RESEARCH PAPER

The Proteasome Paradox: Navigating Carfilzomib-Induced Atypical HUS in Multiple Myeloma

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ABSTRACT

Thrombotic microangiopathy (TMA) encompasses a triad of anaemia, low platelet count and organ damage. Haemolytic uremic syndrome is a thrombotic microangiopathy characterised by thrombocytopenia, hemolysis and renal dysfunction. The pathophysiology of hemolytic uremic syndrome has been extensively explored, however, the mechanisms of carfilzomib induced atypical haemolytic uremic syndrome remains incompletely elucidated. Here we present a unique case of carfilzomib-induced atypical haemolytic uremic syndrome in a female with multiple myeloma on carfilzomib therapy. This atypical haemolytic uremic syndrome was treated with cessation of the offending drug, initiation of Eculizumab and PLEX. Renal function improved within days of carfilzomib cessation.

Keywords: Carfilzomib, Multiple Myeloma, Atypical Hemolytic Uremic Syndrome, Thrombotic Microangiopathy, Proteasome Inhibitors, Eculizumab, Acute Kidney Injury.

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Introduction

Proteasome inhibitors are drugs used in the management of multiple myeloma. The first proteasome inhibitor approved for patients with multiple myeloma was Bortezomib [1]. Carfilzomib is a second-generation tetrapeptide epoxyketone proteasome inhibitor that was approved for patients with resistant multiple myeloma in 2012 [2]. Thrombotic microangiopathy (TMA) is a complex syndrome characterised by microangiopathic haemolytic anaemia, low platelet counts, and organ injury. It is a pathological process which encompasses endothelial injury, vascular damage and platelet fibrin thrombi within vessels. This pathological process can manifest as two clinical entities - Thrombotic thrombocytopenic purpura (TTP) and Hemolytic uremic syndrome (HUS). Congenital and acquired factors can cause haemolytic uremic syndrome. Hemolytic uremic syndrome can be divided into typical HUS and atypical HUS. Typical hemolytic uremic syndrome is most commonly seen in children secondary to Shigella gastrointestinal infections. Atypical HUS can be genetic or drug induced. Anticancer drugs targeting vascular factors (VEGF), tyrosine kinase inhibitors, and, more recently, Bortezomib have been implicated in the development of haemolytic uremic syndrome There is limited data on Carfilzomib-induced atypical haemolytic uremic syndrome (atypical HUS). With the increasing use of carfilzomib for multiple myeloma treatment, the carfilzomib-induced atypical HUS needs to be explored further.

Case Presentation

This case report presents a 51-year-old female diagnosed with multiple myeloma (IgG Kappa subtype),by bone marrow aspiration during an evaluation for low backache. The patient was started on bortezomib therapy 10 days after the confirmation of the diagnosis. Patient received a total of 4 cycles of Bortezomib, Cyclophosphamide, and Dexamethasone. Patient was found to have persistence of plasma cells in bone marrow on evaluation for bone marrow transplant. Hence, bortezomib was stopped and treatment was escalated to Carfilzomib, Lenalidomide, and Dexamethasone. The patient received a total of 2 doses of Carfilzomib, once weekly, and 5 days before the 3rd dose, the patient presented with fever, vomiting, drowsiness, and markedly decreased urine output. On arrival, the patient was conscious, oriented and febrile. Her blood pressure was 160/100 mmHg, and other vital signs were within normal limits. A complete hemogram (see Table *1*) revealed anaemia

(Hb 9.9 g/dl), thrombocytopenia (0.27 lakhs/cu.mm), and elevated total count (25370 cells/cu.mm). The peripheral smear (see Figure *1*) demonstrated mild anaemia, thrombocytopenia, anisopoikilocytosis, burr cells, schistocytes (5%), and neutrophilic leucocytosis. Renal function test revealed elevation of serum creatinine to 6.2 mg/dl from a baseline of 0.6 mg/dl. Liver function tests (Table *1*) showed marginally elevated liver enzymes (AST 56 U/L and ALT 111 U/L).Additional investigations (Table *1*) revealed elevated LDH (2101 U/L) and a decreased free haptoglobin (3 mg/dl). Direct Coombs test was negative. The patient also developed signs of myocardial ischemia along with renal dysfunction. Her ECG revealed T-wave inversion in V2-V4 leads with elevated high-sensitivity Troponin T on two separate occasions. In view of a history of fever, a fever panel comprising of Dengue NS1Ag, IgM Dengue, Leptospira, and scrub typhus was performed, all of which were negative. Viral markers for Hepatitis A, E, B, C and HIV were done in lieu of elevated liver enzymes, which were found to be negative. The clinical scenario, combined with anaemia, thrombocytopenia, renal dysfunction and haemolysis, raised a suspicion of haemolytic uremic syndrome. Further investigations were planned to elucidate the aetiology of haemolytic uremic syndrome.

