

Peer Review File

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Reviewer A

General comments:

The authors showed a patient who experienced recurrent hemoptysis and was made a diagnosis of an uncommon form of bronchopulmonary sequestration (BPS). This case is relatively rare and included educational points; however, several points should be addressed to improve the manuscript.

Reply:

Dear Dr/Prof Reviewer, thank you so much for your kind words, I share the same sentiments as you when we first came across this case, and when we eventually diagnosed this patient with ELS, I was quite excited to write this up and to share our learning points from this case. I will endeavour to revise and improve this manuscript and gear it towards your comments. Thank you again.

Changes in text:

N/A

Specific Comment 1:

In lines 48 and 49, the author wrote the patient had a recent episode of pneumonia.

-What was the cause of pneumonia, and where was the lesion in the lung?

-Does the author think there is a relation between BPS and pneumonia in the present case?

Reply 1:

Dear Dr/Prof Reviewer, thank you for your comment. We note that the pneumonia was treated as an outpatient by her general practitioner who treated it as a community acquired pneumonia with oral ceftriaxone which later resolved over the next week. This general practitioner has been the patient's GP for close to 20 years, and hence was highly experienced and that the patient trusted him entirely. We only found out about this pneumonia when we reviewed her at our hospital's outpatient respiratory clinic about 3 weeks after she has recovered from this episode. In this case, I've reached out to the general practitioner, who has informed me that the pneumonia was most likely a left upper lobe pneumonia based on the patient's clinical history and the general practitioner's examination findings, he used the CURB-65 score, where the patient scored 0 points. He then treated it without a CXR due to his clinical findings being "extremely convincing". However, we definitely considered the fact that her BPS may have contributed to this episode of pneumonia as the initial thought of this density in her lingula segment was probably a collapsed segment of lung that may have been subjected to multiple infections over the course of her life – to which she

denied. And we've confirmed this by taking a collateral history with the patient's mother as well – if there were any recurrent chest infections in her childhood.

Changes in text:

My sincere apologies that I did not include these aspects in our case report previously. I have endeavoured to include them in the lines 50-55 in the revised manuscript in a more concise and hopefully clearer manner to ensure that our thoughts were communicated well.

Specific Comment 2:

Please add an image of the thoracic aortogram at the diagnosis of BPS.

Reply 2:

Dear Dr/Prof Reviewer, thank you for your comment. My sincerest apologies that we did not include the thoracic aortogram in our initial manuscript as we were hoping the arterial phase would suffice for a shorter and quicker read for readers. However, in retrospect, I now realize that the thoracic aortogram is absolutely crucial in helping paint the picture in our case. Thank you for alluding me to this crucial investigation.

Changes in text:

Sincere apologies again. I have now included the combined linked axial and sagittal views for the thoracic aortogram in Figure 3.

Specific Comment 3:

Please add arrows to where the author wants to indicate in Figure 1.

Reply 3:

Dear Dr/Prof Reviewer, thank you and I sincerely apologize again that we did not include arrows in our previous manuscript. I realize that just labelling the figure caption is insufficient especially when it comes to a condition whereby radiological findings are paramount for the diagnosis and for the importance of readership. I apologize for this.

Changes in text:

Sincere apologies. I have now included arrows across the figures in the revised manuscript for a clearer view of what we want to allude the readers to.

Minor Comment 1:

"CT" should be spelled out at the first appearance in a line 43.

Reply 1:

Dear Dr/Prof Reviewer, thank you for pointing this out. I sincerely apologize for this mistake made on my end.

Changes in text:

Sincere apologies again. Line 43 was the first mention of "CT" – this first mention of "CT" is now spelled out instead and I have also gone on to specify if contrast was used. Which in this case, contrast was used for all the studies done. Thank you.

Minor Comment 2:

Please clarify whether the conducted CT utilized contrast enhancement or not.

Reply 2:

Sincere apologies Prof/Dr Reviewer, contrast was used for all CT studies done in this patient.

Changes in text:

Thank you for pointing it out. And I apologize, I have now added this and correctly spelled out Computed Tomography at the first mention. Apologies.

Reviewer B

Comment 1:

Line 31. I suppose that the wording "airway. Whereby..." should be modified into "airway, whereby...".

Reply 1:

Dear Dr/Prof Reviewer, thank you for pointing this out. I sincerely apologize for this grammatical mistake made in our introduction section.

