Reviewer's report

Title: The multiple systemic artery to pulmonary artery fistulas resulting in severe irreversible pulmonary arterial hypertension in patient with previous history of pneumothorax.

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Reviewer: Rocco Rinaldo

Reviewer's report:

This is an interesting case report, that brings attention on the diagnostic process of Pulmonary Arterial Hypertension, a disease with a very bad prognosis that is still underrecognized and that still presents to these days an important delay in final diagnosis.

Although, I have some revisions:

- you should have a revision of your English on the paper (some sentences have a wrong structure, some verbs are wrong - e.i. line 31 of the abstract "shown" instead of showed)

- you may want to consider shortening the title

- you should standardize the acronyms you use throughout the paper

- the international consensus is to indicate pulmonary vascular resistance in Wood Units, so you may want to do that; moreover, you do not need to indicate decimals when reporting the pressures from the right heart cath

- In this case you do not need to underline so widely that the patient was not a responder to vasodilator, as this is the condition in the majority of patients affected by idiopathic PAH, therefore you do not need to report all the hemodynamics data from the vasoreactivity test (for which you utilized a pretty unusual protocol)

- You write a very complex story, and give an intriguing explanation for what you saw, coming to a very strong conclusion that is that "non congenital SA-PAFs are extremely rare, however, they should be excluded in patients with pulmonary arterial hypertension and history of inflammatory or infectious disease of the lung and pleura, with cancer or takayasu's disease and after chest trauma".

As you mention in your background, systemic-to-pulmonary fistulas should not produce pulmonary hypertension, and the chance that a pneumothorax can give such a malformation is per se also very low. In addition, an Eisenmeger syndrome that develops from a non-congenital malformation, that does not involve the whole pulmonary circulation (as your shunts involve
only the right upper lobe circulation) is also extremely rare. As you claim to describe a first case of a coincidence of three very rare conditions, you should be more careful about your conclusion.

I do not believe you can state something so clearly (the conditions that can give a fistula are not so uncommon), while the case is anyway too unclear. According to this, you should at least discuss briefly the chance of other more common (in terms of probability) possible diagnosis: a patient with a SA-PAFs the develops Pulmonary Arterial Hypertension independently from the vascular malformation or the presence of a pulmonary veno-occlusive disease (that would explain the reduced SPO2), for example.

- As you state, at the time of the first RHC the pressures gradient may let you think there is a left to right shunt, and you justify it because of the worsening of the right ventricle, but at the time of the second RHC the PAPS and the PVR increased, while you would expect the opposite in a worsening that bad that would produce the inversion of a shunt. In addition, you do not provide the hemodynamics data, that would be useful to follow the progression of the case (including the cardiac index, and the saturation data including systemic SpO2). Moreover, it would be nice if you had the calculation of pulmonary and systemic flow (Qp/Qs) to support your theory, although I understand how you may not do that during a cath when you do not think of a shunt in clinical practise, as in your case you would need a sample from the pulmonary vein.

In conclusion this is an interesting piece of work, that explain the complexity of the pathophysiology of PAH, but the interpretation of the authors has many limits, that should carefully discussed and supported with more complete data.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Needs some language corrections before being published

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