Peer Review File

Article information: https://dx.doi.org/10.21037/jeccm-22-47

Reviewer A

This is an interesting case report presenting a novel technique for treating PAL.

1. Current case only provided short term follow up, are there any longer follow up information? did this PAL recur later? "There was no recurrence of the air leak"--the most recent follow up time should be added to this statement.

Thank you for the suggestion. A more detailed timeline has been added to the case presentation. The patient did not have recurrence of her air leak with the most recent follow-up being 4 months after her PAL resolved.

Changes to the text: pages 3-5, lines 64-119

2. what is the diagnostic criteria for PAL, as apposed to general pneumothorax caused by other reasons?

The most commonly utilized definition of PAL is a leak lasting >5-7 days, although other sources use a leak lasting more than 2 days. A pneumothorax would become a persistent air leak if it were to meet the time criteria. We have added further definitions of PAL in the introduction

Changes to text: page 2, lines 45-48

Reviewer B

This manuscript showed a case report of successful treatment with endobronchial fibrin sealant and autologous blood patch for persistent air leak in a mechanically ventilated patient. My comments are as below.

1. Line 31 and line 63
I cannot clearly recognize necrotic area in middle lobe in Figure 1. Do you consider that necrosis of the pneumonia resulted in alveolar pleural fistula? If so, please indicate the necrotic area in the figures.

Thank you for the suggestion, we have included further annotation within figure 1a and 1b to help identify the areas of necrosis and suspected site leading to the alveolar pleural fistula.

2. Line 74 and line 82
I guess that the balloon occlusion for 5 minutes is technically important in the success. Authors need to refer to the technique.

Thank you for the insightful comment. We have highlighted the balloon inclusion technique in the text.

Changes to text: abstract page 2, line 34; case presentation page 4, lines 88-92

3. Line 86
Authors observed no air leak and removed chest tube. After that, how long do you observe no recurrence? Autologous blood and fibrin sealant are absorbable, so the observation less than a few weeks is not sufficient.

A more detailed timeline has been added to the case presentation. The patient did not have recurrence of her air leak with the most recent follow-up being 4 months after her PAL resolved.

Changes to the text: pages 5, lines 118-119.

Reviewer C

1. PAL needs to be defined. The ambiguity of duration in the definition could be brought about and at which point in time it was persistent in this case.
Thank you for the recommendation, we have added further definitions of PAL in the introduction, including the varying definitions.

Changes to text: page 2, lines 45-28

2. It will be good to present the timeline between detection of the pneumothorax and the initial chest tube, between each chest tube and eventually the endobronchial procedure which will also convey the timing of procedure from the onset of air leak. This is also important, to see if adequate time was given for the air leak to spontaneously settle, particularly once the cumulative -120cm H2O pressure was applied and the lung expanded.

A more detailed timeline has been added to the case presentation.

Changes to text: pages 3-5, lines 64-119

3. "her chest tubes were removed from suction" has been mentioned for the 3rd attempt but not mentioned after the first and second attempt. This is important to mention, as suction can cause failure of the sealant/blood patch used.

Further details about the suction, and removal of suction post-endobronchial therapy have been added to the manuscript.

Changes to text: pages 4, lines 95-96

4. Pre and post procedure chest x-ray, if feasible would help appreciate the success radiologically.

Radiographically there was no significant change pre and post procedure thus they have not been included in the manuscript.

5. A discussion on the quantity of blood would be useful. For example, why did the authors use 25 ml? This series https://erj.ersjournals.com/content/56/suppl_64/1203 used 100 ml. Quantity used across literature, if reviewed and discussed will make some clear points for those who may consider doing this procedure.

We opted to use 25mL as this was used in the largest case series where autologous blood and thrombin were used (41 patients treated successfully). We also added to the discussion further review of the volumes used for endobronchial treatment of PAL.

Changes to text: page 6, lines 142-147.

Reviewer D

The authors have reported a single successful case of using autologous blood patch followed by fibrin glue in a mechanically ventilated patients with a broncho-pleural fistula due to necrotizing pneumonia.
I have the following comment/queries:
1. please provide the number of days from first occurrence of pneumothorax for the three episodes of endobronchial intervention.