Test	Result	Units	Ref. value
Hemoglobin	9.9	gm/dl	12 - 15
WBC count	25370	Cells/cu.mm	4000 - 11000
Platelets	0.27	lakhs/cu.mm	1.5 – 4.5
Total Bilirubin	1.6	mg/dl	Up to 1.2
Direct Bilirubin	0.6	mg/dl	Less than or equal to 0.3
Indirect Bilirubin	1.0	mg/dl	-
AST(SGOT)	56	U/L	Up to 32
ALT(SGPT)	111	U/L	Up to 33
Serum Creatinine	6.2	mg/dl	0.5 – 0.9
LDH	2101	U/L	135 - 214
Serum haptoglobin	3	mg/dl	30 - 200

Table 1: Showing complete hemogram, LFT, RFT, LDH and haptoglobin at admission

WBC: Whole blood count, AST: Aspartate Aminotransferase, ALT: Alanine Amino transaminase, LDH: Lactate dehydrogenase

ADAMTS13 activity and antibody levels were negative. FDP and D-dimer were within normal limits. Coagulation parameters (PT, aPTT) were also normal. Complement factor C3 levels were normal initially, but later levels decreased while C4 levels remained normal. Anti-Complement factor H antibody, whole exome sequencing, and MLPA analysis were normal. Urine analysis showed proteinuria. Renal biopsy (see Figure *2*), performed for evaluation of renal impairment, demonstrated thrombotic microangiopathy with endothelial swelling, mesangiolysis, and fibrin thrombi in glomerular capillaries/arterioles.

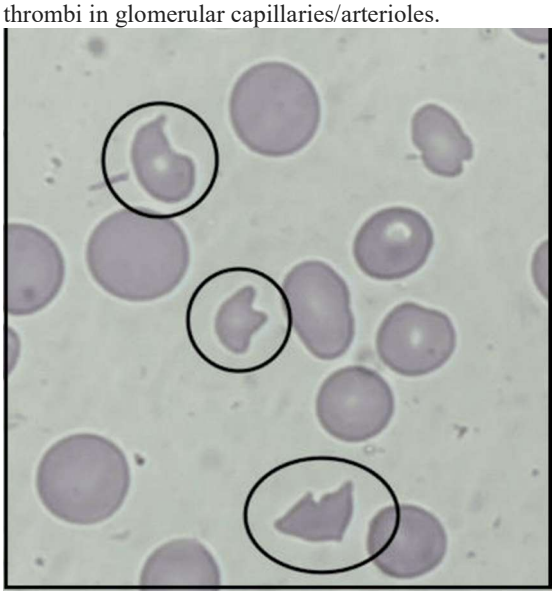

Figure 1: Peripheal smear showing schistocytes (Fresh blood sample, Romanowsky type stain)

1. Schistocytes (rounded images) under the microscope

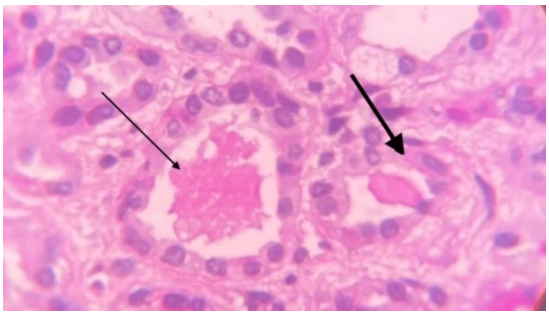

Figure 2: Renal Biopsy of pateint using hematoxylin and eosin stain at 400 magnification

1. fibrin thrombi in glomerular capillaries/arterioles(Thinner arrow), 2. endothelial swelling, mesangiolysis(Thicker arrow)

On arrival, the patient was started on IV antibiotics, fluids, and other supportive management. In view of raised serum creatinine and oliguria, hemodialysis was initiated. The patient was started on intravenous

methylprednisolone and PLEX for suspicion of haemolytic uremic syndrome. A total of 5 cycles of hemodialysis and 4 cycles of PLEX were done over a span of five days. Suspecting drug-induced atypical haemolytic uremic syndrome secondary to carfilzomib, the decision was made to discontinue carfilzomib and the patient was started on intravenous eculizumab. Eculizumab 900 mg in 100 ml of normal saline was given after the pneumococcal conjugate vaccine. Patient's platelet count improved to more than 1 lakh within 6 days and patient was planned for renal biopsy. Patient underwent renal biopsy following which she received second dose of eculizumab. The patient received a total of two doses of Eculizumab. Serum creatinine levels improved, and the patient improved symptomatically. At discharge, the patient's serum creatinine was 3.8 mg/dL, and the patient was followed up in the outpatient setting with RFT and the creatinine value on last follow up was 1.2 mg/dL.

