Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "**Large cystic-solid pulmonary hamartoma: A case report and review of the literature**" (NO: 72967, case report). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope can meet with approval. Revised portion are marked in red in the paper. All page numbers refer to the annotated revised MS, except as specified. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

**Comment:** Specific Comments to Authors: Guo and colleagues have written a surprisingly interesting case report on a large pulmonary hamartoma, which is less common than the typical pulmonary hamartomas. The discussion is well written and interesting as the authors linked histology findings to CT findings. There is a lot of literature on typical pulmonary hamartoma, but the aspects highlighted here by the authors are innovative. I have a few comments to further improve the article: ① Abstract - I suggest rephrasing the first sentence of the background as it now seems that all pulmonary hamartomas are large cystic-solid lesions that are difficult to diagnose. ②Intro - Line 4: I'd rather say "PH can show unusual characteristics" ③ Case presentation - Can the authors explain what the reason was to perform a CT? In many countries, this is not done as routine examination. And for pre-operative evaluation, chest X-ray is performed. - ④The description of the tumor varies, sometimes irregular tumor, sometimes well-defined tumor? I looks like a rather well-defined tumor to me on CT? I would clarify that/be consistent. – ⑤Diagnostic work-up: I would say our hypothesis was… (final diagnosis after histological confirmation). It would be interesting if the authors can explain to the readers why they thought it was a benign tumor at that stage. -⑥ It would be interesting if the authors can provide a bit more information on the IHC (for example, presence of smooth muscle cells (SMA+), low proliferation rate (KI-67 <5%)…) ⑦Discussion - The authors need to check and rephrase the findings of Erber's study as this was a study of malignant neoplasms, mainly sarcomas, and did not give any information on pulmonary hamartomas.

***Response:***

1) *As suggested, we revised Abstract - the first sentence of the background in page 3 and marked in revised paper.*

**2)** *As suggested, we revised Intro - Line 4 "PH shows unusual characteristics and can be clinically and radiologically challenging to diagnose pre-operatively" into "PH can show unusual characteristics" in page 5 and marked in revised paper.*

**3)** *As reported, X-ray cannot reduce lung cancer mortality, and the Low-dose CT (LDCT) lung cancer screening yielded significant survival benefit. Though the patient is exposed to ionizing radiation during CT scan, the average estimated effective dose of one low-dose CT (LDCT) scan is low (1.5 mSv). Therefore, chest CT is recommended in China as an optimal method for physical examinations of older patients and patients with risk factors. We hope this can explain the question"* Case presentation - Can the authors explain what the reason was to perform a CT? In many countries, this is not done as routine examination. And for preoperative evaluation, chest X-ray is performed.*"*

**4)** *Thanks for the suggestion. In this paper, the description of tumor was defined as "well-defined tumor".*

**5)** *As suggested, we revised diagnostic work-up. In addition, we added some explanations about why we thought it was a benign tumor at that stage in page 6, as following:*

*"Due to the well-defined boundary and absence of malignant signs, our hypothesis was a left intrathoracic benign tumor."*

**6)** *As suggested，we added more information on the IHC in page 7-8, as following:*

*Smooth muscle cells were observed in the tumor (SMA +) and were positive for desmin. Ciliated respiratory epithelium that lined clefts tested positive for TTF-1, napsin A and CK7, and basal cells located within these epithelia tested positive for S-100, which indicated that these epithelia represented entrapped bronchioles and alveolar walls. Immunostaining with HMB45 was negative. The proliferation index Ki67 was low (<5%).*

**7)** *As suggested, we checked and rephrased the findings of Erber's study revised in Discussion in page 9, as following:*

*The reason for the cyst formation is still unclear. According to Erber et al.'s study[2], the entrapment of respiratory epithelium in primary and metastatic intrapulmonary nonepithelial neoplasms is a frequent morphological pattern but to variable extents. Their study involved 38 patients with pulmonary metastases (81%) and 8 patients with primary pulmonary nonepithelial lesions. There are two types of histological distribution of the entrapped pulmonary epithelium, In type one, the entrapped pulmonary epithelium is distributed mainly in the peripheral portion of the tumor, and in type two, the entrapped pulmonary epithelium is found throughout the tumor, albeit to a varying extent. Although the number of patients was limited, we thought this*

