Renal failure in multiple myeloma

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This report details the case of a 65-year-old man who was diagnosed with multiple myeloma in 2006 and since 2009, has attempted to control the progression of his disease with the most powerful available treatment regimens, including bortezomib-based regimens, for both induction and consolidation therapy followed by autologous stem-cell transplants. Subsequently, because the patient was deemed treatment refractory, treatment with the newly approved carfilzomib was initiated. Coincidentally, the patient developed acute kidney injury, evidenced by tenfold rise in his creatinine levels, 2 weeks after the initiation of carfilzomib. The etiology of his acute kidney injury was unclear; although initially thought to be secondary to volume depletion, this new chemotherapeutic drug could not be excluded as the causative agent given the correlation with the timing of onset. In addition, because carfilzomib was newly approved, there was little documentation on its toxicities, but nephrotoxicity has been noted as a rare side effect.[1] Nevertheless, multiple myeloma is known to damage kidneys, and this patient had light chain disease, kappa type, the form of multiple myeloma that has been shown to most commonly involve the kidneys. An invasive biopsy was indicated to determine the etiology of the patient's renal failure, as the myeloma could not be excluded, and though the former 2 causes may be reversible, aggressive interventions would be required should the latter have cause his acute kidney injury.

Renal failure in multiple myeloma can be attributed to a number of causes, and it is often unclear on presentation what the precipitating factor is, which makes treatment, and thus recovery of renal function a difficult task. The following case details the patient's clinical presentation and the subsequent investigations and management of his condition, along with a brief discussion of how one can approach and manage renal failure in this patient population.

Case presentation

A 65-year-old man was diagnosed with multiple myeloma, light chain disease, kappa type, in 2006. He began induction treatment with bortezomib and lenalidomide in November 2009, completing a 25-month course of chemotherapy, for which each dose was administered every 3 weeks. During the course of his induction treatment, in 2010, he also received an autologous stem-cell transplant. He began taking zoledronic acid every 6 months as of 2011. His consolidation treatment began in May 2012. He received weekly bortezomib, lenalidomide, and dexamethasone. Despite weekly consolidation therapy, the serum kappa–lambda ratio continued to increase, and had progressed from a value of 55 in May 2012 to 130 in July 2012. Dexamethasone was discontinued after 4 months. Bortezomib was continued for a short amount of time, but was replaced by a new agent, carfilzomib, in August 2012. This was a novel chemotherapeutic agent approved by the Food and Drug Administration in July 2012. It had been approved for patients who, like our patient, have multiple myeloma refractory to bortezomib.

Two weeks after his first dose of carfilizomib, the patient presented to his oncologist's office to receive his second dose of the chemotherapeutic agent. He reported nonspecific symptoms – fatigue, anorexia, and malaise – since his first dose of carfilizomib, and said the symptoms had gradually worsened over the previous 2 weeks. His routine labs were drawn, revealing a creatinine rise to 10.1, blood urea nitrogen (BUN) of 97, and a potassium level of 6.7. Of note, his last creatinine 2 weeks previously was 1.15. Other medications that the patient was taking concomitantly included aspirin, amitriptyline, tamsulosin, revlimid, lenalidomide, and zoledronic acid. Table 1 shows the patient's laboratory results from 2 weeks ear-

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TABLE 1 The patient's laboratory results from earlier labs compared with those from his presentation 2 weeks after crizotinib initiation (2012)

	Aug 23	Sep 6
WBC	4.4	4.7
HGB	10.7	9.7
PLT	85	65
Sodium	135	136
Potassium	4.3	6.7
BUN	24	97
Creatinine	1.15	10.23
CO_2	25	16
Calcium	8.5	9.9
Albumin	3.3	3.6

Abbreviations: BUN, blood urea nitrogen level; HGB, hemaglobin level; PLT, platelet count; WBC, white blood cell count.

lier compared with those from his presentation being described here.

