Carfilzomib-induced thrombotic microangiopathy: A case based review

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CASE REPORT

Carfilzomib-induced Thrombotic Microangiopathy: A Case Based Review

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Abstract

Carfilzomib is an irreversible proteasome inhibitor currently approved for the treatment of relapsed multiple myeloma. It has been implicated as a cause of thrombotic microangiopathy (TMA) in several case reports. The incidence, risk factors, and treatment of carfilzomib-related TMA remain unclear. Here we describe the clinical presentation and outcome of a 58-year-old man with biopsy-proven TMA that occurred following treatment with carfilzomib-based therapy. We also reviewed the published literature with regard to the incidence, risk factors, treatment options, and outcome of carfilzomib-related TMA.

Keywords: Carfilzomib, Proteasome inhibitors, Thrombotic microangiopathy

1. Introduction

Carfilzomib is an irreversible proteasome inhibitor currently approved for the treatment of relapsed refractory multiple myeloma (RRMM). Proteasome inhibitors have been implicated in the development of drug-induced thrombotic microangiopathy (TMA) in several reports \cite{1-10}. It is a class effect and has been reported with bortezomib, carfilzomib, and more recently, ixazomib. TMA is a clinical syndrome of varied etiology characterized by endothelial injury and small vessel thrombosis. It manifests with microangiopathic hemolytic anemia, thrombocytopenia, and organ failure. It has been classically described with ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency, a condition called thrombotic thrombocytopenic purpura. Other etiological types include hemolytic uremic syndrome (HUS) caused by enterotoxigenic \textit{Escherichia coli} (ETEC), atypical HUS (aHUS) caused by defects in the alternate complement pathway, and drug-induced TMA. Here we describe the clinical presentation and outcome of a patient with biopsy-proven TMA that occurred following treatment with carfilzomib-based therapy. We also reviewed the published literature on carfilzomib-related TMA.

2. Case report

A 58-year-old Asian man was diagnosed with immunoglobulin G kappa multiple myeloma (ISS 2) in April 2015. Cytogenetic analysis was not performed. He achieved a very good partial response after six cycles of lenalidomide and dexamethasone and was subsequently planned for early autologous stem cell transplant (ASCT). During pre-transplant assessment, he was incidentally diagnosed with

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renal cell carcinoma of the right kidney. He underwent nephron-sparing surgery and ASCT was deferred. He received bortezomib maintenance and did well for 2 years.

Two years later, in January 2018, he had clinical relapse in the form of new bone lesions along with light chain escape (kappa light chain 1910 mg/L). He achieved partial response to pomalidomide and dexamethasone after two cycles but later progressed biochemically. He was then started on carfilzomib—lenalidomide—dexamethasone (KRD; carfilzomib 36 mg/m² biweekly, lenalidomide 10 mg daily for 21/28 days, and dexamethasone 40 mg weekly). He achieved partial response following two cycles of therapy and underwent ASCT with melphalan 200 mg/m² conditioning in November 2018.

From Day + 46 post-transplant, he received consolidation with KRD (carfilzomib 36 mg/m² biweekly, lenalidomide 10 mg daily for 21/28 days, and dexamethasone 40 mg weekly). He was also on acyclovir for prophylaxis of herpes simplex virus infection and on aspirin 75 mg daily as thromboprophylaxis. On Day + 53, he presented with extreme fatigue, nausea, and oliguria for 2 days. At admission, he had tachycardia (pulse rate 120 beats/minute), tachypnea (respiratory rate 30 breaths/minute), and normal blood pressure (120/80 mmHg). On evaluation, it was found that his hemoglobin level decreased from 13.6 g/dL to 10.6 g/dL, platelet count decreased from 187,000/μL to 10,000/μL, and creatinine level increased from 1.0 mg/dL to 11.6 mg/dL within a week. Peripheral blood film revealed 4–5% schistocytes (Fig. 1). Serum lactate dehydrogenase (LDH) was 3412 U/L (<240 U/L). Coagulogram was normal. Bone marrow examination did not reveal an excess of plasma cells. The serum free light chain assay was normal. He was started on alternate-day hemodialysis. With a presumptive diagnosis of TMA, he received five sessions of therapeutic plasma exchange (TPE) every alternate day. However, there was no increase in platelet count or improvement in urine output. Eculizumab was not considered as the drug is currently not available in India. The plasma ADAMTS levels were normal (48%). Plasma exchange was discontinued and only supportive treatment was provided.

At 10 days since the onset of illness, there was spontaneous rise in platelet count (from 10,000/μL to 45,000/μL) and drop in serum LDH (from 3412 U/L to 217 U/L) (Fig. 2). Renal biopsy revealed acute to sub-acute glomerular and vascular TMA with healed acute cortical necrosis (Fig. 3). After 6 weeks, urine output improved with daily output more than 1 L and dialysis was discontinued. However, he continued to have elevated creatinine levels (4.4 g/dL).

