Peer Review File

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Reviewer A

Comment 1: This is a case series of WLL in PAP syndrome over 20 years. It is descriptive in nature. While the authors have carefully collated their experience, there have been much larger case series described and notably there have been multinational collaborative papers regarding WLL experience. See Campo et al Chest and others. PAP is not a disease but a syndrome.

Reply 1: Thank you very much for your comments. We are fully aware that our study is a small retrospective study; however, in Southeast Asia, especially in developing countries, there are not many studies on whole lung lavage experiences and results after the procedures. We truly intended to demonstrate our experience keeping in mind that this is a rare syndrome in our country and we do not have the test for autoimmune PAP or hereditary PAP. Therefore, WLL is still the best treatment of choice in our setting. It is very effective, not expensive, and it is a safe procedure if we use the correct technique and know how to manage the complications. We wish to explain our experience to others who have the same setting as our centre and hope they do not hesitate to start this procedure. Although our study was from a single reference centre and was less relevant than large multicentre series, it has the advantage of including detailed experiences accumulated over two decades and extensively reviews the characteristics of the patients.

We have modified our text as advised (please see page 4, line 57-59)

Comment 2: To describe PAP as idiopathic is outdated and the number of primary PAP is low in this cohort, primary and autoimmune PAP should account for >90% of cases and this is worldwide. Please see Trapnell et al 2019 Nat Rev Dis Primers.

Reply 2: We initially used the term “idiopathic” instead of primary PAP because we were unable to perform tests for serum GM-CSF autoantibody, serum GM-CSF levels, and GM-CSF signalling that includes gene mutation tests. We hesitated using the term “primary PAP” but we do believe that the majority in our study was primary PAP. Furthermore, in our results, primary PAP was 68% of the patients. In any case, we

decided to change the terminology from “idiopathic PAP” to “primary PAP” according to your suggestion and from the updated literature (Trapnell et al 2019). We agree that the term “idiopathic PAP” is an old-fashion term. However, our study has a limitation since we were unable to separate the subtypes of PAP.
We have modified our term as advised (please see Table 1)

Reviewer B

Comment 1: In the discussion section, the authors made a comparison with the results reported by other series. Due to extreme rarity of PAP is could be reasonable to include also the Italian study (Campo et al. Orphanet Journal of Rare Diseases 2013, 8:40) where the rate of asymptomatic PAP cases at diagnosis demonstrates a marked difference with the other studies and in particular with the Japanese series (5% vs about 30%).
Reply 1: We have included the Italian study in the discussion. However, our study could not show the percentage of asymptomatic patients because all cases were symptomatic and had moderate to severe symptoms that required WLL.
We made changes in the main text. (please see page 10;line 195, page 11; line 220-222)

Comment 2: The current study furtherly underlines that PAP patient’s management is still an evidence-based, best-practice approach based on the single-centre experience. An attempt towards the building of a consensus document for the standardization of the procedure was made by means of a survey of physicians from 20 centres in 14 countries, practicing WLL in adults (Campo et al. Orphanet Journal of Rare Diseases (2016) 11:115). As this survey found that WLL is safe and effective as therapy for PAP while the aim of the present study was to evaluate the efficacy of WLL, the authors should add a couple of sentences discussing this issue.
Reply 2: In our study, we focused on two aims: (1) to determine the long-term efficacy of WLL in the context of a rare syndrome where testing for autoimmune PAP is unavailable, inhaled GM-CSF is unavailable, and a standardized procedure for WLL is lacking, especially in Southeast Asia where the physician’s experiences of WLL is much lower than in Japanese, American and European settings and (2) to thoroughly

describe the clinical characteristics of our patients who had some differences from previous studies.
We added information as advised (please see page 10, line 191-194)