Changes in text:

I have now edited Line 30 to the appropriate sentence structure as pointed out kindly, by yourself. Sincere apologies.

Comment 2:

Line 43. It would be interesting to add some images and a brief description of the imaging findings of the first CT examination. A properly performed and reported CT exam can actually provide a wealth of information allowing to diagnose pulmonary sequestration; such findings may well be incidental, but it is not clear to me why "possible" and not "definite" or at least "probable" BPS. Had that CT exam been ordered without contrast medium administration? Was the report somewhat unclear or misleading? In general, please replace the term "scan" with "examination" or "study".

Reply 2:

Dear Dr/Prof Reviewer, thank you for your comment. I sincerely apologize for not adding the initial CT study, the initial CT study was done at a private imaging facility and initially took a process of patient and hospital authorization before getting my hands on it. Our local respiratory department shares the same sentiments as yourself and absolutely agree that well performed CT study can provide a multitude of information. The initial study was seen and reported by 2 independent radiologists, as a 2nd opinion was sought. Both radiologists were veterans in the field of radiology. Both radiologists shared similar findings and their reports were largely similar in the key aspects reported that I have now included as Figure 1. They had both agreed it was very much like a BPS based on their findings but advised for clinical correlation to be done by the clinicians before deciding if it was the case. Hence the use of the word “possible” in this instance. I had a conversation with the radiologist who further explained that the radiological findings were definitely very alike to that of a BPS, but due to our patient’s BPS being of a somewhat smaller size (which he acknowledges can be rare but can happen) as compared to other BPS in the literature they needed to report the findings as probable instead of reporting it as definite. He alluded to me that this was also for medico-legal reasons as radiologists working in the private stream. However, it was my honest mistake that I misinterpreted the report from the second CT study and failed to convey the right information from that report – which was that the diagnosis of BPS was confidently given (which we expected), and that the type of BPS implied here was an ELS. Once again, I sincerely apologise for misinterpreting the communication through the CT report. Thank you again for pointing out to me some of the subpar sentence structure used in the initial manuscript, I have made the edits and hopefully will now be clearer in articulating our thoughts.

Changes in text:

My sincere apologies, I have made the changes of changing the word “scan” to “study” throughout the manuscript. I have also now acquired the first CT study and have included it into the updated manuscript as Figure 1. I’ve also further edited the areas of the manuscript to endeavour to articulate some of the contents from my reply above. Hopefully it is now communicated much more proper throughout the revised manuscript. Thank you Dr/Prof Reviewer for your time in helping review this manuscript.

Comment 3:

Line 65. Again, are you sure that (even in retrospect) a reliable assessment of the BPS vascular (arterial and venous) and airway connections could not be obtained based on the second CT findings, thereby warranting the need for thoracic aortography and bronchoscopy? Can you provide also 2D and 3D reconstructions from native CT images of the feeding arteries and draining veins? Current multidetector CT technology can do this quite easily obviating the need for invasive aortography, which is being more frequently used more for endovascular treatment than for diagnosis alone.

Reply 3:

Dear Dr/Prof Reviewer, thank you for this comment. Our respiratory department wholly agrees that a 3D reconstruction would be valuable in this case. In fact, during the initial workup for our patient, we had requested and argued for a 3D reconstruction to which we were repeatedly turned down for due to safeguarding of resources and costs involved in our public hospital. We had approached the private radiology firm where the first CT study was done however, were again turned down, as their protocol was that a request for a 3D reconstruction had to be done at the time of the study request. My sincerest apologies for this. The rejection by our local radiology department at that point took a toll on the team and resulted subsequently in multiple meeting with our local director of radiology which till today have not concluded. Please do not misinterpret this situation as we are extremely grateful for our radiologists and the radiology department in all they do, they have always worked hand in hand with us, however the department recently underwent a restructuring which caused the previous director whom we have excellent rapport with to be replaced. The current radiology department emphasizes itself on safe management of resources and costs efficiency – which we do not always agree with. My sincere apologies for this lengthy reply to your comment, but it really does frustrate us till today. However, I've included images from the thoracic aortogram done which demonstrates the tortuous arterial supply into that lingula segment of interest. In this case, the diagnostic bronchoscopy was carried out due to recommendations from the radiology department after reviewing the CT study to which they ironically denied the 3D reconstruction for – it was helpful in the sense that it helped determine with certainty if there was any forms of a fistulous bronchial communications of sorts, to further ascertain if her episode of pneumonia may have been the case of the first of many lung infections to come. Once again Dr/Prof Reviewer, I sincerely apologize for this lengthy reply in attempting to provide some context with our patient.

