UCLA Health

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Abstract Form

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Project Title:	Carfilzomib-induced thrombotic microangiopathy successfully treated with eculizumab

Research Category (please check one):

☐	**Original Research**	X	**Clinical Vignette**	☐	**Quality Improvement**	☐	**Medical Education Innovation**

Abstract

We present the case of a 70-year-old woman with history of atrial fibrillation and hypertension who was diagnosed with IgA lambda multiple myeloma. On initial presentation she complained of rapidly progressive back and hip pain and was found to have multiple lytic lesions on imaging. She underwent bone marrow biopsy which showed 40% plasma cells with high-risk translocation t(4;14). She underwent induction with lenalidomide, bortezomib, and dexamethasone (RVD) with complete remission, followed by high-dose melphalan with autologous stem cell transplant with subsequent ixazomib maintenance. Three years later she was noted to have rising lambda light chains and IgA and was transitioned to carfilzomib and dexamethasone.

Four months after starting carfilzomib, the patient presented to the emergency department with complaints of increased nausea, vomiting, and malaise. Vital signs, mentation, and physical exam were normal aside from dry mucous membranes. Admission labs demonstrated evidence of acute renal failure with serum creatinine of 5.4 mg/dL (ref 0.6-1.3) and blood urea nitrogen (BUN) of 85 mg/dL (ref 7-25), hyponatremia with sodium of 117 mmol/L (ref 136-145), and evidence of microangiopathic hemolytic anemia with platelets of 12 10^3/uL (ref 163-369), hemoglobin of 9.8 g/dL (ref 11.2-15.7), haptoglobin undetectable (ref 21-210 mg/dL), total bilirubin of 0.8 mg/dL (ref 0.3-1.0), lactate dehydrogenase (LDH) of 548 U/L (ref 125-256), and red blood cell fragmentation present on peripheral smear. Direct antiglobulin test (DAT) was negative, and fibrinogen was within normal limits at 277 mg/dL (ref 235-490) (however dropped to 68 mg/dL on hospital day 2). ADAMTS13 activity was slightly low at 54% (ref >= 67%), with low C3 level of 59 mg/dL (ref 86-175), normal C4 level of 12 mg/dL (ref 10-40), low CH50 of <12.5 U/mL (ref 38.7-89.9), homocysteine of 32 mcmol/L (ref <= 15), and methylmalonic acid (MMA) of 0.36 umol/L (ref 0.0-0.4).

Based on the above presentation, there was high clinical suspicion for drug-induced thrombotic microangiopathy (TMA) secondary to carfilzomib. Treatment with carfilzomib was discontinued, and eculizumab was ordered for treatment. While awaiting availability of eculizumab, the patient underwent therapeutic plasma exchange (TPE) on hospital days 2 through 5. She was then treated with eculizumab starting on hospital day 6 (900 mg intravenous weekly for four doses followed by 1200 mg at week five, then 1200 mg every two weeks thereafter). She did not require hemodialysis as serum creatinine downtrended upon initiation of eculizumab. Thrombocytopenia and anemia also rapidly improved after eculizumab initiation. The patient developed electrolyte derangements and metabolic acidosis (total CO2 to 10 mmol/L, ref 20-30) which were resolved at time of post-discharge follow-up, likely due to acute kidney injury and TPE therapy.

After a two-week hospitalization, the patient was discharged and followed closely in hematology-oncology clinic. Hemolysis labs and renal function returned to her prior baseline. Three months after this event, the patient remained in complete remission with stable laboratory values and clinical status and was started on daratumumab maintenance therapy.

Discussion:
Carfilzomib is an irreversible proteasome inhibitor approved in 2012 for the treatment in of relapsed or refractory multiple myeloma. Carfilzomib-induced TMA is a rare and serious syndrome recognized in recent years and characterized by acute kidney injury, hemolysis, and thrombocytopenia. Clinicians should have a high index of suspicion and a low threshold to stop carfilzomib and initiate treatment if TMA is suspected. Successful treatment with the monoclonal antibody eculizumab has been reported, however definitive management protocols have not yet been defined.