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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PULM-D-17-00400

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

Dear Dr. Sanjay Haresh Chotirmall,

Thank you and reviewers for assessing our manuscript "Secondary pulmonary alveolar proteinosis: A Single-center Retrospective Study (A case series and literature review)” (PULM-D-17-00400), and giving us useful comments to improve our manuscript. In the following part, we responded to the comments point-by-point. We also adjust the format of our manuscript according to the journal style of BMC Pulmonary Medicine.
We wish our revised version to be considered for publication, and we look forward to hearing from you. If you have any questions, please don’t hesitate to contact us.

Thank you and best regards.

Shinya Ohkouchi (Reviewer 1): Dear Shinya Ohkouchi

Comments

1. sPAP is a rare and a difficult disease to diagnose for the physician. Probably, many sPAP patients are diagnosed other diseases such as non-specific interstitial pneumonia. The author mentioned the prevalence rate of pulmonary alveolar proteinosis (PAP) by quoting one article of Israel group (Page 3, line 3). However, Japanese physician group report different prevalence rate of PAP in Japan in AJRCCM 2008 177 p.752. The prevalence of sPAP may be various degrees because the medical system and facilities are different in each country. They should mention this thing in the paper.

Thank you for your useful suggestion, we changed the prevalence (Page 3, line 3) and add the explanation (Page 3, line 4-6).

2. There is no description of the threshold of GM-CSF antibody differentiating aPAP or non-aPAP (Page 3, Line 29).

The concentration of GM-CSF above 5 μg/mL was considered as positive in our hospital.

3. How about ethnic composition of nine patients with sPAP? (Page 3 Line 40).

All of patients with sPAP in our group are Chinese Han origin.
4. Author should mention the subtypes of MDS (RA, RARS etc.) (Page 4 Line 7).

We add the subtypes of MDS in the table 1, MDS-MLD, MDS-SLD, MDS-U and MDS-EB, respectively (according to 2016 WHO MDS classification).

5. GATA2 mutation is not main cause of s-PAP. s-PAP is accompanied with several hematologic diseases with different pathologies. They should mention other causes of s-PAP reported in several articles.

The patho-mechanism of sPAP secondary to hematological diseases remains unknown (Page 5 Line 34). And the research about it is rare. We add a result of mice modle study that T-bet-over-expressing T cells act to initiate the pathogenesis of sPAP (Page 5, Line 39).

6. MDS is main population in Japanese s-PAP patients however leukemia is main population in Caucasian s-PAP patients. The deviation suggests ethnic or other variation of s-PAP. The author ignore this ethnic problem. Therefore, the selection methods of the article in Table 2 and Figure 1 are insensible. Table 2 and Figure 1 are meaningless and may mislead the readers. They should remove Table 2 and Figure 1.

Thank you for your advice.

In this manuscript, we are afraid that we cannot clarified the racial differences between our group and others in such limited cases, so we ignore the ethnic influence, and try to review all published cases of sPAP to figure out the characteristics of all sPAP from different countries.

Figure 1 present the process of searching papers, we deleted it and listed it as a supplement data.
One of our objective for the manuscript is to know more about the characteristics of sPAP around worlds, so we think it is important to keep Table 2 in our article since it include a summary of all cases from published literature.

And we add the ignorance of ethic in limitation to avoid the misleading (Page 4, line 24).

7. Most interesting things in the article are the high rate of MDS and Tbc and the good prognosis of Tbc cases. The presentation of the representable cases are more informative for the readers.

Thank you for your comment. We think it is hard to present details of the cases in this manuscript because of words limitation. We hope we can write another case report to describe more details about the four sPAP cases secondary to Tbc.

Stéphane Jouneau (Reviewer 2):

- Major Essential Revisions

General comments:

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).

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.

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.

3. Reviews of literature take a large place in this article, especially 2 figures and 1 table. Table 1 is the one really necessary and is very relevant to the topic.

Thank you for your advice. Table 1 is the characteristics of our case series, but these cases were also being contained in table 2 and figure 2. To balance cases and review, we move figure 1 into supplement.

