

Case Report

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Renal Thrombotic Microangiopathy Associated with Carfilzomib Use in Treatment of Multiple Myeloma

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Abstract

Carfilzomib is a newer class of selective proteasome inhibitor approved by FDA in 2012. It is used for the treatment of refractory multiple myeloma in patients who have received two prior therapies. We report a case of drug induced thrombotic microangiopathy associated with carfilzomib in a patient with refractory multiple myeloma.

Keywords: Carfilzomib; Proteasome inhibitor; Thrombotic microangiopathy; Refractory

Abbreviations: AKI: Acute Kidney Injury; TMA: Thrombotic Microangiopathy; LDH: Lactate Dehydrogenase; CKD: Chronic Kidney Disease; RA: Rheumatoid Arthritis; TTP: Thrombotic Thrombocytopenic Purpura; HUS: Hemolytic Uremic Syndrome

Case Presentation

A 68-year-old female with IgA multiple myeloma (currently on 3rd recurrence) presented with 3 days of abdominal pain, nausea, vomiting and diarrhea after starting chemotherapy with Carfilzomib for her relapsing Multiple Myeloma. A past medical history of COPD, Rheumatoid Arthritis, Chronic Kidney disease stage 4, and MI status post PCI was identified. During an inpatient stay at a local hospital, she developed new Acute Kidney Injury (AKI). Serum Creatinine was 3.03 with normal baseline level <1. She had a progressive decline in her platelets from 148K to 7K in 3 days. Her hematology workup was concerning for Drug Induced Thrombotic Microangiopathy (DITMA). Further diagnostic evaluation demonstrated elevated LDH > 1200, Schistocytes on smear, and haptoglobin < 10. The patient was urgently started on Therapeutic Plasma Exchange (TPE) along with hemodialysis. Her condition stabilized and slowly improved after starting TPE. After evaluation and assessment of the medical team, she was discharged with plans of close outpatient follow up.

Background

Multiple myeloma is a B cell malignancy, in which abnormal clonal plasma cells proliferate and accumulate in bone marrow. It is a relatively uncommon disorder; in the USA the lifetime risk is

(0.76%). Myeloma cells disrupt normal bone marrow function, and invade surrounding bone causing bone destruction. The course of disease is characterized by recurrent relapses. The quality of response to treatment deteriorates with subsequent line of therapies, and the risk of another relapse increases. There is excessive production of immunoglobulins and high rate of protein synthesis in myeloma cells, thus these cells have increased demand of protein turnover. This alternatively increases the need for degradation of rapidly accumulating misfolded proteins by proteasomes. Proteasome activity is vital in helping myeloma cells survive by preventing unfolded protein response activating apoptosis in myeloma cells. Proteasome inhibitors are a new class of drugs that have proven to be an excellent regimen in the treatment of multiple myeloma. They prevent degradation of proapoptotic factors, by proteasome, thus activating programmed cell death in neoplastic cells. Carfilzomib is a newer class of protease inhibitor, it differs from its prototype Bortezomib, in that it irreversibly binds to the proteasome more selectively primarily inhibiting chymotrypsin-like activity of this enzyme. Carfilzomib has been effective in patients with refractory multiple myeloma.

Case Presentation

We present a 68-year-old female with past medical history of COPD, RA, CKD (Stage 4), MI s/p PCI, and relapsing IgA multiple myeloma. She was diagnosed with multiple myeloma in 2008. She received an autologous stem transplant in 2009, and IVIG in 2011 that was discontinued due to fatigue. Skeletal surveys in 2015 were negative for lytic lesions, however an elevation in Kappa light chain immunoglobulins in 2016 was noted. The patient was not a candidate for another transplant; hence she was started on 4 cycles of Carfilzomib/ Revlimid per provider's advice.

After beginning treatment with Carfilzomib, she presented with 3-4 days of persistent abdominal pain, nausea, vomiting, and diarrhea. She has been feeling unwell since she restarted her chemotherapy on 11/20/2018. On presentation she was hypotensive, tachypneic, and tachycardic for which 3L NS was given as per sepsis protocol after which she became normotensive. Blood cultures (2), stool studies (PCR), and influenza at that time were negative. Furthermore, during her hospital stay she developed acute renal failure with creatinine of 3.03, and acute respiratory failure requiring BIPAP. Additionally, her platelets progressively declined from 148K to 7K in 3 days (normal values ranging 150K-400K). Hematology workup was concerning for Drug Induced Thrombotic Microangiopathy (DITMA). Lab studies illustrated sharply elevated LDH (>1200), Schistocytes on smear, haptoglobin <10, and thrombocytopenia. ADAMS TS test done on 12/12/2018 was 67% (within normal limits).