3. Discussion

We performed a literature search on MEDLINE (via PubMed) using keywords like “carfilzomib,” “proteasome inhibitor,” and “thrombotic microangiopathy”. We reviewed all relevant articles and found 16 cases of carfilzomib-related TMA between 2012 and 2019 (7 case reports and 3 case series with 2, 3, and 4 patients)[1–10]. A retrospective review series of 11 patients with proteasome inhibitor-induced TMA was published in 2016[11]; it included three patients and eight patients with bortezomib- and carfilzomib-induced TMA, respectively. These eight patients with carfilzomib-induced TMA have not been included in this analysis as individual case details were not available from the review. We describe the clinical profile and outcome of the 16 patients and this index case. The findings have been summarized in Table 1.

3.1. Incidence

The incidence of carfilzomib-related TMA is unknown. In the Phase 2 trial of carfilzomib in RRMM, fatigue (48%), nausea (45%), anemia (46%), and thrombocytopenia (39%) were reported as the most common adverse events. Acute renal failure occurred in 4.9% of patients, but was attributed to carfilzomib in only 1.5% of cases[12]. The investigators did not attribute renal failure to TMA in this trial. TMA as an adverse event has not been reported in drug trials so far and the only published data comes from case reports and retrospective case series. In a series from Singapore, an estimated incidence of 16.7% (4/24 patients) was reported[6]. The authors attributed the
high incidence of TMA after carfilzomib administration in their cohort to preceding infections and possibly ethnic factors (all affected patients were of Chinese descent). Because the clinical trials failed to report it, the incidence of carfilzomib-related TMA is unlikely to be more than 1%.

### 3.2. Onset and risk factors

Most cases of TMA have been reported with second and third cycle of therapy (10/17). However, it can be seen at any stage of therapy. Three patients had onset during the first cycle of therapy and one patient had TMA during 26th cycle [1,3,4,10]. The median interval between the start of carfilzomib therapy and onset of TMA was 43.5 (1–690) days. No specific dose cutoff has been identified with TMA reported at carfilzomib dose of 20 mg/m², 23 mg/m², 27 mg/m², 32 mg/m², 36 mg/m², and 56 mg/m².

Of the 17 patients, five had preexisting renal dysfunction and five had underlying diabetes mellitus or hypertension. However, there is no clear evidence to suggest an increased risk of TMA in patients with preexisting renal disease or risk factors.

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**Fig. 2.** Temporal relationship between plasma exchange (indicated by arrows) and (A) platelet count and (B) lactate dehydrogenase. Note. KRD = carfilzomib–lenalidomide–dexamethasone; LDH = lactate dehydrogenase.

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**Fig. 3.** (A) Renal biopsy showing healed cortical necrosis in the form of loss of proximal tubules (PAS, 20×). (B) Glomeruli with endotheliosis along with thickening and duplication of basement membrane (PAS, 40×). (C) Ischemic glomeruli with vascular changes (PAS, 20×). D) High power of the vessels showing subacute thrombotic microangiopathy (PAS, 40×).
for renal dysfunction. In the series from Singapore, two patients had evidence of a preceding viral illness with polymerase chain reaction positive for parainfluenza and rhinovirus [6]. The authors suggested the role of preceding infection as a trigger for TMA in such patients, but similar presentation has not been described in other reports.

3.3. Pathophysiology

Specifically, TMA is a class effect reported with bortezomib and ixazomib [13,14]. Despite several published reports, the mechanism remains unknown. ADAMTS levels, available for 12 patients, were normal suggesting a von Willebrand factor-independent mechanism in the pathogenesis of proteasome inhibitor-related TMA. Two hypotheses have been postulated. First is the inhibition of NF-κB pathway by proteasome inhibitor leading to a decrease in vascular endothelial growth factor (VEGF) in podocytes, resulting in endothelial dysfunction and TMA [4]. However, hypertension and proteinuria, considered as hallmarks of VEGF inhibition, have not been reported in all cases of carfilzomib-related TMA. A second explanation that has been suggested is the increased activation of alternate complement pathway in a setting of predisposing mutations in complement regulatory proteins, although such mutations were identified in only two of the three patients tested. Both patients were heterozygous for CFHR3-CFHR1 deletion. This mutation in homozygous state has been associated with aHUS. However, heterozygous deletion is considered a common benign variant. The authors postulated that carfilzomib may decrease CFH expression, diminishing alternative complement pathway inhibition, leaving the alternative complement pathway susceptible to dysfunction in the setting of innate impairment of CFH-related protein function [8]. In a more recent report of carfilzomib-related TMA, Bhutani et al. [15] found elevated Bb fragment level and soluble membrane attack complex (C5b-9), again reflecting alternate pathway complement activation. As of now, the mechanism remains speculative. Involvement of multiple pathways with or without an acute inciting event appears to be a more plausible explanation.