Thank you for the suggestion, we have further clarified the timeline of the patient's management of her PAL.

Changes to text: pages 3-5, lines 64-119

2. how many days after the 3rd intervention was the chest tube taken off?

The chest tube was removed 8 days after the 3rd intervention.

Changes to text: page 5, lines 116-117

3. was there any radiological evidence of collapse of the medial segment of the right middle lobe immediately following the interventions? If yes did it resolve later, and after how much time?

There was no radiographic evidence of RML collapse after the interventions.

4. the medial segment of the right middle lobe was identified by the balloon test to be implicated in the broncho-pleural fistula in the first intervention. Would you agree that inserting an endobrochial one-way valve at that juncture might have effected immediately cessation of air-leak, thus shortening ventilator time and ICU stay significantly?

We agree that an EBV may have led to immediate cessation of the airleak. Unfortunately, EBVs are not readily available at our institution.

Changes to text: page 4, lines 86-87

5. Fissure integrity has been reported to be correlated to success of EBV in treating PAL. Do you think it is similarly implicated in the current reported form of treatment?

Fissural integrity and collateral ventilation is also relevant for endobronchial instillation treatment. In our case the leak fully resolved with occlusion of the RML, thus suggesting there was no clinically significant collateral ventilation. We have clarified this in the text.

Changes to text: page 4, lines 91-93

Reviewer E

The authors present an experimental intervention that happened to be successful. They failed to utilize more standard of care modalities first despite not being in a clinical trial. I would caution against publishing this. There are also large gaps in the clinical story and discussion section.

Comments to the authors:
Introduction:
Please provide a citation for the use of endobronchially instilled substances previously.

Thank you for the recommendation, citations have been added for the endobronchially instilled substances

Changes to text: page 3, lines 56-59

Case:
Why did she require so many chest tubes? Three tubes for pneumothorax is highly unusual. Clarify number of tubes, why other failed

After her initial 8F chest tube which was attached to suction at -20cm H2O, she developed re-expansion of her pneumothorax and hypotension thought to be secondary to this so she had a 14F chest tube inserted. Despite having two chest tubes in situ, both attached to suction her lung did not fully re-expand. As per the recommendation of thoracic surgery, a third 24F chest tube was inserted and attached to suction at -40cm H2O which led to full expansion of the lung. This has been further characterized in the case presentation.

Changes to text: pages 3-5, lines 72-81

How vigorous was the air leak? Please provide the grade according to established systems.
Was water seal even tried, and if so, did she fail?

Further details have been added including the grading of the air leak. She was off suction multiple times but had failure with recurrence of her leak and reaccumulation of the pneumothorax.

Changes to text: pages 3-5, lines 72-81

Why was she not a surgical candidate?

Thoracic surgery felt she was not a candidate due to her frailty, hemodynamic instability, and no focal area for resection. This has been added to the text.

Changes to text: page 4, lines 77-79

Why was a bronchoscopic approach tried first? Why wasn't a pleural blood patch tried first?

We opted for more local endobronchial therapy as on CT imaging there was an identifiable source of the leak. There was also the concern about the complication of ARDS from chemical pleurodesis, which would be detrimental in this patient already requiring mechanical ventilation with bilateral necrotizing pneumonia.

Changes to text: page 4, lines 83-87

How did you identify the RML as the culprit? This would be a good opportunity to mention sequential balloon occlusion.

We have added further description of the sequential balloon occlusion technique that was utilized.

Changes to text: page 4, lines 88-95

Was suction still required after the first two blood patches, or was she able to tolerate water seal?

Further information regarding the timeline for the management of the PAL, including suction, have been added to the text. She was only able to tolerate water seal for a few days after each of the first two blood patches.

Changes to text: pages 4-5, lines 95-96, 102-106

What is the time course from instillation of the Tisseel to chest tube removal and extubation?

Further information regarding the timeline for the management of the PAL has been added. It took 8 days from the Tisseel and blood patch intervention to removal of the chest tube, and 17 days to be freed from mechanical ventilation.

