Author’s response to reviews

Title: A case of early diagnosis of pulmonary capillary hemangiomatosis in a worker with exposure to silica

Authors:

CHANGDONG YEO (brainyeo@catholic.ac.kr)
Deok Jae Han (h7930292@gmail.com)
Jongmin Lee (dibs03@gmail.com)
Woo-Baek Chung (peace816@daum.net)
Jung Im Jung (jjung@catholic.ac.kr)
Kyo-Young Lee (leekyoyo@catholic.ac.kr)
Tae-Jung Kim (kimecho@catholic.ac.kr)
Woori Jang (jangwr@catholic.ac.kr)
Myungshin Kim (microkim@catholic.ac.kr)
Ji Young Kang (rkdwldud@catholic.ac.kr)

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Author’s response to reviews:

Dear Editor-in-Chief

BMC Pulmonary Medicine

Thank you very much for your e-mail of April 24, 2019. We are pleased to hear that our manuscript “A case of early diagnosis of pulmonary capillary hemangiomatosis in a worker with exposure to silica” is needed to resubmitted for consideration. We are submitting the revised manuscript, on which we indicated where we made changes in response to the suggestion of you and reviewers.

I guarantee that this or similar material has not been and will not be submitted by me or my colleagues to any other publication prior to its appearance in BMC Pulmonary Medicine, and that all of my co-authors have made a substantive and specific intellectual contribution to the article.
We wish to thank you and the reviewers for the valuable comments and helpful suggestions which contributed significantly to the revision of our manuscript.

With regards,

Ji Young Kang, MD, PhD

Responses to the Reviewer #1’s Comments

1) This patient had no pulmonary hypertension at diagnosis. But finally, right ventricular systolic pressure elevated, which suggested pulmonary hypertension. We suggest changing title such as "A case of early diagnosis of PCH in a worker with exposure to silica”.

Response: We appreciate the reviewer’s thoughtful suggestion. We changed the title as “A case of early diagnosis of pulmonary capillary hemangiomatosis in a worker with exposure to silica”.

2) Pulmonary hypertension was defined with right heart catheterization. Did author perfume right heart catheterization? If not, authors must not use the word 'pulmonary hypertension’.

Response: We totally agree with the reviewer’s comment. We did not mention the word ‘pulmonary hypertension’.

3) Author should show the echocardiographic image in figure.

Response: We added it in the Figure 2 as below.

4) Did authors distinguish allergic lung disorders, silicosis and asbestosis? Authors should discuss the possibility of these diseases.

Response: We appreciate the reviewer’s thoughtful suggestion. We described why the above-mentioned diseases were excluded in the discussion section.

5) Did authors perform ventilation-perfusion scintigraphy?

Response: Unfortunately, we did not perform the ventilation-perfusion scintigraphy. We are sorry that we are not able to answer this question.
6) Authors should show the clinical time course in Figure including TRPG, respiratory function test, BNP and so on.

Response: We appreciate your great comment. We inserted the Figure 4 which shows SaO2 at room air, FVC & DLCo, RVSP as below. Unfortunately, BNP was measured only twice, so we did not add the parameter.

7) Are there any associations between PCH and silica?

Response: Thank you for your comment. As we described in the section of Discussion, there are little established association between PCH and silica exposure. However, according to the reference 10 article, 12.5% patients of PVOD had occupational silica exposure. PVOD and PCH frequently overlap, and have similar clinical and radiologic presentation. So we presumed that occupational exposure to silica or organic solvent in the current patient might have influenced the clinical course of PCH.

Responses to the Reviewer #2’s Comments

1) please correct the abstract as "om echocardiography" to "on echo.."

Response: We apologize for not being clear. We rephrased the typographical error.

2) please shorten the discussion, because it is very long for a case report.

Response: We totally agree with the reviewer’s comment. We shorten the discussion.

Responses to the Reviewer #3’s Comments

Abstract:

1) The authors state "Pulmonary capillary hemangiomatosis (PCH) is a benign but refractory disease in the lung." This statement is not entirely correct. PCH is generally considered a progressive and fatal disease (as the authors state in the Background of their case report); even though capillary proliferation may be observed by pathologists in absence of pulmonary hypertension: Havlik DM, Massie LW, Williams WL, et al. Pulmonary capillary hemangiomatosis-like foci. An autopsy study of 8 cases. Am J Clin Pathol 2000; 113:655-662.

Response: Thank you for your comment. We rephrased the sentence “Pulmonary capillary hemangiomatosis (PCH) is a progressive and refractory vascular disease in the lung.” as suggested.
2) The authors state that it is (can be) difficult to differentiate PCH from other diseases such as pulmonary veno-occlusive disease (PVOD) and pulmonary arterial hypertension. This is correct, and most would agree that PVOD and PCH frequently overlap. The authors should make this point in the abstract.

