Author’s response to reviews

Title: Secondary pulmonary alveolar proteinosis: A Single-center Retrospective Study (A case series and literature review)

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Author’s response to reviews:

Dear Editor,

We are very pleased to receive your email and inform us such a good news. Thank you. We are deeply appreciated you and reviewers. We have responded the additional comments, made a few modifications and submitted the revised manuscript.

We hope that with your help our manuscript will be accepted for publication in BMC Pulmonary Medicine. If you have any other questions, please do not hesitate to contact us. We are looking forward to receiving your email.

Best Regards,

Xinlun Tian
Editor Comments:

BMC Pulmonary Medicine operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Shinya Ohkouchi (Reviewer 1): Authors answer all my question adequately. I admit this article is acceptable for the journal.

Stéphane Jouneau (Reviewer 2): Zhang et al. present a revised version of their single-centre retrospective study of 9 Chinese patients with secondary PAP.

In my opinion, the two first points of major essential revision have not been really addressed. However, adding the total number of PAP seen in their centre (157) is a good point.

A: We put the previous two questions and our answers as below and try to add more information on them.

1. The authors state in "background" that Ishii study included sPAP patients from Japan and therefore, due to "racial" differences, another series was needed to ascertain Ishii’s conclusions. I do not think that another small series (n=9) from Asia will really add something new compared to the large series of Ishii (n=40). The only new data from this Chinese series are on the pulmonary tuberculosis associated with PAP which were not addressed in Ishii’s study (only haematological diseases associated with PAP).

A: Since our hospital is the largest center of difficult and rare diseases in China, we have reviewed all the 157 PAP patients admitted to our hospital from 2000 to 2016 and found 9 sPAP patients among them. We believe our data have representative features of Chinese sPAP. In our manuscript, we attempt to know the clinical feature of Chinese sPAP patients and compare our patients with other case series. We found there are 4 patients secondary to tuberculosis, which may because of the high TB burden both on the absolute number and the severity of the disease
in China (WHO, Global tuberculosis report 2017). The other 5 cases of sPAP were secondary to haematological
diseases.

Thank you. Your suggestions are much appreciated because they give us an opportunity to rethink the value of our manuscript. Admittedly, both of Japanese and Chinese are Asians, and their racial differences are small. The reason of pulmonary tuberculosis associated with PAP in our case series which were not addressed in Ishii’s study is most likely the geographical factors including local economy, health status and the prevalence of diseases. So ‘racial differences’ is revised as ‘geographical differences’.

2. There are a lot of missing data such as arterial blood gases, pulmonary function tests, DLCO. It limits the impact of this rather small series.

Since this was a retrospective study, there were some limitations about the data. In our 9 patients, 8 had arterial blood gases (Page 4, Line 24), 7 patients had lung function. The other 2 patients were too weak to perform lung function.

A: Since it is hard to get accurate DLCO results when FVC < 1L in our hospital, this issue lead to the more missing data of DLCO. We are also very sorry about the missing data.

Other comments have been taken into account.

Daniel Culver (Reviewer 3): The authors have addressed my points well.

The only addition I can suggest to strengthen the paper would be to perform a statistical test (e.g. log rank) to demonstrate a statistical impact of hematologic versus non-hematologic causes of sPAP as depicted in Figure 1.

A: We are very obliged to you. We notice that with your professional suggestions, the value of our whole manuscript has a high improvement. During the last review, we have done the statistical test (in the following table) according to your advice, but didn’t present statistical results in text or Figure 1. Thank you for your additional suggestion, we list the x2 = 11.78 and P< 0.001 of Log-rank test in the remark of Figure 1.
Log-rank (Mantel-Cox) test
Chi square 11.78
df 1
P value 0.0006
P value summary ***
Are the survival curves sig different? Yes

Gehan-Breslow-Wilcoxon test
Chi square 8.779
df 1
P value 0.0030
P value summary **
Are the survival curves sig different? Yes

Median survival
hematological diseases 14.95
others Undefined

Hazard Ratio (Mantel-Haenszel)
Ratio (and its reciprocal) 2.238 0.4469
95% CI of ratio 1.413 to 3.545 0.2821 to 0.7079

Hazard Ratio (logrank)
Ratio (and its reciprocal) 2.627 0.3807
95% CI of ratio 1.417 to 3.535 0.2829 to 0.7058