Approach to acute renal failure in biopsy proven myeloma cast nephropathy: Is there still a role for plasmapheresis?

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CASE PRESENTATION
A 75-year-old Caucasian man with hypertension and severe, emphysema, presented to the Veterans Administration New York Harbor Health Care System Hospital outpatient clinic, for his bi-yearly physical in March 2003. The patient had a macrocytic anemia and a serum creatinine (Scr) level of 3.3 mg per 100 ml (baseline Scr, 0.9 mg per 100 ml 1 month earlier). An outpatient nephrology consultation was initiated after a comprehensive negative gastrointestinal workup. Detailed history and physical examination were performed. He denied the following symptoms: headache, visual changes, hesitancy, frequency, oliguria, dysuria, nausea, vomiting, fever, chills, bone pain, and change in weight, appetite or bowel habits. He also denied the following: hematochezia, melena, fatigue, dyspnea, dizziness, or chest pain. His medications on presentation included lisinopril day\(^{-1}\) and combination albuterol and atrovent inhaler. He denied occupational or chemical exposure, and use of herbal or over-the-counter medications. The patient quit smoking and drinking over 20 years ago. He had no history of diabetes mellitus, macroscopic hematuria, or tuberculosis. His family history was non-contributory. Physical examination revealed an alert, healthy-appearing older male with a blood pressure of 134/83 mm Hg (without orthostasis), pulse rate of 78 beats min\(^{-1}\), weight of 89 kg, and body mass index of 29 kg m\(^{-2}\). There was no lymphadenopathy. Heart examination showed regular rate and rhythm, without murmurs, rubs, or gallops. Lungs were clear to percussion and auscultation. Abdomen had normal bowel sounds, was soft, non-tender, with no masses or hepatomegaly.

There was dullness in Traube’s space on deep inspiration. Extremities revealed no clubbing, cyanosis, rash, or edema. Neurological examination was essentially normal. Diagnostic studies were performed. Renal ultrasound showed 11.7 and 12.4 cm right and left kidney, respectively. Both kidneys demonstrated mildly increased, diffuse parenchymal echogenicity, consistent with mild medical renal disease, with no scarring or masses. There was no hydronephrosis. Renal veins were patent bilaterally. The bladder was not distended. Spleen was enlarged, measuring 12.6 cm. Results of the laboratory studies are detailed in Table 1. Urinary dipstick showed trace protein but sulfosalicyclic acid testing was not performed. Twenty-four-hour urine protein level was 3.1 g day\(^{-1}\). Urine protein electrophoresis was unremarkable, but urine and serum immunofixation electrophoresis and serum protein electrophoresis showed a monoclonal band (IgA\(_k\)). His quantitative serum immunoglobulin A (IgA) level was 2330 mg per 100 ml. Bone marrow biopsy revealed 90% plasma cells (Figure 1). Skeletal survey was negative. A diagnosis of multiple myeloma (MM) Durie-Salmon stage III was made.

CLINICAL COURSE
The patient’s age and comorbidities precluded consideration of stem cell transplant. Initial therapy was directed at correcting reversible factors contributing to a reduction in glomerular filtration rate (GFR), which included discontinuation of lisinopril and volume expansion. Blood pressure was thereafter managed with a \(\beta\)-blocker. Concurrent treatment with thalidomide and dexamethasone was started. On this regimen, reductions in serum creatinine (Scr) levels to 1.2 mg per 100 ml and serum immunoglobulin A (IgA) to 121 mg per 100 ml occurred within several months. Thalidomide was discontinued after 6 months because of severe peripheral neuropathy.

Two years later (August 2005), serum IgA level increased to 767 mg per 100 ml and Scr reached 1.7 mg per 100 ml.
Having relapsed, the patient was started on melphalan and prednisone. Over the next month, the IgA levels plateaued. However, chemotherapy was discontinued because of profound neutropenia and pneumonia requiring hospitalization. In February 2006 (2.5 years following the original diagnosis), the patient was hospitalized for both respiratory and urinary infections, and was again found to have disease recurrence. Repeat bone marrow biopsy at that time showed 90% plasma cells. Serum IgA level was 2403 mg per 100 ml, with proteinuria level of 2.4 g day\(^{-1}\). Scr of 4 mg per 100 ml. B₂-microglobulin was 30 mg per 100 ml. Corrected serum calcium and uric acid levels were 8.4 and 7.4 mg per 100 ml, respectively. In addition to antibiotic treatment for his infections, his acute-on-chronic renal failure was treated with bicarbonate alkalinization to maintain a urine pH > 6.5 and volume expansion to sustain a urine output > 2 l day\(^{-1}\). Despite these measures, the patient developed anuria and a Scr level of 7.5 mg per 100 ml. This observation, and the need for blood products to treat a new spontaneous retroperitoneal bleed, prompted temporary hemodialysis (HD) initiation. A renal biopsy detailed below, showed myeloma cast nephropathy (MCN) (Figure 2). Plasmapheresis was started, resulting in reduction in serum IgA, Scr, and improvement in urinary output. Chemotherapy was postponed until infection resolved. After 10 sessions of alternate-day plasmapheresis with fresh frozen plasma, IgA level declined roughly 50% from 2403 to 1329 mg per 100 ml (Figure 3). Dialysis was discontinued after two HD sessions, when the patient became non-oliguric and Scr stabilized at 3.7 mg per 100 ml. Two months later (April 2006), triple therapy with bortezomib, thalidomide, and dexamethasone was started. The IgA level and renal function did not improve further despite chemotherapy.