Discussion

This case report presents a multiple myeloma patient on carfilzomib who presented with an abrupt worsening of renal function. Renal dysfunction in multiple myeloma patients can be caused by light chain nephropathy, hypercalcemia, acute tubular injury secondary to bisphosphonate use, TMA and lenalidomide toxicity [3-6]. Therefore, determining the cause of renal dysfunction can be technically challenging. Renal dysfunction in the patient was coupled with anaemia (Hb 6.9 mg/dl), thrombocytopenia (0.27 lakhs/cu.mm) and hemolysis. The clinical and biochemical parameters were consistent with thrombotic microangiopathy. Further evaluation was planned to distinguish among HUS, TTP, and DIC. A normal FDP, d-dimer, and coagulation parameters essentially ruled out DIC. ADAMTS 13 activity levels were normal, and ADAMTS 13 antibody levels were found to be negative, suggesting TTP as an unlikely cause. Thus, a working diagnosis of HUS was made. Complement factor analysis revealed low C3 with normal C4 levels. The patient had no gastrointestinal symptoms, and stool cultures were negative. A negative MLPA analysis and anti-Complement Factor H antibody levels rule out genetic causes of HUS. Atypical HUS was suspected in the patient. A renal biopsy showing endothelial swelling, mesangiolysis, and fibrin thrombi in glomerular capillaries/arterioles confirmed the diagnosis. The patient did not receive any HSCT, which could have caused the TMA. The absence of gastrointestinal infection in the patient pointed towards atypical hemolytic uremic syndrome. Drug-induced haemolytic uremic syndrome was considered as one of the differentials. Patient with atypical hemolytic uremic syndrome can also present with extra-renal manifestations. Symptomatic cardiac involvement is rare in microangiopathy; however, the patient demonstrated features of myocardial ischemia. Cardiac involvement in TMA may be attributed to anaemia-induced high-output cardiac failure, with microthrombi among the postulated mechanisms [7].

Thrombotic microangiopathy results in microthrombi within vessels, leading to organ injury. This can occur in any organ system, and its renal manifestation is termed HUS. Vascular endothelial growth factor (VEGF) is quintessential in maintaining the structural and functional integrity of the glomerular basement membrane. It is produced by podocytes in high concentrations. Drug-induced TMA (DITMA) constitutes 20%-30% of secondary TMAs [8].

Drugs affecting VEGF directly or indirectly can result in haemolytic uremic syndrome by disrupting glomerular architecture. Anti-VEGF antibodies (bevacizumab), VEGF inhibitors (pazopanib), VEGF tyrosine kinase inhibitors (sunitinib), and calcineurin inhibitors can cause TMA. These drugs cause TMA by direct endothelial injury. However, the pathogenesis of atypical HUS in patients receiving proteasome inhibitors remains incompletely understood. One proposed mechanism is inhibition of NFKB by proteasome inhibitors, which indirectly affects VEGF synthesis and hence causes atypical HUS. Bortezomib is thought to cause DITMA by inhibiting IL-6-mediated angiogenesis and by indirect pathways that inhibit VEGF [9]. There are very few case reports of carfilzomib-induced atypical HUS. The patient had not received any calcineurin inhibitors during her treatment course, which can also precipitate atypical HUS. Thus, carfilzomib was considered the probable cause of atypical haemolytic uremic syndrome.

Naranjo's criteria for adverse reactions were applied to the patient regarding carfilzomib induced atypical HUS[10]. The worsening of renal function coincided with carfilzomib administration in our patient, establishing a temporal association with the drug. Renal parameters improved after cessation of carfilzomib therapy, with the addition of eculizumab, PLEX, and haemodialysis. There was no concurrent use of any other drug implicated in causing atypical HUS. Furthermore, carfilzomib has been shown to result in atypical HUS in patients with multiple myeloma, all pointing towards the possibility of carfilzomib-induced atypical HUS.

The incidence of carfilzomib-related TMA in prospective studies ranges from 1% to 10% [11-15], while in retrospective studies it ranges from 0.89% to 16.7% [16-18], indicating that carfilzomib-induced TMA is more common than previously thought. This might be due to the irreversible inhibition of the ubiquitin-proteasome system by carfilzomib, compared to the reversible inhibition

caused by bortezomib [19]. The development of TMA can occur months or even years after the first proteasome inhibitor exposure [20]. Most cases of Bortezomib-induced TMA occurred within 21 days of drug initiation [20]. Carfilzomib-induced TMA have presented after months of exposure to the drug. In our patient, atypical HUS developed 5 days before the 3rd cycle. Hemolytic uremic syndrome can result in irreversible renal dysfunction, so timely diagnosis is critical. Early administration of a weekly 900 mg dose of eculizumab, was found to be beneficial in many case reports [21,22]. A total duration of 4 weeks is generally recommended. However, a case series of patients on carfilzomib with severe AKI treated with eculizumab, showed no apparent improvement in pathophysiology or prognosis of the disease [23]. The lack of response to eculizumab may imply that factors other than the complement pathway are also involved in atypical HUS. Moreover, unlike other atypical HUS, response to PLEX and eculizumab may be partial in drug induced atypical HUS. Timely cessation of the offending drug is the core principle of the management of drug induced haemolytic uremic syndrome.

Conclusions

To sum up, we recommend clinicians to be mindful of carfilzomib-induced haemolytic uremic syndrome, given the increasing use of carfilzomib in clinical practice. Cessation of the drug should be considered only after a careful assessment of the risk-benefit ratio of the chemotherapeutic agent and the prognosis of the existing malignancy.

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