Changes to text: page 5, lines 116-119

Why wasn't a reversible intervention tried, such as an endobronchial valve? Non-reversible interventions should be an option of last resort.

Unfortunately, EBVs are not readily available at our institution. We have clarified this in the text and also discussed reversibility of endobronchial therapies as a consideration.

Changes to text: page 4, lines 86-87; page 7 lines 153-157

Discussion:
A large case series of endobronchial valves in ICU patients was published by Mahajan et al (PMID: 23207358). This should at least be recognized, if not cited.

This case series was cited in the discussion regarding EBV use in mechanically ventilated patients.

Pneumothorax is not a complication of endobronchial valves for PAL; it's the exact reason they're being used in the first place.

Thank you for pointing out this error in the text, we have removed pneumothorax as a complication of EBV in the context of PAL management.

The rate of post-obstructive pneumonia is not significantly higher with valves since they allow air and secretions to egress.

Thank you for the suggestion, we have removed pneumonia as a complication.

You claim sealants are more economical than valves without discussing cost data of each or referencing prior literature on the cost.

We clarified that it is the product cost of fibrin sealant that is less than an EBV and have cited texts discussing costs of the products themselves.

Changes to text: page 7, lines 148-150

It is important to recognize the primary limitation of a fibrin sealant. Although it does not require a repeat procedure for removal like valves, it is also not immediately reversible. If it does cause a complication, there is no easy recourse.

We added further discussion regarding reversibility of endobronchial therapies.

Changes to text: page 7, lines 153-157

Reviewer F

This is a nice case not only highlighting a cost-effective technique to treat PAL but also demonstrating challenges in managing PAL in mechanically ventilated patients. I think the most important point to add to the case is the timeline, in days. Specifically, what was the definition of PAL used by authors? If < 5 days, what was the indication for invasive intervention? was the patient hemodynamically unstable?

Thank you for your comments, we have added further details regarding the timeline of the PAL management.

Changes to text: pages 3-5, lines 64-119

Reviewer G

Summary:
The authors present a case of a mechanically ventilated 61 year old woman with persistent air leak (PAL) from an alveolar-pleural fistula (APF) caused by necrotizing pneumonia. After two unsuccessful attempts at treatment with endobronchial blood patches, the PAL resolved after treatment with a combination of blood patch and fibrin sealant. The novel aspect of the case is the successful combined use of blood patch and fibrin sealant, which would be of interest to clinicians who perform bronchoscopy. In general, the case presentation lacks important details. I am also concerned that specific management decisions prevented earlier PAL healing.

Abstract:
1. The summary of the timeline should mention the x2 failed attempts to control the PAL with blood patches.

Thank you for the comments, we have further clarified in the abstract the 2 failed blood patches.

Changes to text: page 2, line 32

2. **Line 37 mentions the approach is "safe and affordable". Have the authors formally assessed the costs/affordability? If so, this analysis should be included. If not, instead of "safe and affordable" it would be more accurate to simply say "effective".**

We have not formally assessed the costs associated with each therapy and have changed the wording as suggested. We clarified that it is the initial cost of fibrin sealant that is less than an EBV and have cited texts discussing costs of the products themselves.

Changes to text: page 7, lines 148-150

Introduction:
3. The first two sentences of the introduction relate to PALs in general. The third then changes suddenly to PAL treatments in the context of mechanically ventilated patients, however this context isn't explained. Please ensure the context of mechanical ventilation is clear. As the sentence currently stands, it seems as if mechanical ventilation is a supportive treatment for PAL, which it isn't.

Thank you for identifying an area of confusion for readers, the phrasing has been changed to

clarify that the supportive treatments are in the context of mechanically ventilated patients.

Changes to text: page 3, lines 49

4. The section on endobronchial valves (EBVs) and other PAL treatments from lines 48 to 55 requires references.

References have been added to that section of the text.

Changes to text: page 3, lines 56-59

Case presentation:
5. Please include the patient's relevant past medical history.

