Author’s response to reviews

Title: Severe but reversible pulmonary hypertension in scleromyxedema and multiple myeloma

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Version: 2 Date: 10 Oct 2019

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Reviewer #1, Wayne Freyereisn, MD, Comment #1: I have reviewed your article with interest… If you review reference 23, we presented a case and reviewed the 4 cases of reversible pulmonary hypertension known to exist at that point in time in 2015. Prior to reference 22, there were no known cases of reversible pulmonary hypertension. The 4 case review included one patient similar to yours with scleromyxedema. In all cases, treating the plasma cell dyscrasia with Bortezomib and Dexamethasone or Thalidomide and Dexamethisone or Stem Cell Transplantation all were capable of reducing the Monoclonal Protein and resulted in improvement and or resolution in the Pulmonary Hypertension. The overarching presence of a monoclonal gammopathy would make it less likely that there is a unique pathophysiology in Scleromyxedema (mucin deposition) as the etiology. Your paper nicely documents in one patient the improvement on multiple occasions of his pulmonary hypertension with treatment based on clinical assessment however the echocardiograms do not include estimated RVSP on all occasions, and this information should be included if available. It does reference changes in the monoclonal protein that was evident.

Response to Dr. Freyereisn, Comment #1: Thank you for reviewing our manuscript and for your insight regarding the alteration of hemodynamic parameters in response to treatment with anti-neoplastic and immunomodulatory agents. We have included additional hemodynamic parameters throughout the “Case Presentation” section (pages 6, 8, 9, and 10) and incorporated additional information regarding the connections between plasma cell dyscrasias and elevated serum paraprotein levels with the development of PH and corresponding hemodynamic improvements in response to anti-neoplastic agents in our and similar cases (Discussion and Conclusion sections, pages 10-23).
Dr. Freyereisn, Comment 2: Your conclusion is about a possible treatment regimen for scleromyxedema based on the treatment of one patient but does not sum up the article/case reports. It also broadens the scope to say this regimen may be effective for connective tissue disease-induced PH though, other than Monoclonal Gammmopathies, there are no connective tissue diseases independently that show this degree of reversibility to the Pulmonary Hypertension. Your case study shows the monoclonal gammopathy measurements yet this is not addressed in your conclusions and jumps to effects on connective tissue diseases.

Response to Dr. Freyereisn, Comment #2: You are correct that we were approaching this case report from the perspective of a connective tissue disorder. The case report was structured in this manner because scleromyxedema was the presenting condition and presumably primary condition associated with PH development in this patient. Furthermore, as you have mentioned, there are instances where patients with connective tissue disorders with corresponding paraproteinemia have responded to cyclophosphamide-containing regimens. However, we acknowledge that the overlapping etiology of scleromyxedema and multiple myeloma in the context of a plasma cell dyscrasia makes it challenging to surmise which pathophysiological condition came first and precipitated the development of PH. Therefore, we have shifted our focus from the contribution of abnormal connective tissue deposition toward the underlying plasma cell dyscrasia and paraprotein levels in scleromyxedema and other disorders with similar hematopoietic effects and correlated these conditions to the development and treatment response of PH to anti-neoplastic agents (Abstract: page 2, Background: page 5, Discussion: pages 10-20, and Conclusion: pages 21-23).

Reviewer #2, General Comments: This is an interesting and (very) well-written case report of development of potentially reversible pulmonary hypertension in a case of scleromyxedema (SC). The authors do a great job of highlighting the take-home message of how the PH improved upon the treatment of the underlying SC and the superimposed multiple myeloma. A strength of the report is the detailed follow up with available hemodynamic data; it is unfortunate that no autopsy was available to complement on the pulmonary arteries looked like with the improvement post-therapy.

Response to #2, General Comments: We appreciate your compliments, and we thank you for reviewing our manuscript.
Reviewer #2, Comment 1: DISCUSSION OF THE CASE - Does the discussion appropriately analyze the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Has an adequate literature review pertinent to the case been included? No - there are minor issues

Response to Reviewer #2, Comment 1: We agree that some of our conclusions regarding the case warranted additional information. Therefore, we have reworked the Discussion section and included additional references to highlight the relationship between paraproteinemia and plasma cell dyscrasias to PH development. We build upon this information to support our conclusion that targeting the underlying pathophysiological processes of secondary PH with anti-neoplastic and immunomodulatory agents is necessary to improve the hemodynamic and cardiovascular parameters in patients with vasodilator-resistant PH (pages 10-20).

Reviewer #2, Comment 2: REQUESTED REVISIONS: I have some minor suggestions to increase the potential interest in the case; a brief discussion or a table on the available knowledge on how each of the drugs used in the patient might affect animal models or prior evidence in humans with the respective reference. This is particularly interesting in the context of glucocorticoids, proteasome inhibitors, plasmapheresis, anti-CD20 antibodies, and intravenous IgG administration. The interest arises as many of these have been used or proposed as effective in PH treatment.

Response to Reviewer #2, Comment 2: This is an excellent suggestion, and we agree that including this information has strengthened the overall impact of our case report. We have incorporated an additional section highlighting the cross-functionality of anti-neoplastic and immunomodulatory agents used in cancer to effectively treat patients with PH and idiopathic PH in the Discussion section (pages 10-20) and reference this information again in our Conclusion section (pages 21-23).

Thank you once again for your critical review of our manuscript, and we look forward to future communications with you all. Have a great day!