With these findings, she was urgently started on Therapeutic Plasma Exchange (TPE) on the evening of 12/3/18 and Hemodialysis the following day 12/4/18. An improvement was noted after starting TPE. Her platelets started increasing to normal without transfusion, as well as stabilization and improvement in creatinine. Her overall strength and appetite markedly improved addition to decreasing sign and symptoms of pain, nausea, vomiting, and diarrhea. Based on medical teams' assessment she was discharged with plan of close outpatient follow up.

Discussion

We present the case of an individual who developed new AKI, serum creatinine up to 3.03, along with a decline in her platelets after starting Carfilzomib for her multiple myeloma. Further workup showed Schistocytes on smear, elevated LDH (>1200), and Haptoglobin <10 which was concerning for Drug induced thrombotic microangiopathy. With these acute findings, she was started on therapeutic plasma exchange followed by hemodialysis next day. Her condition was noted to improve rapidly. Her creatinine stabilized, and platelets values improved. She was discharged with plans of close outpatient follow up.

Several factors correspond with the usage of Carfilzomib and clinical symptoms of renal TMA. First, the onset of symptoms after the initiation of treatment supports it. A similar case study in 2017 reported 61-year-old women with kappa light chain multiple myeloma with multiple relapses. She was finally started on Carfilzomib and dexamethasone for her worsening disease status, on the fifth day of treatment she presented to the hospital with chest pain and worsening shortness of breath. Workup was concerning for drug induced thrombotic microangiopathy. Labs showed raised creatinine and drop in her Hb, and platelets and schistocytes in her peripheral blood smear. She was started on Hemodialysis and Eculizumab after which her labs normalized, and clinical status significantly improved [1]. Additionally, heme work up illustrating normal ADAM TS levels in the setting of microangiopathic anemia,

thrombocytopenia, and AKI is very revealing for drug induced TMA. Finally, improvement in symptoms after discontinuing Carfilzomib, and initiation of TPE was reassured of diagnosis as well.

Thrombotic microangiopathy is characterized by injured endothelial cells that are thickened, swollen, or detached mainly from arterioles and capillaries. This causes thrombotic changes in small vessels, causing platelet consumption and fragmentation of Red Blood Cells (RBC) clinically known as schistocytes which can be viewed in peripheral smear. Acute renal injury stems from decrease perfusion from blockage of vessels by damaged red blood cells and platelet plugs [2,3].

Known etiologies of TMA include ADAMSTS13 deficiency TTP, infection induced HUS, complement abnormalities, malignancies, organ transplantation, pregnancy, and drugs. Drug induced TMA is a recognized complication of treatment with some chemotherapeutic agents [4]. Two different mechanisms have been described. Endothelial damage is the main cause of TMA that develop in association with chemotherapeutic agents this process is more likely dose dependent. Alternatively, TMA may develop as a result of drug induced antibodies, this form is less likely to be dose dependent.

There is an association of Hematopoietic Stem Cell Transplant (HSCT) with TMA. The annual incidence is about 8.2%. Etiological factors include conditioning regimens, immunosuppression's, infection, and graft versus host disease. HSCT -TMA occurs within first 100 days of transplant. In our case the HSCT was done in 2009, therefore the time of presentation of clinical symptoms does not favor HSCT as the primary etiology in TMA [3,5].

Drug induced TMA is a rare condition, there have been a few case reports associated with proteasome related TMA. Although, the exact incidence of Carfilzomib induced TMA is unknown. Early diagnosis, with prompt discontinuation of the drug along with supportive treatment significantly reduces morbidity [6].

Conclusion

We consider Carfilzomib as a potential etiology of TMA. Discontinuation of the drug along with TPE resulted in significant improvement in the patients' condition and resolution of her symptoms. We suggest clinicians should be aware of the association between Carfilzomib and TMA. Discontinuation of drug should be considered after careful evaluation of risks and benefits of chemotherapy, and the prognosis of existing malignancy.

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