Three years following diagnosis of multiple myeloma (MM) (June 2006), he was readmitted with weakness and hypotension. He had serum-κ free light chain (sFLC) levels of 1180 mg per 100 ml, IgA of 1917 mg per 100 ml, and was developing worsening non-oliguric renal failure (Scr 5.7 mg per 100 ml).
per 100 ml). Peripheral edema (2 + to the knees) and proteinuria (2.7 g day$^{-1}$) were present. Corrected SCA level was 8.7 mg per 100 ml and urinary uric acid-to-cr ratio was 0.7 (urate nephropathy considered if ratio > 1). After volume expansion and bicarbonate alkalization of urine, the patient underwent a second series (12 alternate day sessions) of plasmapheresis with albumin. The objective of treatment was to reduce proteinuria (2.7 g day$^{-1}$) and uric acid-to-cr ratio to 45 mg per 100 ml, and Scr to 4 mg per 100 ml (Figure 3). Four years after diagnosis of MM, Scr level was stable at 2.6 mg per 100 ml. Serial skeletal surveys remained negative.

At his most recent hospital visit (March 2007) prompted by pulmonary infection, laboratory findings showed progressive disease. A severe reduction in serum Ig levels prompted administration of intravenous Ig. In May 2007, once infection had been treated, therapy was initiated with lenolidomide and dexamethasone concomitant with volume repletion and urine bicarbonate alkalization.

**RENAL BIOPSY FINDINGS**

Paraffin sections (light microscopy) stained with hematoxylin and eosin, periodic acid–Schiff, trichrome, and silver showed the renal cortex to contain 61 glomeruli, 50 of which were globally sclerotic or obsolescent. Most of the glomeruli revealed periglomerular fibrosis. The remaining glomeruli were normal in size and in cellularity. The capillary walls were normal in thickness and contour. The tubulointerstitial compartment had moderate acute tubular injury, with blebbing of the apical cytoplasm. Vacuolizations as well as focal flattening of the epithelium were identified. Occasional intratubular, weakly periodic acid–Schiff-positive casts were noted. Some casts had a dense, angulated, and ‘fractured’ appearance, and were surrounded by a cellular reaction. There was a patchy interstitial fibrosis and tubular atrophy involving approximately 50% of the parenchyma in the areas of globally sclerotic glomeruli. A moderate infiltrate of macrophages and giant cells surrounded the casts. Eosinophils were rarely present. Neutrophilic tubulitis was not present. Immunofluorescence showed the renal cortex to contain six glomeruli, five of which were globally sclerotic. Occasional intratubular casts were noted, some of which were positive for κ- but negative for λ-light chains. IgG, IgM, IgA, C1q, and albumin were negative. Electron microscopy showed glomerular basement membranes to be of normal thickness. Electron densities were rarely noted within paramesangial and the glomerular basement membrane. Podocytes were acutely injured and revealed focal foot-process effacement involving 20% of the area studied.

**DISCUSSION**

**Renal disease in multiple myeloma**

MM is a hematopoietic malignancy of terminally differentiated plasma cells in the bone marrow. The incidence of 4 per 100 000 accounts for 10% of all hematological malignancies. It occurs most often in the elderly: 68% of patients are above 65 years, 15% are 60–65 years, 15% are 59 years or younger, and fewer than 2% are younger than age 40. This age distribution has profound negative implications, since in these patients aggressive treatment, such as high-dose chemotherapy and peripheral blood stem cells or bone marrow transplantation, may not be well tolerated. In two large biopsy series, the incidence of renal insufficiency in 869 and 141 patients with MM was 55 and 56%, respectively, a complication linked to higher mortality, in part because renal failure further limits some chemotherapeutic options.

Renal failure (RF) has been shown to significantly shorten survival, but if renal function recovers, the effect is reversible. In previous studies, recovery of renal function has been reported in up to 58% of cases, depending on the etiology of the RF. The most frequent renal pathologies are as follows: cast nephropathy occurring in up to 55% of cases, Ig light-chain-associated disease with amyloidosis in 30% of cases, light-chain deposition disease in 19%, and interstitial nephritis in 10% of patients with MM. Other renal pathological manifestations of immunoglobulin diseases include cryoglobulinemic glomerulonephritis, proliferative glomerulonephritis, crystalline nephropathy, and fibrillary/immunotactoid glomerulonephritis (Table 2a). More than one histological pattern can coexist in the same kidney. For this reason, clinical presentation may differ from the expected classical clinical findings (Table 2b), making differential diagnosis of renal disease in MM vast, and diagnosis impossible without renal biopsy.

The clinical entity of acute tubular necrosis is frequently seen either alone or with other renal pathologies. The most common combinations are cast nephropathy with acute tubular necrosis or with monoclonal immunoglobulin deposition disease. In the following series, patients with cast nephropathy had coexisting light-chain deposition disease: Lin et al., n = 34, 11%, Paueksakon et al., n = 20, 12%, and
Lin et al. excessive production of monoclonal MCN refers to acute or chronic renal failure caused by the rather than intra-parenchymal paraprotein deposition. The pathophysiological mechanism involves mainly intra-tubular by plasma cell dyscrasias, MCN differs from others in that the disadvantage over the entire 40 month follow-up.


Buxbaum and co-workers, n = 26, 5%. In the study by Lin et al., patients with cast nephropathy and monoclonal immunoglobulin deposition disease had a significant survival disadvantage over the entire 40 month follow-up.

MCN is the most common cause of RF in patients with MM. Among the many patterns of renal involvement by plasma cell dyscrasias, MCN differs from others in that the pathophysiological mechanism involves mainly intra-tubular rather than intra-parenchymal paraprotein deposition. MCN refers to acute or chronic renal failure caused by the excessive production of monoclonal κ- or λ-light chains. Light chains (22.5–31 kDa) are freely filtered across the glomerulus and then reabsorbed and catabolized by proximal tubular epithelial cells. In myeloma patients, up to 85 g of monoclonal light chains may be synthesized, in comparison with less than 30 mg produced in a healthy person. In the setting of plasma cell dyscrasias, the overproduction of light chains results in excessive amounts of filtered, intraluminal, toxic sFLCs, leading to proximal tubular injury. The accumulation within the proximal tubular cell may interfere with lysosomal function. The quantity of light chains in the tubular filtrate often exceeds the maximum tubular reabsorptive capacity, providing a substrate for binding and aggregation with the Tamm–Horsfall protein (THP), a heavily glycosylated protein synthesized only in the apical cell membrane and secreted in the medullary thick ascending limb of the loop of Henle. The intrinsic affinity of the light chains to THP, as well as the quantity, influences cast formation. The diagnosis of cast nephropathy is based on demonstration of eosinophilic tubular casts in the distal nephron that are composed of either Ig light chains, intact Ig, and/or other proteins, including THP. The casts are surrounded by macrophages and giant cells. These casts are associated with tubular rupture and when this occurs, this results in interstitial nephritis. In vivo and in vitro animal studies in which nephrotoxic light chains were infused into the rat nephron, have demonstrated that a loop diuretic can enhance cast formation. Indirectly, hypercalcemia causing renal vasoconstriction, hyperuricemia, infection, dehydration, as well as exogenous nephrotoxic drugs, such as non steroidal anti-inflammatory agents and iodinated contrast media, are other notable precipitants of RF.

Median survival in patients with myeloma is 36 months, with a 5-year survival of 18–27%. RF is the most common cause of death second only to infection. Patients with Scr level ≤1.4 mg per 100 ml have a median survival of 44 months compared with 18 months if Scr level 1.4–2 mg per 100 ml and <4 months if Scr is >2 mg per 100 ml. Dialysis patients with myeloma have an adjusted relative risk for death of 2.5 times that of other dialysis patients, and a significantly greater 2-year mortality rate (58 versus 31%). Median survival for patients on dialysis with MM and Durie-Salmon stages I–III has been reported to be 18, 6, and 2 months, respectively. Early and aggressive management of renal insufficiency and myeloma is therefore critical.