Comment 3: Finally, in the methods section the description of WLL procedure is taken from an article that is not referenced (Campo et al. Multidisciplinary Respiratory Medicine 2012, 7:4). In particular, lines 82 to 90 of the present manuscript "The WLL technique is performed under general anaesthesia in an operating room. The patient is intubated with a double-lumen endotracheal tube (DL-ETT) and fiberoptic bronchoscopy is performed to confirm appropriate tube placement. The patient is placed in the lateral decubitus position. The lung is then lavaged in the uppermost position while the non-lavaged lung is mechanically ventilated. Warmed saline (37°C, 500–1000 mL) is injected into the lung per one cycle. Fluid is then collected by gravity after opening the outflow tube. Manual chest percussion may be performed to improve drainage. Lavage and percussion are continued until the outflow fluid becomes definitively clear (Figure 2), which may take several hours and a total of 15–20 L of saline for a single lung lavage" correspond to "The WLL technique at the Pavia Center is performed under general anaesthesia in an operating room or an intensive care unit. The patient is intubated with a double lumen endotracheal tube and fibre-optic bronchoscopy is performed to confirm the appropriate tube placement. The patient is placed in the lateral decubitus position; the lung is lavaged in the uppermost position, while the non lavaged lung is mechanically ventilated. 500–600 mL of warmed (37°C) saline is injected in the lung. Fluid is then collected by gravity after opening the outflow tube. Manual chest percussion may be performed to improve drainage. When the outflow, initially milky, becomes clear, chest wall percussion, which restarts and greatly enhances the removal of proteinaceous material, is added. Lavage and percussion are continued until the outflow fluid became definitively clear, which may take 3 hrs and a total of 15–20 L saline for a single lung" in Campo et al. Multidisciplinary Respiratory Medicine 2012, 7:4.
Please add the reference.
Reply 3: We regret that we missed this important reference. We revised our manuscript and added this reference. (please see page 6, line 109)

Reviewer C

An important data from Asia, about a rare disease, with worldwide interest on these data.

Comment 1: A lot of work correcting English.

Reply 1: We corrected the English.

Comment 2: Need an urgent correction about the PH data - otherwise, should not be accepted.

Reply 2: It was a huge mistake on our part. We used right heart catheterization for the diagnosis of PH, not echocardiography. (please see page 8, line 147)

Comment 3: Line 2: change "Songklanagarind Hospital" for "an Asian or Thai reference centre"

Reply 3: We changed the text. (please see page 1 line 2

Comment 4: Line 49: include information on treatment options as anti-CD20 monoclonal antibody (rituximab) and lung transplant

Reply 4: We revised the text to include this information. (please see page 4 line 67-69)

Comment 5: Line 52: Suppress information "...in Thailand. Songklanagarind Hospital is a university hospital in southern Thailand". If preferable, refer as "limited data are available in Thailand, Asia and worldwide. We manage several PAP patients as a reference centre..." All those pieces of information about the place of the study should be on the author's information. When we see the author's location, we know the origin of the study.

Reply 5: We revised the text. (please see page 4, line 71-72)

Comment 6: Line 60: the same – "from a health information database system".

Reply 6: We revised the text. (please see page 5, line 82)

Comment 7: Line 69: change "chest X-ray" for "chest radiograph"

Reply 7: We revised the text. (please see page 5, line 93)

Comment 8: Line 72: change “ratio FEV1/FVC” for “FEV1/FVC ratio”
Reply 8: We made this revision. (please see page 5, line 97)

Comment 9: Line 110: normal physical examinations? How to indicate WLL? Or absent of Digital clubbing?
Reply 9: We revised the text. (please see page 7, line 138)

Comment 10: Line 112: “done” – change for “performed” or “available”
Reply 10: We revised the text. (please see page 7, line 140)

Comment 11: Line 118: “ had secondary pulmonary hypertension defined as a mean pulmonary arterial pressure >25 mmHg from echocardiography” - The definition of PH is wrong – the correct one is pulmonary hypertension (PH) is defined by a mean pulmonary arterial pressure (mPAP) ≥20 mmHg in a right heart catheterization – this mistake urge to revisit and change the data about PH
Reply 11: We made the appropriate changes. (please see page 8, line 147)

Comment 12: Line 123 – make it simple – a lot of decimal is unnecessary;
Reply 12: We simplified the data to the nearest tenth. (please see page 8, line 152-154)

Comment 13: Line 140: The same with “x-ray”
Reply 13: We revised the text. (please see page 9, line 170).

Comment 14: Line 145: Add a Kaplan-Meier survival curve;
Reply 14: We added the curve in main text. (please see page 9, line 174-176, figure 3)

Comment 15: Line 150: change “right-sided heart” for “right heart”
Reply 15: We made changes in the text. (please see page 9, line 181).

Comment 16: Line 198: change “Nobody” for “none of those patients”
Reply 16: We deleted “Nobody” and inserted “None of those patients”. (please see page

12, line 237)

Comment 17: Line 239: change “Songklanagarind Hospital” for “our centre”

Reply 17: We revised the terminology. (please see page 14, line 295)

Comment 18: Table 2: decimal numbers..the same

Reply 18: We made the appropriate changes. (please see Table2)

Reviewer D

The authors present a single center experience of WLL for PAP. Article is well written and with important results that validate WLL as a treatment measure.