- Minor Essential Revisions

General comment

1. The authors have to use the updated classification of PAP (Borie et al. Eur Respir Rev 2011) with "auto-immune PAP" (aPAP, instead of "idiopathic PAP"). Changes have to be made in the whole manuscript.

Thank you for your suggestion. We have changed the term into auto-immune PAP.
Reference

1. Reference 3 (Trapnell et al.) is a bit old (2003). I suggest to the authors to add another more recent review on PAP (Borie et al. Eur Respir Rev 2011).

2. Reference 11 is not the correct one (letter to the Editor and not a case report). The correct article is Ballerie A et al. Eur Respir J 2016: Association of pulmonary alveolar proteinosis and fibrosis: patient with GATA2 deficiency.

- Minor Presentation Revisions

Discussion:

3. Page 6, line 2: Aspergillus

Thank you so much! We have added new review in references, correct the reference 11 and the word ‘Aspergillus’.

Daniel Culver (Reviewer 3):

1. It is not entirely clear why sPAP related to dust exposure was excluded from the Chinese cohort, especially since several occupational exposures including silica are currently very high in China.

In a study published before (Xiao YL et al. Occupational inhalational exposure and serum GM-CSF autoantibody in pulmonary alveolar proteinosis. Occup Environ Med. 2015;72(7):504-512), authors found that 34.2% of patients with autoimmune PAP had a history of occupational inhalational exposure, and only 4 patients with occupational exposure showed negative GM-CSF-Ab. Dust exposure was not a specified factor of sPAP( Costabel U, Nakata K. Pulmonary alveolar proteinosis associated with dust inhalation: not secondary but autoimmune. Am J Respir Crit Care Med. 2010; 181: 427-428). In China, occupational diseases were diagnosed and treated in designated hospitals, but our hospital is not belonging to them. For these reasons, none of our sPAP patients was secondary to occupational exposure. We add this information in the limitation part of our discussion.
2. The authors state that examining whether there are racial differences in the prevalence of sPAP, but the methodology they used does not address this question. If there were a comparison of the fraction of sPAP compared to aPAP, or some other comparison of the features of the Chinese versus other patients, this point could be more fully explored.

In our revised, we calculate that sPAP takes 5.73% of all PAP cases, the percentage is a little lower than that in Japanese case series (8.3 % ~ 10 %)(Page 5, Line33-34). Just as you mentioned, we cannot clarified the racial differences between our group and others, the difference of underline diseases may more likely because of the territory difference. It is more accurate to say that “we reviewed all published cases in literature to know more about the characteristics of sPAP around worlds.” We change the words in our manuscript (in Page 1, Line 21-22) and hope these changes may not mislead our readers.

3. The authors emphasized the absence of septal thickening in sPAP in the discussion, but the more frequently described difference, which was also present in their results, is the absence of a geographic pattern in sPAP. This should be noted also in the discussion.

Thank you. We add this in the discussion now (Page 6, Line 11-14. In our study, only 33.3% of cases show interlobular septal thickening, which is regarded as a typical feature in the CT scan of autoimmune PAP patients. And only 22.2 % of them present GGO with patchy geographic pattern, which is more common in autoimmune PAP. As a result, sPAP should be suspected in PAP patients whose CT scans only present GGO without interlobular septal thickening or in the absence of a geographic pattern.).

4. Some of the terminology is non-standard for the English-language medical literature, including "debilitation", "emaciation", "dust exploration", and "vesicles" as a radiographic descriptor. Please define what these mean or use other terminology.

Thank you! We change"debilitation", "emaciation", "dust exploration", and "vesicles" into “weakness”, “weight loss”, “dust inhalation” and “cysts”.

5. The Kaplan-Meier plot is useful, but it would be even more useful if the authors separated the hematologic causes from the other causes in the plot.
Thank you for your advice. We separate cases secondary to hematological diseases and the other causes in Figure 1. In 92 cases secondary to hematological diseases, the median survival was 14.95 months as 66 (71.3%) died within 5 years. In 40 cases secondary to other causes, the median survival was 60 months and 14 (35%) died within 5 years.

6. In how many of the 9 patients was the PAP the presenting issue?

5 out of 9 patients had PAP-related respiratory symptom.