*conclusion could be extrapolated to more primary and metastatic intrapulmonary nonepithelial neoplasms in the lungs. Because PH is the most common form of primary pulmonary nonepithelial lesions, the same applies to our case.*

***Special thanks to you for your good comments. If there are any other modifications we could make, we would like very much to modify.***

Reviewer #2:
**Comment**: Specific Comments to Authors: At the present time, there are a wide range of immunotherapeutic options in lung diseases. The authors should discuss if immune check point inhibitors can be used in PH using the relevant publications such as; Alfredo Tartarone, et al - 2019 - Fausto Petrelli, et al - 2021 - Monireh Mohsenzadegan, et al - 2020.
***Response:*** *Thanks for the good suggestion. We added some discuss about chromosomal rearrangements and immune check point in PH in page11, as following:*

*Previous studies have demonstrated a high frequency of rearrangements involving 6p21 or 12q14-15 in PH[14], and HMGI-C and HMGI(Y) protein expression as a consequence of rearrangements involving 6p21 and 12q15[15]. These findings support the view that mesenchymal components of PHs represent neoplastic mesenchymal proliferation rather than neoplasms. Today, even with advancements in medical therapy, pulmonary resection remains the most important treatment measure for patients with PH[16, 17]. However, controversy exists about the indication for surgery.*

*At this part we added 4 references:*

*14 Fletcher J, Pinkus G, Donovan K, Naeem R, Sugarbaker D, Mentzer S, Pinkus J, Longtine J. Clonal rearrangement of chromosome band 6p21 in the mesenchymal component of pulmonary chondroid hamartoma. Cancer Res 1992; 52: 6224-6228. [PMID: 1423265]*

*15 G T, R V, G M, B K, G F, P P, J B, V G, H VDB, P DC. HMGI-C and HMGI(Y) Immunoreactivity Correlates with Cytogenetic Abnormalities in Lipomas, Pulmonary Chondroid Hamartomas, Endometrial Polyps, and Uterine Leiomyomas and is Compatible with Rearrangement of the HMGI-C and HMGI(Y) Genes. Lab Invest 2000; 80: 359-369. [PMID: 10744071 DOI: 10.1038/labinvest.3780040]*

*16 Guo W, Zhao Y, Jiang Y, Wang R, Ma Z. Surgical treatment and outcome of pulmonary hamartoma: a retrospective study of 20-year experience. J Exp Clin Cancer Res 2008; 27: 1756-9966. [PMID: 18577258 DOI: 10.1186/1756-9966-27-8]*

*17 Esme H, Id O, Duran F, Unlu Y. Surgical treatment and outcome of pulmonary hamartoma: a retrospective study of 10-year experience. Indian J Thorac Cardiovasc Surg 2019; 35: 31-35. [PMID: 33060966 DOI: 10.1007/s12055-018-0728-x]*

***Special thanks to you for your good comments. If there are any other modifications we could make, we would like very much to modify.***

Reviewer #3:

**Comment**: Specific Comments to Authors: The article is very interesting, providing a rare case report about an unusual entity. Title is adequate, as well as abstract. In my personal opinion, it is necessary to reorganize the case report, avoiding different sections to make it more fluid. English language requires a minor revision.

***Response:*** *Special thanks to you for your good comments. We reorganized the case report, and the full article was polished by AJE which offers professional and native English editing service, and the editorial certificate have been attached in supplementary.*

Science editor

**Comment:** The manuscript elaborated a case of large cystic-solid pulmonary hamartoma. I find it a well-structured interesting study. 1. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly. 2. Did the author use drug adjuvant therapy?

***Response:*** *As suggested, we resolved the reference issue, and in our case no drug adjuvant therapy was used, because no malignant lesion was found in pathological sections.*

Company editor-in-chief:

**Comment:** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

***Response:*** *Original figure documents were prepared and arranged using PowerPoint, and the PowerPoint have been attached in supplementary.*