Initially, his hypercalcemia was so severe as to display electrocardiographic changes, and the patient was subsequently managed with aggressive treatment to lower the plasma potassium levels. The serum potassium responded appropriately to calcium gluconate, kayexalate, insulin/dextrose. The patient was seen by a nephrologist upon admission, who decided not to immediately dialyze him, as it was possible that there was a prerenal component to this sudden rise in creatinine and therefore opted for aggressive fluid administration in attempts to correct this. That evening, the patient had an episode of prolonged epistaxis, which persisted for an hour before the nose required packing. In the setting of his BUN of 97, this was attributed, at least in part, to uremia. As uremic bleeding is an acute indication for dialysis, the patient had a right central catheter placed and underwent hemodialysis the following day. His creatinine dropped appropriately following dialysis. The etiology of this patient's acute renal failure was still unknown. Multiple myeloma is a known cause of renal failure, and in the setting of this patient's light chain disease, this was likely precipitating factor: the patient's corrected serum calcium was mildly elevated, at 10.2, and in the setting of acute renal failure this value was inappropriately elevated. A new agent had been administered at a time corresponding to this sudden rise in creatinine, and this seemed far too convincing to classify as a coincidence. In addition, he had been receiving zoledronic acid, which has been known to cause acute tubular necrosis. As laboratory results specific for multiple myeloma were pending, a renal biopsy was performed to isolate the cause of his renal failure (Figure 1).

The patient's laboratory results (specific to his myeloma), drawn at the time of admission returned, revealing a free kappa–lambda ratio of 919.05 (reference range, 0.26-1.65); kappa light chain free, 7,720.0 mg/dL (3.3-19.4 mg/dL); lambda light chain free, 8.4 mg/dL (5.7-26.5 mg/dL). Table 2 shows the progressive increase in these values over the previous month. The diagnosis was confirmed. The patient's renal failure was attributable to light chain deposition disease secondary to his multiple myeloma, which had subsequently led to a cast nephropathy. The initiation of carfilzomib was deemed to be a coincidence, and his renal failure had progressed rapidly in a matter of weeks despite initiation of the new agent.

Discussion

Multiple myeloma is characterized by neoplastic proliferation of a clone of plasma cells producing a monoclonal immunoglobulin.[2] It affects multiple organ systems, but this discussion will focus on the effects of multiple myeloma within the kidney, which is one of the organs that is more commonly affected in multiple myeloma. Renal disease is a poor prognostic indicator for those with multiple myeloma. The United Kingdom Medical Research Council Multiple Myeloma trials, performed between 1980 and 2002, had outcomes showing that renal failure contributed to 28% of documented early mortality.[3] At diagnosis, 30%-40% of patients have a serum creatinine above the upper limit of normal, and up to 10% of these patients require prompt dialysis.[4] At least half of the patients with multiple myeloma will develop renal failure through the course of their disease. Half of these patients will respond to supportive treatment with reversibility of renal impairment, which correlates to a better prognosis. That being said, 2%-12% will progress to ESRD and require dialysis.[5]

Multiple myeloma can lead to renal failure via a number of causes, both metabolic and neoplastic, and can affect the glomerular basement membrane, tubules, or the interstitium. Renal impairment in multiple myeloma has been attributed to a number of pathological mechanisms and etiological factors, however, almost all cases of renal failure result from an elevated serum concentration of monoclonal free light chains. This correlation can be explained by the fact that free light chains are removed from the circulation predominantly by glomerular filtration. They are filtered in the glomerulus and either pass directly into the tubules or are transported into the mesangium. Their deposition leads to obstruction, amyloid formation, and inflammation.[4] The 3 most common causes of renal failure in multiple myeloma are:

