Reviewer’s report

Title: A case of renal thrombotic microangiopathy associated with the use of Carfilzomib following autologous stem cell transplantation for multiple myeloma

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Reviewer: Anthony Chang

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Hobeika and Velez describe a case of thrombotic microangiopathy (TMA) associated with carfilzomib after autologous stem cell transplantation. This report is confounded by several factors that are more likely to account for the finding of TMA.

Major Compulsory Revisions:

1. More details about the kidney biopsy should be provided. Were there any thrombi in glomerular capillaries or arterioles by light microscopy? Could the possible arterial thrombus that was staining for fibrin, C1q, IgM and C3 be visualized on the H&E cryosections of the IF specimen?

2. Was there evidence of “myeloma” cast nephropathy or monoclonal immunoglobulin deposition disease? If these findings were absent, it should be stated.

3. The pathologist should at least be acknowledged for providing figures 2a-c and probably should be included as a co-author.

4. In two of the largest kidney biopsy series by Chang A et al (Clin J Am Soc Nephrol 2007; 2: 1014-1023) and Troxell M et al (Mod Pathol 2008; 21:396-406), radiation and chemotherapy are both well known causes of TMA. Radiation therapy is not mentioned for this patient, but the chemotherapy (particularly cyclophosphamide) is the more likely cause of this patient’s TMA particularly the chronic features of duplication of the GBM (as seen in figure 2c). This needs to be acknowledged. Many of the patients in these 2 series had similar timeframes when their symptoms presented as the current case report. The timing of the administration of carfilzomib is more likely a coincidence.

5. P.7, Conclusion – Therefore, the 3rd point that “no alternate explanation was plausible” is not accurate. The authors even acknowledge (at the end of page 9) that “the long-standing history of essential hypertension could be responsible of some of the histologic findings…,” but they dismiss this possibility by simply restating their hypothesis.

6. Discontinuation of carfilzomib is unlikely to reverse the mesangiolyisis or duplication of the GBM, which are the features of TMA. The serum creatinine did not improve after discontinuation of carfilzomib.

7. The patient ultimately succumbed to myeloma and carfilzomib may have been his only hope to treat the myeloma. Was any other therapy given after
discontinuation of carfilzomib? Was there a consideration to re-administer carfilzomib when there was only a modest improvement in proteinuria? The authors should be careful, because this portion of the manuscript currently gives the impression that the myeloma was not adequately treated. This may have been a joint decision with the patient but that should be a bit more clear.

8. Were there serial quantitations of the paraprotein before and after discontinuation of carfilzomib? Was the improvement in proteinuria due to a decrease in the paraprotein?

9. It may be true that bortezomib and carfilzomib have anti-VEGF activity, but the exact contribution of this pathway is unclear and speculative. Citing reports of TMA in myeloma patients treated with bortezomib is not compelling, because these myeloma patients undergo many other therapies as previously mentioned that can cause TMA. The authors might consider reviewing the literature on kidney transplant patients that have been treated with bortezomib in the setting of antibody-mediated rejection.

10. The authors are very focused on creating a compelling argument that carfilzomib caused their patient’s TMA. However, what lesson can be learned about treating future patients like this one? Would they treat this patient differently if confronted with the same situation in the future?

Minor Essential Revision:
1. page 4 – the authors state that “bortezomib has also been reported to be associated with TMA.” There is another mention in the conclusion, references #15 and 16 should be added each time this is mentioned.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests