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Acute Tubular Necrosis in a Patient With Myeloma Treated With Carfilzomib

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INTRODUCTION

Carfilzomib is a selective proteasome inhibitor approved in 2012 for the treatment of relapsed and refractory multiple myeloma. It was developed with the aim of achieving improved safety profile and greater efficacy in patients who failed conventional treatments. A phase II trial for single-agent carfilzomib analyzed safety data in 526 treated patients and reported a rise in serum creatinine in 127 (24.1%) patients.[1] In 73.2% of these 127 patients, the rise in serum creatinine was attributed to the carfilzomib with no other precipitating event identified.[1] These data suggest that carfilzomib may be a cause of acute kidney injury (AKI), although the mechanism has not been determined. There have been several case reports providing evidence of AKI secondary to carfilzomib.[2–7] Two recent reports describe thrombotic microangiopathy associated with carfilzomib administration, although causality was not definitively established.[4,5] To our knowledge this is the first case report of biopsy-proven acute tubular necrosis (ATN) in a patient with multiple myeloma who was treated with carfilzomib.

CASE PRESENTATION

A 60-year-old man with IgG-λ multiple myeloma who had received autologous stem cell transplantation 2 years prior and suffered a recent relapse presented to the hospital with shortness of breath and chest discomfort. Past medical history was also notable for atrial fibrillation and congestive heart failure with preserved ejection fraction. In the emergency department he appeared to be in mild distress with blood pressure of 141/74 mm Hg, heart rate 83 bpm, respirations 16 per minute, and an oxygen saturation of 97% on room air. Physical examination revealed clear lungs, normal S_1 and S_2 without murmur, and pitting edema of both legs. Electrocardiogram revealed normal sinus rhythm with peaked T waves in the anterior leads with right bundle branch block. Laboratory data, which are summarized in Table 1, were significant for serum sodium of 131 mmol/l, potassium of 6.3 mmol/l, and creatinine of 3.4 mg/dl.

Table 1. Summary of laboratory results

Laboratory variable	Prior to carfilzomib	After carfilzomib	References
White blood cells	8.2 K/μl	9.3 K/μl	3.9–11.0 K/μl
Hb	8.8 g/dl	9.1 g/dl	12.7–18.0 g/dl
Platelets	100 K/μl	122 K/μl	160–392 K/μl
Haptoglobin	150 mg/dl	151 mg/dl	40–290 mg/dl
Lactate dehydrogenase	Unavailable	144 IU/liter	100–250 IU/liter
Sodium	137 mEq/l	131 mEq/l	138–145 mEq/l
Potassium	4.1 mEq/l	6.3 mEq/l	3.7–5.2 mEq/l
Creatinine	0.8 mg/dl	3.4 mg/dl	0.6–1.2 mg/dl
Calcium	8.0 mg/dl	8.6 mg/dl	8.6–10.3 mg/dl
Albumin	3.2 g/dl	3.9 g/dl	3.5–4.8 g/dl
Urine protein/creatinine ratio	Unavailable	3 g/g	<0.2 g/g
Urine albumin/creatinine ratio	Unavailable	0.14 g/g	<0.03 g/g
Serum κ light chains	3.96 mg/l	5.55 mg/l	1.35–24.19 mg/l
Serum λ light chains	1880 mg/l	3630 mg/l	0.24–6.66 mg/l
Serum κ/λ light chain ratio	0.002	0.0015	0.26–1.65
Urine κ light chains	Unavailable	13.50 mg/l	1.35–24.19 mg/l
Urine λ light chains	Unavailable	8190.00 mg/l	0.24–6.66 mg/l
Urine κ/λ ratio	Unavailable	0.0016	2.04–10.37
Urine sodium	Unavailable	49 mEq/l	
Urine potassium	Unavailable	32 mEq/l	
Urine chloride	Unavailable	41 mEq/l	
Urine osmolarity	Unavailable	352 mOsm/l	
Urine creatinine	Unavailable	49.8 mg/dl	
Fractional excretion of sodium	Unavailable	2.55%	
Urinalysis			
pH	7.0	6.0	5.0–8.0
Specific gravity	1.011	1.008	1.002–1.035
Protein	Negative	1+	Negative
Blood	1+	2+	Negative
Red blood cell number	0/hpf	63/hpf	<3/hpf
White blood cell number	0/hpf	2/hpf	<3/hpf

hpf, high-power field.