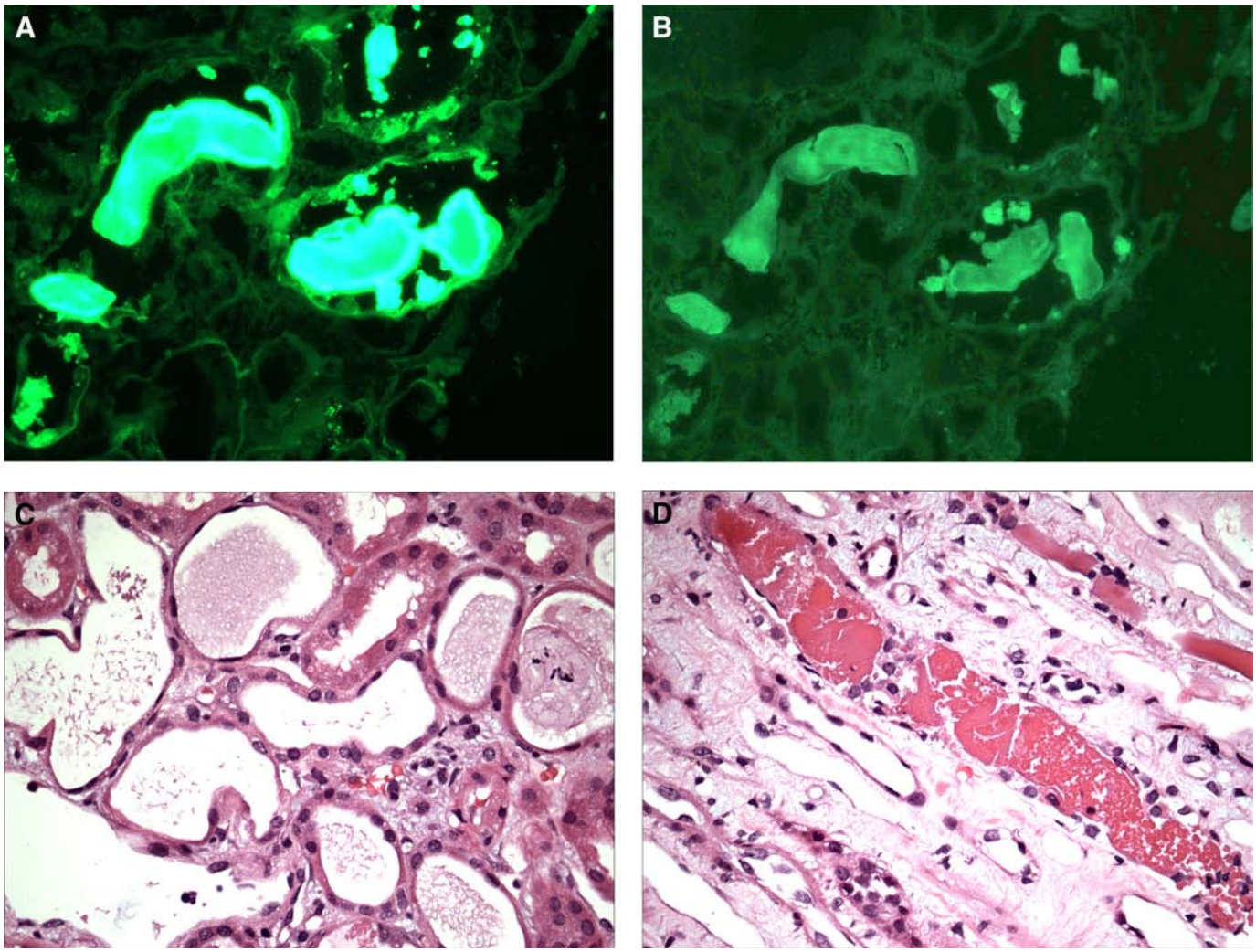

FIGURE 1 Biopsy specimens displaying foot process effacement consistent with myeloma cast nephropathy, kappa type. (A) Immunofluorescence revealed tubular cast for kappa but negative for lambda (B). Sampling for light microscopy showed diffuse interstitial edema, tubular degenerative changes (C) and atypical distal tubular casts (D).

- Monoclonal immunoglobulin deposition disease due to deposition of light chains (LCDD) or heavy chains (HCDD) – light chains are usually made in excess of heavy chains. These may deposit along the glomerular basement membrane or within the tubular basement membrane, either in the form of fragments or intact chains.
- AL amyloidosis where the light chains form beta pleated sheets which deposit in the renal blood vessels or glomeruli.
- Cast nephropathy, which causes tubulointerstitial nephritis secondary to distal tubule obstruction by the deposition of immunoglobulin light chains.[5] Of note, cast formation has been shown to occur in LCDD in up to one third of cases. Cast nephropathy, also referred to as myeloma kidney, is most often correlated to as a direct consequence of an elevated serum concentration of immunoglobulin free light chains (FLCs).[4] The formation of casts in the distal tubules, caused by the deposition of light chains and Tamm-Horsfall protein, is the main cause of this renal failure. Therefore, it is necessary to rapidly reduce blood levels of free light chains in order to facilitate the recovery of renal function.[6]