Response: We appreciate the reviewer’s thoughtful suggestion. We added that point in the abstract.

3) Consider replacing "central dominant" with "centrilobular ground glass opacities". Centrilobular opacities are not specific for PCH. They are also observed in pneumoconiosis (an important point in the patient with the occupational history of exposure to silicates that the authors describe).

Response: We totally agree with the reviewer’s comment. We replaced "central dominant" with "centrilobular ground glass opacities".

Background

4) Unlike PAH which affects women more often than men, heritable PVOD and PCH occur with similar frequencies in young men and young women; and occupational PVOD/PCH occurs more commonly in older men.

Response: Thank you for your comment. We deleted that sentence of female predominancy.

5) The background statements would benefit from more attention to detail. For example, lines 35 and 36 should state that "…..other causes of unexplained pulmonary hypertension such as [PVOD] or pulmonary arterial hypertension [6]."

Response: We appreciate the reviewer’s thoughtful suggestion. We described the detailed description as suggested.

6) The background statements (and the manuscript in general) would also benefit from more attention to grammar. For example, "Prostacyclin as a treatment option for pulmonary hypertension can deteriorate pulmonary edema in PCH."

Response: We totally agree with the reviewer’s comment. We rephrased that sentence correctly.

7) The statement "Therefore, confirmational diagnosis with early biopsy should be performed." requires revision because (1) lung biopsy is not necessary in patients with clinical features typical for PCH and identification of biallelic pathogenic mutations in EIF2AK4 (see ESC/ERS
Guidelines 2015), and (2) lung biopsy cannot be performed safely in the presence of severe pulmonary hypertension, especially with right heart failure.

Response: Thank you for your comment. We agree with thoughtful comment. We revised that sentence correctly.

Case presentation

8) The occupational history can be improved. What was her job? What was she exposed to [the case presentation says "silica or organic solvent"]. What silica products were used? Which organic solvent(s)? Was she exposed to both silicates and organic solvents? How was she exposed? A more detailed description of her exposure history would enhance this report. The report by Montani et al (Eur Respir J 2015; 46: 1721-1731) provides the necessary elements for the exposure history.

Response: We appreciate the reviewer’s thoughtful suggestion. The patient was exposed to silica and various organic solvent (mainly resin detergent and acetone solvent). According to the detailed discussion with the clinician in our occupational medicine, those exposures and her occupational environment were seemed to rarely associated with asbestosis. In addition, her x-ray before her job showed that there was possibility of early stage of PCH. So, we presumed exposure to silica or organic solvent might have influenced the clinical course of PCH.

9) The authors note that her disease progressed. Pulmonary hypertension was suggested by a subsequent echocardiogram. Pulmonary artery catheterization was not performed. These points underscore the opportunity for the authors to revise their manuscript by pointing out that echocardiographic findings suggestive of pulmonary hypertension may be absent early in the natural history of PCH.

Response: Thank you for your comment. We agree with thoughtful comment. We revised that sentence in Case presentation and Discussion as suggested.

Discussion

10) The authors nicely discuss atypical findings of air trapping, cystic lesions, and focal bronchiolectasis. The discussion might be improved by (1) clear description of the radiographic findings (2) clear description of the pathologic observations which explained the radiographic findings (3) a clear detailed description of the patient's occupation and her exposures with consideration of the interplay of the patient's occupational exposures, her exposure to tobacco smoke, and the radiographic and pathologic observations (specifically, you should identify all occupational exposures, and consider the possibility that some exposures e.g. organic solvents
plus tobacco smoke are associated with PCH/PVOD; and other exposures are associated with airway disease e.g. silicates etc.).

Response: We totally agree with the reviewer’s comment. We described the radiologic and pathologic findings, and atypical features which are uncommon in the other patients. And, we rephrased the possibility of the silica and organic solvent exposure might affect the course of the PCH.

11) On page 10, the authors assert that "this is the first report of pathologically diagnosed PCH in a patient with occupational history." Once again, grammatical and conceptual opportunities exist for improvement. The key is the specific occupational exposure(s). Is this the first case of PCH pathology reported in association with organic solvent exposure (which organic solvent?). If so, then it is important to carefully examine Montani's report of PVOD (cited above) associated with organic solvent exposure to assure that the pathology of PCH was not identified (it was in Figure 4); and it is also important to assure that your case only had pathologic findings of PCH, not PVOD and PCH. Specifically, can you state that a careful examination of lung tissue did not demonstrate obliteration of septal and pre-septal veins with collagen rich loose fibrosis?

Response: Thank you for your comment. We removed that sentence because it was inappropriate in the context. In addition, we rephrased the pathologic finding and its association with clinic-radiologic feature in the current patient.