Free serum κ light chains were 5.55 mg/l, and serum λ light chains were 3630 mg/l (ratio 0.0015). Twenty days earlier, the patient had a baseline serum creatinine of 0.8 mg/dl, a serum free λ light chain level of 1800 mg/l, and a serum free κ light chain level of 3.96 mg/l (ratio 0.0022). Notably, the patient was given 2 consecutive injections of carfilzomib with decadron at a dose of 20 mg/m^2 7 days prior to presentation. He denied nonsteroidal anti-inflammatory drug use, radiocontrast exposure, or any other changes in medications. His outpatient medications included acyclovir, warfarin, fentanyl patch, furosemide, gabapentin, digoxin, metoprolol, olanzapine, ramipril, potassium chloride, bupropion, and alprazolam. A urine sample obtained by bladder catheterization revealed pH 6.0, specific gravity 1.008, 1+ protein, 2+ blood, and 2 white blood cells and 63 red blood cells per high-power field. The spot urine protein/creatinine ratio was 3 g/g, and the albumin/creatinine ratio was 0.14 g/g. Urine κ light chains were 13.5 mg/l, and urine λ light chains were 8190.0 mg/l, yielding a urine κ/λ ratio of 0.0016. Renal ultrasound revealed no hydronephrosis and normal kidney size (right kidney 12.8 cm and left kidney 12 cm). Several days later the creatinine stabilized at 2.6 mg/dl, at which point a kidney biopsy was performed.

Renal Biopsy Findings

The 7 glomeruli sampled for light microscopy were unremarkable. The major histologic finding was diffuse acute tubular injury involving 100% of the cortical parenchyma, affecting both proximal and distal tubules, associated with mild interstitial edema and sparse interstitial inflammation. The cortical tubules exhibited luminal ectasia, attenuation of brush border, focal coarse clear cytoplasmic vacuolization, and enlarged reparative nuclei containing nucleoli (Figure 1). A minority of distal tubules contained atypical hard crystalline casts of the myeloma type with giant cell reaction (Figure 2). By immunofluorescence microscopy, the casts revealed restricted 3+ staining for λ light chain, with negative staining for κ light chain. Congo red stain for amyloid was negative. The presence of diffuse acute tubular injury out of proportion to the sparse crystalline casts suggested ischemic or toxic ATN superimposed on mild myeloma cast nephropathy. The close temporal association with the initiation of carfilzomib and the absence of other obvious recent insults suggested that the medication had a role in development of the severe acute tubular injury.

The patient's light-chain burden continued to increase, and he was treated with cyclophosphamide. His kidney function progressively worsened and he eventually required renal replacement therapy.

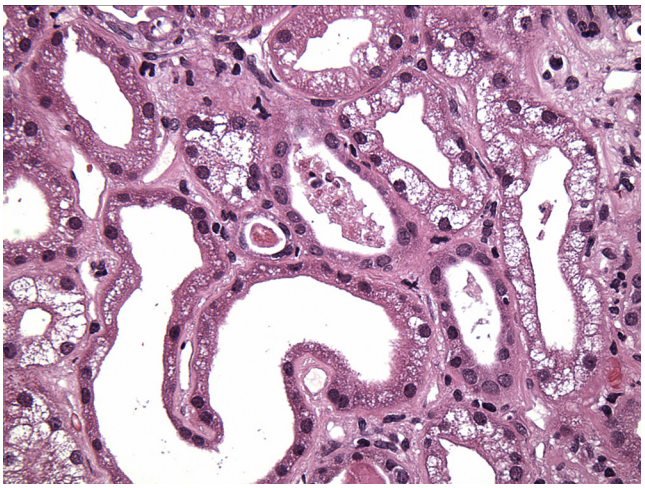

Figure 1. The major finding was diffuse acute tubular injury affecting both proximal and distal tubules with epithelial simplification, luminal ectasia, attenuation of brush border, coarse clear cytoplasmic vacuolization, and focal shedding of degenerating epithelial cells into the lumen. These degenerative tubular changes were present in tubules lacking myeloma-type casts (hematoxylin and eosin, original magnification X400).

