DM. There were many PM/DM cases with normal CK level have been reported, so it is not a diagnostic criterion for ASS.

7. Response to comment: Line 83 : "Sputum culture results showed 7 respiratory viruses and

blood capsular polysaccharide antigen of cryptococcus neoformans” Is viral culture performed routinely on sputum? Which are the viruses detected? Is there any treatment for these?

Response :We are very sorry we don't describe clearly.7 respiratory viral RNA in Sputum(including influenzavirus, respiratory syncytial virus, parainfluenza virus) and blood capsular polysaccharide antigen of cryptococcus neoformans were negative.

8.Response to comment:Line 86 : “The concentration of blood tumor markers was” Why assay tumor markers? This is not recommended in the diagnostic process.

Response : In our medical institutions, we routinely detect tumor markers and have carried out tumor screening.

9.Response to comment:Line 92 : “NGS data from the broncho-alveolar lavage fluid showed the presence of Acinetobacter baumannii (30 series) and enterobacter cloacae (5 series). On the other hand, microbiological assessment provided no reliable evidence for viral, fungal or tuberculosis infection under sputum and BALF cultures” What is “NGS” abbreviation ? Microbiological analysis shows microorganisms or not ? Contradiction that I don't understand. Furthermore, what did show the anatomy-pathologist of bronchoalveolar lavage ?

Response :I'm very sorry that we didn't express it clearly. Next-generation sequencing(NGS)can be used to identify causative pathogens of bronchoalveolar lavage. NGS data from the broncho-alveolar lavage fluid showed the presence of Acinetobacter baumannii (30 series) and enterobacter cloacae (5 series), We can't exclude these as the pathogen of pneumonia although its detection series number were relatively low.I'm sorry, we haven't test the anatomy-pathologist of bronchoalveolar lavage.

10.Response to comment:Line 97:We then changed the antibiotics to cefoperazone/sulbactam (2g every 8 hours) plus Tigecycline (100mg loading dose, followed by 50mg every 12 hours) to cover for a resistant Gram-negative Bacilli. Antibiotic therapy is extended for the second time despite negative microbiological results ? Why ?

Response :Because the patient's condition was still progressing and based on the results of NGS in bronchoalveolar lavage. we changed antibiotics.

11. Response to comment: Line 107-111 : “We then considered inflammation of the lymph nodes.” “we presumed an infectious/inflammatory disease. » Why is a hypercaptive lymph node biopsy not performed?

Response : The lymph node biopsy in our medical institution needs to be carried out in the operating room. The patient was in critical condition and could not tolerate such examination.

12. Response to comment: Line 112 : “In addition, the patient developed a mild heliotrope rash” Others cutaneous signs such as Raynaud ? chilblains-like lesions ? acrocyanosis ? ulcers ? necrosis ?

Response : I'm very sorry that we didn't express it clearly. The patient had no other cutaneous signs such as Raynaud, chilblains-like lesions , acrocyanosis , ulcers and necrosis .

13. Response to comment: Line 118 : Indication of a muscular RMI ? If not performed, why ? And about nailfold capillaroscopy ?

Response : I'm very sorry I wonder if you mean muscle MRI. The patient underwent a thigh muscle MRI examination. The results showed that the soft tissues around the thighs and pelvis were edema. Thank you very much for your reminding and we have added this part to the article. Our hospital has not developed nailfold capillaroscopy technology.

14. Response to comment: Line 120 : “bone marrow biopsy results revealed high invasive B cell lymphoma in the bone marrow, which was confirmed by bright CD138 reactivity on immunohistochemistry assays “ Is it a second bone marrow biopsy than the first (normal) mentioned in line 108 ? Why a second bone marrow biopsy is performed ?

Response : I'm very sorry that we didn't express it clearly. The patient received only one bone marrow biopsy. Line 120 is the bone marrow biopsy results reported a week later and Line 108 is the routine bone marrow examination report.

15. Response to comment: Line 125 : “The patient finally succumbed to respiratory failure, three days after the diagnosis.” The authors mention the administration of methylprednisolone: for how long? After the diagnosis; has the anti-inflammatory treatment been changed?

Response : I'm very sorry that we didn't express it clearly. The administration of intravenous methylprednisolone : 40 mg every 12 hours, for 3 days, 40 mg every day, for 3 days, 20 mg

every day, for 3 days. We added intravenous methylprednisolone treatment (40 mg every 8 hours) again and discontinued anti-infective treatment after the diagnosis. It has been supplemented in the relevant part of this paper.

16. Response to comment: Line 135 : “Whereas PM/DM is frequently accompanied with interstitial lung disease (ILD)” Contradictory with line 10 (see comment above)

Response : We are very sorry for our mistake. Line 10 has been modified.

17. Response to comment: Line 157 : “A retrospective review of 32 PM/DM patients with hematological malignancy indicated that the top three malignancies are B-cell lymphoma (62.5%), T-cell lymphoma, and Hodgkin's disease. The study also suggested that PM/DM often precedes the onset of hematological malignancy [15] » Contradictory with line 156 : “Non-Hodgkin’s lymphoma (NHL) and other hematologic neoplasms associated with PM/DM (especially ASS) are relatively rare” and line 165 : “literature of anti-PL7 ASS and its association with lymphoma remains very limited” , or need reformulation.

Response : Thank you very much for your suggestion. It has been modified in this paper.

18. Response to comment: Line 179 : “difficulty to distinguish the disease from severe community acquired pneumonia” Clinical and radiological presentation does not suggest community-acquired pneumonia which should progress well under first-line empiric antibiotic therapy !

Response : We use empiric antibiotic therapy because 1) the patient's condition progressed after empirical anti-infective treatment with the high levels of PCT and CRP. 2) The patients may have high risk factors of aeruginosa/acinetobacter infection such as structural lung disease and diabetic. 3) We considered to cover hospital acquired pneumonia related pathogens due to the patient with long hospital stay.

19. Response to comment: A general comment / paragraph on diagnostic and therapeutic management is missing ; examples of references :

Response : We are very sorry for our mistake. It has been modified in this paper.

Responds to the editor’s comments:

1. The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend:

<https://www.wjgnet.com/bpg/gerinfo/240>;

Response : Thank you very much for your suggestion. Our manuscript has been polished by professional English language editing companies. The “non-Native Speakers of English Editing Certificate” will be upload.

2.The title is too long, and it should be no more than 18 words;

Response : We are very sorry for our mistake. It has been modified in this paper.

3.The “Author Contributions” section is missing. Please provide the author contributions;

Response : We are very sorry for our mistake. It has been added in this paper.

4. The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)

Response : “the approved grant application forms” will be upload.

5.The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response : “the original pictures” will be upload.

6. PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

Please revise throughout;

Response : We are very sorry for our mistake. It has been added in this paper.

7.The “Case Presentation” section was not written according to the Guidelines for Manuscript Preparation. Please re-write the “Case Presentation” section, and add the “FINAL DIAGNOSIS”, “TREATMENT”, and “OUTCOME AND FOLLOW-UP” sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.

Response : We are very sorry for our mistake. It has been added in this paper.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.