3.4. Presentation

The onset of carfilzomib-related TMA is usually sudden with rapid worsening and all reported patients had symptom duration of less than 7 days. The most common presenting complaints were weakness, easy fatigability, and shortness of breath.
due to rapid drop in hemoglobin. Fever and diarrhea was reported in five and four patients, respectively. Whether these manifestations are related to an inciting infection or a manifestation of TMA per se is not clear. Other presenting symptoms included oliguria in four patients and nausea and vomiting in three patients. Although thrombocytopenia is usually severe, bleeding was seen in only one patient. New onset or worsening of preexisting hypertension, considered as a hallmark of VEGF-mediated TMA, was observed in five patients. Of the 17 patients, only one patient had extra-renal manifestation with neurological involvement in the form of confusion and altered behavior [3].

3.5. Investigations

A precipitous drop in hemoglobin level and platelet count along with evidence of microangiopathic hemolytic anemia in the form of circulating schistocytes, elevated LDH, and bilirubin was seen consistently across all reported patients, except in one. This patient presented with worsening hypertension and proteinuria with no evidence of hemolysis on peripheral blood examination. Renal biopsy was done in view of proteinuria which revealed findings of TMA, along with podocytopathy and hypertension-related changes. Thrombocytopenia is usually significant with median platelet count of 19,000/μL (3000–58,000/μL). Acute kidney injury was seen in all patients with serum creatinine ranging from 2.1 mg/dL to 12.8 mg/dL.

Ancillary testing differed in different case reports and was mostly directed at ruling out alternate etiologies of TMA. Coagulogram for disseminated intravascular coagulation, complement levels for complement-mediated injury, stool culture or polymerase chain reaction for enterotoxigenic E coli to rule out HUS, and heparin-induced thrombocytopenia (HIT) antibodies to rule out HIT were few such investigations. ADAMTS levels were available for 12 patients and were normal in all these patients. Including our patient, biopsy was performed for five patients and all revealed findings consistent with TMA. Severe thrombocytopenia, history of an inciting drug known to cause TMA, and clinical response to conservative treatment were the reasons mentioned for not considering renal biopsy.

Drug-induced TMA is a diagnosis of exclusion and there is no specific diagnostic test. Several other confounding factors including infections, concomitant medications, underlying ADMATS13 deficiency, and complement pathway defects may play a role. It is important to rule out other etiologies before attributing TMA to carfilzomib.

3.6. Treatment

Carfilzomib was discontinued in all patients. Supportive care with transfusions and empirical antibiotics remained the mainstay of management. Nine patients (60%) required haemodialysis. TPE (10 patients) and eculizumab (4 patients) were the common TMA-directed therapies. Steroids were used in one patient only. The dose, frequency, and number of cycles of TPE as well as eculizumab differed in different reports. Although few reports have suggested efficacy of these modalities, the evidence is inconclusive [3,7,15]. In patients who had reportedly responded to therapy, improvement in thrombocytopenia, creatinine, and other parameters could be seen prior to as well as after discontinuation of these modalities. Also, there are five patients with no response to either therapy including the index case [1,5,8] and four in which there have been complete responses without any specific TMA-directed therapy [2,6].

3.7. Outcome

Of the 17 patients reported, one died of TMA-related complications (5.8%), five had partial platelet recovery, and 11 had complete platelet recovery. The median time to recovery was 14 (3–56) days. In comparison to thrombocytopenia, renal improvement was less common and took more time. Six patients had partial recovery in renal function (dialysis independence without creatinine returning to baseline) and six other patients had complete recovery. Importantly, five patients (29.4%) had no improvement in renal function and remained dialysis dependent. Median time to renal recovery was 38.5 (3–270) days.

4. Conclusion

In conclusion, TMA is a rare but serious complication of proteasome inhibitors. An abrupt drop in hemoglobin level and platelet count along with evidence of hemolysis and circulating schistocytes should raise a suspicion of TMA. Management includes supportive care and transfusion support. TPE may be started empirically till ADAMTS levels are available. TPE and eculizumab have been used in TMA therapy, but the evidence for their efficacy is anecdotal. Genetic testing for complement regulatory proteins should be encouraged wherever possible as it may provide insight into the mechanism of proteasome inhibitor-induced TMA. Despite treatment, up to 30% patients may remain dialysis dependent.
Authors’ contributions
NJ conceived the idea and wrote the first draft. A Jandial, A Jain, DL, GP, AK, RN, JS, JA, and PM supervised, edited, and wrote the final draft. All authors discussed the case and contributed to the final manuscript.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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