Author's response to reviews

Title: Multiple myeloma presenting with high output heart failure and improving with anti-angiogenesis therapy: a case series and review of the literature

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Author's response to reviews: see over
Dear Editors,

On behalf of my colleagues at Northwestern Memorial Hospital, we greatly appreciate your very thoughtful comments regarding our manuscript, “Multiple myeloma presenting with high output heart failure and improving with anti-angiogenesis therapy: a case series and review of the literature.” Below you will find a response to each of the questions you have posed:

Nicola Mumoli:
1) You point out that not all patients with extensive bone involvement develop high output failure. We agree with this statement and have changed the second paragraph of page 8 from, “Thus, extensive bone involvement seems to promote a high output state” to “Thus, extensive bone involvement has the propensity to promote a high output state.”

2) You raise the question as to whether diuretic therapy in the setting of hypercalcemia may have contributed to his death. First, I must point out that although hypercalcemia is associated with volume contraction, in his case, he was clearly intravascularly volume overloaded based on his prominent jugular venous distension. In addition, I propose that if he was indeed intravascularly volume depleted, the diuretic therapy would have led to renal dysfunction which it did not. Thus, his ultimate demise was more related to his progressive disease related cytopenias.

3) You appropriately point out that both patients were treated with steroids in addition to Lenalidomide and Thalidomide and this may be related to the favorable change in hemodynamics. We believe that this is a fair statement and have thus included the statements, ”we utilized systemic steroids in conjunction with the agents Lenalidomide and Thalidomide” in our discussion and ”Systemic steroids used in conjunction with Lenalidomide and Thalidomide were shown to be very successful in the management of myeloma induced high output failure in this case series” in the conclusion. We have reservations about stating that steroids were the main contributor to the improvement in hemodynamics as the first patient had been on and off steroids for the past three years with progressive disease, and we feel that steroids alone would have worsened volume status via increased salt and water retention. However, there may be a synergistic effect which we do acknowledge and state multiple times throughout the text.

4) Your last comment suggests that we minimize speculative statements which require special investigations to validate. We certainly do realize that this is observational data. We feel that this is well conveyed to the reader with statements such as “plausible hypothesis,” (page 9) and “Further studies including larger numbers of patients are needed to validate these results.” (Conclusion)
Cherif Boutros

1) You recommend that the conclusion only be of “suggestion.” We believe this is well conveyed with the concluding statement, “Further studies including larger numbers of patients are needed to validate these results.”

2) You also recommend that we include the potential side effects of Lenalidomide, including the hematological toxicities. The reason we do not feel the need to do this in our manuscript is because the patient already had profound thrombocytopenia from the underlying myeloma as well as past therapies. Thus, his massive upper gastrointestinal bleed could have occurred even without the addition of the new therapy.

3) You also comment that we do not discuss treatments such as blood transfusion. We have changed the last sentence of the first paragraph on page 6 to read; “Unfortunately, on hospital day 35 in the setting of his long standing refractory thrombocytopenia, he developed a massive upper gastrointestinal bleed that could not be controlled despite aggressive resuscitative efforts and died within hours.” We feel that aggressive resuscitative efforts infers blood product transfusion.

4) You suggest that a single anecdotal patient cannot be used to determine treatment modality. We feel that this statement underscores the importance of this paper because there is essentially no literature as to which treatment should be used in this scenario. Thus, we had to rely on one previous experience in order to treat patient number two. We hope that this paper promotes further research in this area of oncology/heart failure. Therefore, we feel that keeping the statement, “Based on the diuresis noted in the first case, it was decided to initiate Thalidomide 50 mg daily and increase the dose to 200 mg over the next 4 weeks” is appropriate.

5) Next, we would like to respond to your last comment related to the discussion. As the most likely mechanism of action of myeloma induced high output failure is AV shunting, it is reasonable to extrapolate the improved findings from the exam (patient 1) and catheterization (patient 2) and suggest that it is indeed an inhibition of AV shunting which led to the favorable change in hemodynamics. Thus, although it would be very interesting to have AV shunting data, this is not necessary at this time to support our hypothesis. We would like to reiterate that we are proposing nothing more than a hypothesis; “Based on the proposed mechanism of high output failure in these patients, this is an appealing and plausible hypothesis. In essence, when used in conjunction with steroids, these agents may have the ability to pharmacologically ligate intramedially arteriovenous fistulas.” In addition, as the patient had no other concurrent treatment for his high output failure, we feel very confident that it was indeed pharmacologic inhibition of AV shunting that improved the patient’s clinical status.
6) Inanir et al now has a reference.