The patient had a history of diabetes which has been included. Otherwise her other comorbidities of anxiety, dyslipidemia, spontaneously cleared hepatitis C, traumatic brain injury, peptic ulcer disease, and hypertension were not felt to be relevant but can certainly be added if preferred.

Changes to text: page 3, line 61

6. **Multiple pathogens were isolated. How were they isolated? Please also add the antimicrobial agents that were used.**

We have added from what types of samples the pathogens were isolation and the antimicrobials used.

Changes to text: page 3, lines 67-20

7. In general, much more information on the timeline of events is required. Specifically, please describe on which day of admission the pneumothorax occurred; when and why the patient was intubated; why the patient was deemed unfit for surgery; when the chest tubes were inserted; on which days bronchoscopy/endobronchial interventions were performed; when the chest tubes were removed; when she was extubated etc.

Further details regarding the timeline and specific management has been added.

Changes to text: pages 3-5, lines 64-119

8. Can the authors please explain the rationale behind the use of -40cmH2O wall

suction? If suction is used for PAL, a 'low' pressure i.e. -2kpa/-20cmH2O is generally recommended. I am concerned that the level of suction used in this case prevented the PAL from healing earlier. Likewise, mechanical ventilation of the right lung could potentially prevent healing. Was single (left) lung ventilation ever attempted/considered?

Suction of -40cm H2O was used as the patient did not have re-expansion of their lung at suction of -20 cm H2O. Suction was eventually decreased later on during her time in the ICU. Single left lung ventilation was not attempted, as our ICU does not do this and also felt that she would not tolerate it given the severity of her bilateral necrotizing pneumonia.

Changes to text: pages 3-5, lines 72-80 +103-106

9. The air leak was localized to the medial segment of the right middle lobe. The common approach in centres with access to endobronchial valves would be to attempt EBV insertion into the affected segment, an approach that would require two procedures (one for insertion, and a later one for removal). This patient ended up requiring three procedures to control the air leak. Why was autologous blood patch chosen instead of EBV insertion at the time of the first bronchoscopy?
Unfortunately, EBVs are not readily available at our institution. We have clarified this in the text.

Changes to text: page 4, lines 86-87

Discussion
10. On line 94, pneumothorax is listed as a complication of EBVs. Do the authors mean that EBV insertion for PAL could cause another air leak? EBV can certainly cause pneumothorax when used for lung volume reduction in hyperinflated patients with COPD, but I'm not so sure about this instance.

Thank you for pointing out this error in the text, we have removed pneumothorax as a complication of EBV in the context of PAL management.

11**. The argument that use of absorbable materials has an advantage of EBVs because they don't require a repeat bronchoscopy needs to be tempered with an acknowledgement that their use doesn't always lead to resolution of the PAL on the first attempt**, **as highlighted by this very case.**

We have made changes to the discussion highlighting this point.

Changes to text: page 7, lines 152-153
Figures:
12. **Figure 1 could be improved with an arrow pointing to the suspected APF, for the benefit of readers.**

We have added arrows to figure 1 to help identify the suspected APF.

Reviewer H

1) can you comment on why blood patch was done alone the first two times, when it has been shown to be effective with fibrin AND blood patch?

Thank you for the comments, there have been successful cases of endobronchial autologous blood patches without the addition of fibrin so this was attempted first. In retrospect we could have attempted the combined technique earlier, such as with her second intervention.

2) what were the specific reasons thoracic surgery would not even at least do a small VATS pleurodesis with doxy or talc? or had the authors thought about instilling doxy or talc via the chest tube, pretty low risk.

We opted for more local endobronchial therapy as on CT imaging there was an identifiable source of the leak. There was also the concern about the complication of ARDS from chemical pleurodesis, which would be detrimental in this patient already requiring mechanical ventilation with bilateral necrotizing pneumonia.

Changes to text: page 4, lines 83-86

3) Why 25 cc of blood, seems like a lot down an airway? did patient tolerate this well in terms of respiratory status?

The patient tolerated each of the interventions well with no worsening in her respiratory status, which we clarified in the manuscript.

Changes to text: page 5, line 115