Changes in text:

Sincere apologies, I have included the thoracic aortogram in Figure 3, I have labelled them to which it would now show the findings rather clearly. Thank you, and I apologize again for this lengthy response. Thank you for your time.

Comment 4:

Line 119. Please provide a broader overview of the current role of the various imaging modalities (including not only CT, but also chest X-ray, ultrasonography / Doppler ultrasonography and MRI) in the diagnosis and treatment planning of BPS. Several recent papers could be mentioned as additional references to support this part, including (but not limited to) the review article by Gabelloni M et al, Clin Imaging 2021; 61-72, doi: 10.1016/j.clinimag.2020.11.040.

Reply 4:

Dear Dr/Prof Reviewer, thank you for your recommendation of this article, this article is an amazing piece of resource! It truly contains a wealth of information pertaining to

imaging modalities for BPS. In fact, I've now used it to supplement and to add on to this revised manuscript in providing a broader overview of the use of imaging modalities in BPS. It is truly interesting to note the use of ultrasound and dopplers in the paediatric population. I'd always thought MRI was the go-to with modern paediatricians or paediatric cardiothoracic surgeons. Thank you once again for recommending me this read and reference, it has definitely helped a lot in my learnings and revision of this manuscript.

Changes in text:

Thank you, again kindly Dr/Prof Reviewer, for this recommendation. I've now included this in various segments of my discussion to ensure a broader overview as you have suggested. The manuscript now reads and flows much better than it was before. Sincere thanks for that.

Reviewer C

Comment 1:

Extralobar BPS is by definition not connected to the bronchial tree and therefore unlikely to cause haemoptysis unless as a consequence of a high-output cardiac failure which although in this case that was ruled out. Another option is a mass effect on the normal lung which, however, does not seem to be the case since the BPS appears to be small.

Reply 1:

Dear Dr/Prof Reviewer, we wholly agree with you and your comment. Thank you for that. We had initially thought it could be a mass effect and was one of a few reasons why we went through with the recommended bronchoscopy to help assess for possible reasons for her haemoptysis. In addition, we also wanted to look for fistulous type connections or if there could be an obvious finding that could account for her recent pneumonia episode. Which we note to be once off, as she did not have any recurrent chest infections growing up. In this case, we did a search of the literature and found some evidence that suggests the tortuosity of the aberrant arterial supply (which in our case was rather intense and extreme in its level of tortuosity) can sometimes lead to really high pressures within that localized region and sometime causes the development of small vessels into the areas of lower pressures such as the bronchiolar regions leading to haemoptysis especially in high physiologic output states.

Reference:

- Sato Y, Endo S, Saito N, Otani S, Hasegawa T, Sohara Y. A rare case of extralobar sequestration with hemoptysis. *J Thorac Cardiovasc Surg.* 2004;128(5):778-779. doi:10.1016/j.jtcvs.2004.03.004

- Gabelloni M, Faggioni L, Accogli S, Aringhieri G, Neri E. Pulmonary sequestration: What the radiologist should know. *Clin Imaging*. 2021;73:61-72. doi:10.1016/j.clinimag.2020.11.040

Changes in text:

Thank you again Prof/Dr Reviewer for your time in reviewing our manuscript and discussing with us your impressions and thoughts of this case. I've further edited the areas of the manuscript to endeavour to articulate some of the contents from my reply above. Hopefully it is now communicated much more properly throughout the revised manuscript. Thank you Dr/Prof Reviewer again, for your time.

Comment 2:

Also, the CT images reported in the paper are not typical of a EBPS. It looks more like sequelae from a pulmonary infection. The aberrant vessel is not clearly visible either on the images reported.