DISCUSSION

Carfilzomib is a relatively new agent approved for the treatment of relapsed and refractory multiple myeloma. It has been associated with AKI as an adverse event in a phase II trial.[1] Most of the cases of AKI in this phase II trial were attributed to carfilzomib, as no other precipitating cause could be identified; however, the mechanism of AKI was not determined. There have also been a number of case reports[2–7] attributing AKI to carfilzomib, some suggesting that thrombotic microangiopathy may have been the mechanism of injury based on clinical presentation and evidence from kidney biopsies, but definitive causality was not established.[4,5]

It can be difficult to determine the mechanism of AKI in patients with multiple myeloma because the differential is typically broad and includes a prerenal state from nausea and vomiting, hypercalcemia leading to renal vasoconstriction, monoclonal Ig deposition disease, myeloma cast nephropathy, infections, and drug-induced toxicity, among others (Table 2). A prerenal state was unlikely in our patient because he did not present with clinical signs of volume depletion, he had no vomiting, diarrhea, or hypercalcemia, and his fractional excretion of sodium was >2% approximately 24 hours after he last received furosemide. He presented with a rise in serum λ light chains and markedly reduced κ/λ ratio that can be explained by both worsening myeloma with increased production of light chains and decreased excretion due to kidney failure. Several case reports in the literature have

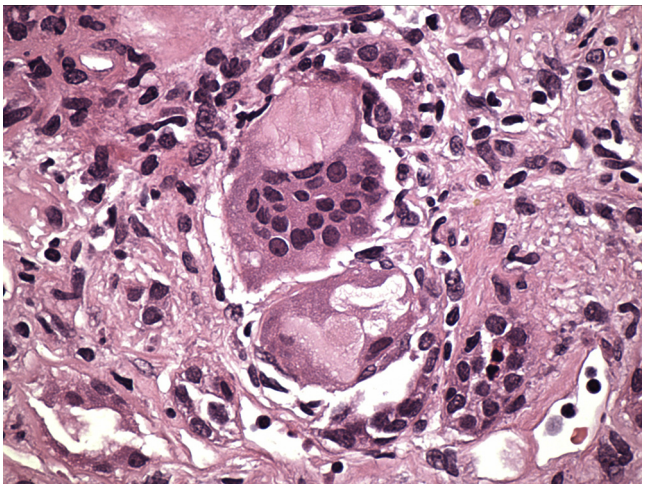

Figure 2. The biopsy contained several atypical casts surrounded by multinucleated giant cells and dehisced tubular epithelial cells, typical of myeloma casts (hematoxylin and eosin, original magnification X600).

suggested an association between carfilzomib and thrombotic microangiopathy.[4,5,7] However, our patient had no clinical manifestations of thrombotic microangiopathy, such as hemolytic anemia, thrombocytopenia, or schistocytes, and no histologic evidence of thrombosis. There was no evidence on kidney biopsy of acute interstitial nephritis, which has been described in a single patient treated with bortezomib, a similar proteasome inhibitor.[8]

The patient presented herein suffered AKI 1 week after receiving 2 consecutive doses of carfilzomib. In the phase II trial,[1] the incidence of first episodes of worsening renal function was evenly distributed across earlier and later time points, suggesting that a high cumulative exposure is not required for development of toxic AKI.[1] The renal biopsy revealed ATN. While the renal biopsy also showed mild focal myeloma cast nephropathy, the degree of acute tubular injury appeared far out of proportion to the few myeloma casts. To our knowledge this is the first case report of biopsy-proven ATN in a patient with multiple myeloma treated with carfilzomib.