While LCDD and amyloidosis tend to result in chronic kidney disease, often with nephrotic range proteinuria, cast nephropathy will usually present with a sudden rise in creatinine representing an acute kidney injury.[5] A cast nephropathy may occur secondary to aggravating factors, such as dehydration, hypercalcemia, nephrotoxic drugs, or intercurrent infections.[4] In a native renal biopsy study of patients with multiple myeloma, cast nephropathy was found to be the most common renal manifestation, occurring in

TABLE 2 The patient's laboratory results specific to his myeloma (2012)

	Aug 9	Aug 23	Sep 6
Kappa light free chains	1,340.0	3,390.0	7,720.0
Lambda light free chains	9.20	2.80	8.40
Kappa/Lambda ratio	145.65	> 1000	919.05

40%-63% of patients, followed by LCDD in 19%-26%, and AL amyloidosis in 7%-30%.[5]

In attempts to limit the need for invasive biopsy, which is preferably avoided in the setting of multiple myeloma given these patients' predisposition to bleeding, screening modalities have been instituted. It has been concluded that in patients with acute kidney injury, the presence of an FLC concentration greater than 500 mg/L along with proteinuria consisting mainly of light chains, there is a high likelihood of myeloma kidney and a biopsy in these cases can be avoided. In cases in which significant albuminuria is present, amyloidosis or MIDD are likely contributing disease processes, and amyloid deposits may be found on a biopsy, which luckily may be demonstrated on subcutaneous fat or a salivary gland biopsy, thus limiting the need for an invasive renal investigation. If these biopsies prove to be negative, a renal biopsy is required. In patients with chronic kidney disease whose etiology is attributable to multiple myeloma of a monoclonal protein, a renal biopsy is essential in order to determine the etiology of the kidney damage.[4]

This section will focus on the treatment of myeloma cast nephropathy; of note, similar therapeutic treatment regimens are used for both AL amyloidosis and MIDD though their outcomes are not discussed below.

Recent evidence shows that early reduction of circulating free light chains improves renal function in patients with multiple myeloma. In a recent study, it was concluded that a free light chain reduction of 60% by day 21 would result in 80% of patients recovering their renal function.[7] In addition, the introduction of aggressive chemotherapeutic agents to decrease the burden of the free light chains has been shown to rescue kidney function in more than two thirds of patients. Most recently, the glomerular filtration rate has been assessed when monitoring patients response to multiple myeloma therapy, and this has proven to increase as a result of therapy, although, unfortunately, a sustained response represented by an elevated GFR is still not the most likely outcome in these circumstances.[4]

In patients with cast nephropathy, the current mainstay of therapy is the removal of aggravating factors. As with prerenal and renal failure of other commonly known etiologies, it is important to optimize intravascular volume with oral or intravenous fluids and avoid loop diuretics, along with correcting any existing metabolic acidosis and hypercalcemia.[4] Kidney function in these cases may also be preserved by limiting the use of contrast agents, along with the avoidance of certain drugs, namely certain bisphosphonates such as zoledronic acid (which can cause acute tubular necrosis) and pamidronic acid (which can cause focal segmental glomerulosclerosis).[8]

Both high-dose chemotherapy as well as autologous stem-cell transplants (ASCT) may be performed in attempts to decrease the burden of disease. Chemotherapeutic agents are generally used initially to induce a remission and suitable patients will then receive high-dose mephalan followed by an ASCT. ASCT is generally preferred in patients younger than 60 years; the difficulty with this form of treatment in the setting of renal disease is that treatment should be initiated quickly in multiple myeloma patients to successfully recover their renal function and there can be significant delays with starting ASCT. This has been shown to improve renal function, but is more efficacious when commenced early on in the course of the disease.[5]