Reply 2:

Dear Prof/Dr Reviewer, my sincerest apologies, as I realize I have provided insufficient images from these imaging studies. I should have provided more shots of the imaging studies done. I have re-done all these images to better suit this manuscript and have included the thoracic aortogram study that was done. I attempted to give the best view possible and hence decided on axial and sagittal views. We do note that the inferior lingula segment of interest does look like a sequelae as you mention, we had initially thought of it as a loculated effusion. Our thoughts are that it is a congenital development and definitely a BPS that could have collapsed over the years given how tortuous the arterial supply to that segment is, which could have led to multiple secondary infection over the years – to which the patient denied. Collateral history obtained also confirmed that she indeed did not have recurrent chest infections growing up.

Changes in text:

My apologies again for not including sufficient images in our previous manuscript for a condition that is so dependent on good imaging studies/modalities for a diagnosis. I have now included the studies from the first CT study that warranted the referral to us (respiratory team), the aortogram as well as the 2nd CT study. I have now sought to include as much as we can in a clear concise and informative way in the hopes our thoughts are properly delivered in this revised manuscript. Sincere apologies. Thank you for your time in reviewing this revised manuscript.

Comment 3:

Moreover, pathological confirmation is also lacking in this case, leaving the diagnosis questionable.

Reply 3:

Dear Prof/Dr Reviewer, thank you for pointing this out. In this case the option of biopsy was offered (but not pushed for) however was rejected by patient after the multidisciplinary discussion involving the cardiothoracic team. I apologize that we did not put this crucial portion in our manuscript. The cardiothoracic teams' reasoning was in the fact that our patient was pretty much asymptomatic at the time of the multidisciplinary discussion happening, and due to the risks involved. They alluded to the fact that though the procedure was simple, it was not without post biopsy complications. All of which the patient and her family agreed with and hence decided to go without the biopsy. We did however mention that the option of biopsy would always be open for her, should she decide to go through with it.

Changes in text:

My apologies. I have now attempted to include this information into the revised manuscript concisely and in a manner which would flow well for readers. Thank you again for pointing this out Prof/Dr Reviewer.

Comment 4:

In my opinion the BPS was either intralobar, or if it was extra lobar it is more likely to be an incidental finding in a case of post-infective haemoptysis.

Reply 4:

Dear Prof/Dr Reviewer, thank you for your comment on this manuscript. We steered away from the diagnosis of intralobar BPS given that she was asymptomatic up until this point in her mid 50s. She was completely asymptomatic as a young child, and never had any chest infections or recurrent infections growing up – which alluded us more to the diagnosis of extralobar ELS. As a result of this conundrum, we included the help of the 4 cardiothoracic surgeons, along with 2 other respiratory physicians and 1 thoracic radiologist, all of which we work closely with, for their kind input. They agreed that given the CT findings of both studies along with our patient's clinical history, it was very much in keeping with an extralobar BPS. And it is interesting that you mentioned "...extra lobar it is more likely to be an incidental finding in a case of post-infective haemoptysis" because that was exactly the reasoning given by 6 of the 7 panel members we engaged the help of in finalizing the discussion of extralobar BPS in our patient. As a result, we were convinced and confirmed the diagnosis of extralobar BPS for her an incidental finding secondary to post infective +/- high physiologic output state derived haemoptysis.

Changes in text:

Thank you again Prof/Dr Reviewer for pointing this out. Your sentiments from an experienced external reviewer have definitely provided more confirmation for us in

this case, given that it was congruent to what was mentioned by the other panel members. I have endeavoured to include as much of these in the manuscript's case report now, and I sincerely apologize that the previous manuscript left out some of this key information. I hope the revised manuscript would delight you. Thank you for your time in reviewing this manuscript.

Comment 5:

Furthermore, the current recommendation for symptomatic BPS is surgical excision, which was not done in this case.

Reply 5:

Dear Prof/Dr Reviewer, thank you for your time in reviewing this manuscript. We do note that surgical excision is usually recommended, however when we risk stratified our patient she was classed as low (to which we expected), and hence stuck to the option of observation as opposed to surgical resection. Our patient was healthy and was definitely well suited as a surgical candidate. However, we had decided that given her haemoptysis had settled with the help of activity modification and has since had no reoccurrences, we left the ultimate decision up to the patient who decided on the observation choice of management.

Changes in text:

Thank you, Prof/Dr Reviewer. I have now included this in the end of the case report along with the end of the discussion, I hope I manage to capture some of these more broadly in the revised manuscript. I sincerely apologize for leaving out some of this crucial information from the initial manuscript which in retrospect I acknowledge as a silly mistake. My sincere apologies.