Although not previously demonstrated, it is plausible that carfilzomib could cause ATN by its cellular effects on renal tubular epithelium. Carfilzomib is a selective proteasome inhibitor similar to bortezomib. Both drugs target the ubiquitin–proteasome system and inhibit the 20s proteasome. The ubiquitin–proteasome system is an intracellular degradation pathway in eukaryotic cells that normally leads to degradation of proteins such as p53 and nuclear factor-κB, which are involved in apoptosis, inflammation, senescence, and angiogenesis.[9] Normal function of the 20s proteasomal system is critical to cellular maintenance and survival pathways. Inhibition of the 20s proteasome system, by reducing the degradation of proteins such as p53, could enhance apoptosis. While this is a desirable result for malignant cells, proteasome inhibition could exert harmful effects in renal tubular epithelial cells and potentially other cell types, resulting in AKI. In a murine model of ischemia–reperfusion injury, mice receiving the 20s proteasome inhibitor bortezomib experienced a significant increase in tubular cell apoptosis and greater decline in kidney function compared to control mice subjected to ischemia–reperfusion injury alone.[9] Bortezomib and carfilzomib have similar mechanisms of action. However, acute kidney injury is less frequently reported following exposure to bortezomib as compared to carfilzomib. One explanation could be that carfilzomib is used in refractory or relapsed multiple myeloma where some tubular injury might already have occurred secondary to monoclonal light chains, thereby predisposing to further tubular injury by the drug.

While carfilzomib may have been the etiologic factor causing ATN, we must also consider that the ATN could result from a combined effect of the drug and monoclonal light chains. Excessive production of monoclonal light chains may be directly toxic to tubular epithelial cells.[10] For example, in an *in vitro* study, exposure to λ light chains induced a 6-fold increase in the number of apoptotic cultured human proximal tubule cells.[10] Monoclonal light chains have been shown to generate intracellular oxidative stress in the form of hydrogen peroxide, which in turn promotes synthesis of chemokines and cytokines that lead to inflammation.[11] In particular, monoclonal light chains activate apoptosis signal–regulating kinase 1, which is a key mediator of oxidative stress–induced apoptosis.[11]

Given the potential for tubular toxicity from light chains, one must consider at least 2 additional possible mechanisms for ATN in this clinical setting. First, it is plausible that our patient suffered light chain–induced tubular injury that was then compounded by the "second hit" of carfilzomib, with the combined insult being sufficient to cause ATN. Second, it is plausible that the carfilzomib caused acute

Table 2. Teaching points

Acute kidney injury in patients with multiple myeloma has many potential etiologies, including direct consequences of the hematologic malignancy and nephrotoxicity of therapeutic agents.
Carfilzomib has been associated with acute kidney injury, but few patients have been subjected to diagnostic kidney biopsy.
The patient presented here, who had multiple myeloma for years, developed acute tubular necrosis and mild myeloma cast nephropathy 1 week following exposure to carfilzomib.
It is plausible that carfilzomib may promote acute tubular necrosis by direct cellular toxicity, possibly exacerbated by the toxic effects of monoclonal light chains.

tubular injury, which in turn suddenly compromised the ability of the proximal tubules to endocytose and catabolize the high filtered load of monoclonal light chains, resulting in the development of cast nephropathy. However, it should be noted that there was no evidence of light chain proximal tubulopathy, in which crystalline intracytoplasmic inclusions develop within proximal tubular cells. Whether acting alone or in combination with nephrotoxic light chains, the close temporal relationship between carfilzomib therapy and AKI suggests that the drug played some pathogenetic role in the development of AKI.

CONCLUSION

To our knowledge this is the first report of biopsy-proven ATN occurring after carfilzomib treatment for multiple myeloma. Although our case demonstrates an association of carfilzomib administration and ATN, an exact mechanism of injury remains to be determined. This adverse event could be the result of a combined cellular effect of the drug itself and nephrotoxicity of monoclonal light chains. Greater use of renal biopsy in this setting may provide insight into the prevalence of ATN in multiple myeloma patients treated with carfilzomib.

DISCLOSURES

All the authors declared no competing interests.

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