With regards to chemotherapy regimens, those including high dose dexamethasone have been found to be the most effective in patients with myeloma-related acute kidney injury as it quickly and effectively decreases the serum concentration of FLCs.[5] This is likely attributable to the rapidity of onset of these regimens. The International Myeloma Working Group has published a consensus statement stating that patients with multiple myeloma and renal failure will have the most positive response to bortezomib-based regimens, which include any combination of bortezomib, thalidomide, lenalidomide, and high-dose dexamethasone. Mephalan is generally added to this regimen in elderly patients with renal impairment.[4] These agents may in fact be able to reverse renal impairment resulting from multiple myeloma and prevent permanent renal damage.[5]

Carfilzomib is a new chemotherapeutic agent that was approved by the Food and Drug Administration in 2012. The patient had been started on carfilzomib 2 weeks before the development of his acute kidney injury. This agent is a proteasome inhibitor, similar in its mechanism of action to bortezomib but it differs from bortezomib in that it binds irreversibly to the proteasome, selectively inhibiting chymotrypsin-like activity of the enzyme. This agent was designed for patients deemed to have "double refractory" myeloma, that is, to have developed resistance to bortezomib and lenalidomide following an initial period of clinical response. Seigal et al carried out a large

phase 2 trial in patients who had undergone 5 prior lines of therapy and they found that patients who were double refractory had a response rate of 20.1% following carfilzomib, and the survival of these patients was approximately 1 year. Overall, the response rate was 23.7% with median duration of response of 7.8 months. For the most part, this agent has been shown to be well tolerated thus far, however common toxicities include fatigue, anemia, nausea, thrombocytopenia, and dyspnea and in the study mentioned above, peripheral neuropathy was reported in a notable number of cases. In the above study, it was shown that 4.1% of patients died within the first 2 cycles of carfilzomib secondary to toxicities. That being said, many of these patients have advanced disease and multiple systemic complications once they are considered candidates for this agent, thus confounding factors cannot be excluded and will likely be considered in further trials.[9] With regards to renal function in the setting of this agent, the PX-171-005 trial was carried out with a patient population who displayed varying degrees of renal dysfunction. Patients were stratified based on their creatinine clearance and the results of this study showed that there is no requirement to adjust the dose of this medication based on renal function, an important factor to consider in this patient population.[1]

Hemodialysis has been shown to be an alternative form of treatment for these patients and it is also used in conjunction with chemotherapy to more effectively decrease the serum concentrations of FLCs. Although useful in patients with chronic renal failure, this has also been proven effective in patients with acute kidney injury caused by renal tubular disease, and one study revealed an achieved recovery rate of 50% in this given patient population. What is remarkable is that dialysis is most often perceived as a chronic form of therapy, however when treating patients concomitantly with both dialysis and high dose chemotherapy, one quarter of patients achieved complete independence from dialysis.[6]

Renal transplantation may be considered, especially in younger patients. Again, appropriate transplant candidates need to be carefully selected with regard to age and functional status. Initial guidelines advised for a 2-year waiting period between induction treatment and transplantation, however with newer, more potent treatment regimens and ASCT, optimal time for renal transplantation has been considered shortly after induction of first remission and consolidation with ACST. The overall prognosis for these patients following a renal transplant is still in question; an early study of renal transplant in this patient population reported a 14-114 month survival in 9 multiple myeloma patients following renal transplantation and similar studies more recently carried out have revealed similar outcomes. A better outcome was shown in most case studies if transplantation was carried out while in remission.[5]

Conclusion

In summary, renal failure in patients with multiple myeloma may present in an acute or chronic manner, depending on the etiology of the renal failure. In this patient, a cast nephropathy led to a sudden rise in creatinine, from 1.15 mg/dL to 10.23 mg/dL in 2 weeks. Multiple etiologies were considered, including initiation of the new chemotherapeutic agent, carfilzomib, prerenal failure secondary to volume depletion, multiple myeloma itself, or other drugs, including zoledronic acid. The definitive diagnosis was confirmed by biopsy. As detailed above, myeloma kidney classically presents with this sudden rise in creatinine as shown in this patient. There are many treatment options in these cases, almost all of which consist of lowering the serum concentration of free light chains, and the rate at which these free light chains are removed has shown to correlate with the degree of response. However, with the exception of hemodialysis and a renal transplant, at this time, only the treatment of multiple myeloma itself is efficacious in treating renal failure in this patient population.

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