Management of cast nephropathy

This case presentation illustrates the clinical course of an elderly gentleman diagnosed with MM Durie-Salmon stage III, presenting with acute on chronic renal failure. Years after initial diagnosis, the patient had biopsy-proven MCN, with further deteriorating renal function. Given a median survival of 2 months in similar patients, we now focus on the treatment of this patient who continues to be dialysis-free 5 years after the original diagnosis.

A MM patient’s survival decreases in proportion to the severity and chronicity of RF. The key events in cast nephropathy are twofold- direct toxicity of sFLCs and obstruction occurring when the pathological light chains bind to THP. The most important determinants of the obstructive component to the pathogenesis of cast nephropathy are the quantity of sFLCs, the affinity of sFLCs to THP, and the intravascular volume status (urine volume and flow rate). Accordingly, part of our therapy was aimed at maintaining volume expansion while increasing urine output and decreasing the pathological light-chain concentration and positive charge. Alkalization increases the urine pH above the isoelectric point of cationic sFLCs, making them neutral or anionic, thereby decreasing their affinity toward anionic THP. Alkalization of urine is somewhat controversial, since not all pathological light chains have an alkaline isoelectric point.

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<th>Table 2a</th>
<th>Pathological renal disease associated with dysproteinemia</th>
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<tr>
<td>Myeloma cast nephropathy (MCN)/light-chain cast nephropathy (LCCN)</td>
<td>Amyloidosis (AL)</td>
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<td>Monoclonal immunoglobulin deposition disease (MIDD): Light-chain deposition disease (LCDD), light-heavy-chain deposition disease (LHCD)</td>
<td>Renal plasma cell infiltrates</td>
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<td>Cryoglobulinemic (membranoproliferative) GN</td>
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<td>Proliferative GN with monoclonal immunoglobulin deposits</td>
<td>Crystalline GN</td>
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<td>Immune complex-mediated GN</td>
<td>Immune complex-mediated GN</td>
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<tr>
<td>Fibrillary/immunotactoid GN</td>
<td>Crescentic GN (rare)</td>
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| GN, glomerulonephritis. |

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<th>Table 2b</th>
<th>Clinical renal disease associated with dysproteinemia</th>
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<tr>
<td>Nephrotic syndrome</td>
<td>MIDD, amyloidosis, cryoglobulinemic GN</td>
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<tr>
<td>Proteinuria</td>
<td>Cast nephropathy, cryoglobulinemic GN, immune complex-mediated GN, crystalline GN (variable hematuria)</td>
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<td>Tubular injury</td>
<td>Proximal renal tubular acidosis</td>
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<td>Fanconi’s syndrome</td>
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<td>Diabetes insipidus</td>
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<td>Hyperviscosity</td>
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<td>Rhabdomyolysis</td>
<td>Pyelonephritis</td>
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<td>Acute tubular necrosis (ATN)</td>
<td>Urate nephropathy</td>
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| GN, glomerulonephritis; MIDD, monoclonal immunoglobulin deposition disease. |
and since heart failure can be precipitated in patients with significant cardiac and renal failure. In this case, because cardiac function was not a limitation and Scr was documented to fall with its use, it was likely a useful adjunctive therapy. Since diuretics can lead to increased cast formation by increasing tubular sodium concentration, decreasing intravascular volume and flow rate in the tubules, lengthening toxic light-chain exposure, and favoring light-chain precipitation, they were avoided in this patient. Agents that would lead to decreased GFR and urine flow rate in potentially volume-depleted patients, such as angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, were avoided.

Plasmapheresis has been in use for treating acute myeloma kidney since 1976. The role of plasmapheresis in the management of renal failure in myeloma patients has been explored in three randomized, controlled trials (Table 3). We critically evaluated evidence available from these studies to help guide management in our patient. Zucchelli et al. studied 29 patients with Scr level >5 mg per 100 ml who did not respond to volume expansion. Patients were randomized to receive HD and plasmapheresis or peritoneal dialysis (control group). All received methylprednisolone and cyclophosphamide. At baseline, 13 and 11 patients from the plasmapheresis group and from the control group, respectively, required dialysis. Renal function improved in 11 of 13 plasmapheresed patients, versus only 2 of the 14 patients in the control group. There was also a significant difference in 1-year survival between the two groups, 66% in the plasmapheresis group and 28% in the control group. A drawback to this study is that the control group received peritoneal dialysis, whereas the experimental group received HD. Comparing the two dialysis treatment modalities, five patients in the peritoneal dialysis group died from infection within the first 2 months of the study.

In the second trial, Johnson et al. studied 21 patients, 12 of whom required dialysis at baseline. Eleven patients were randomized to receive plasmapheresis. All patients received melphalan, prednisone, and forced diuresis. No differences in overall renal recovery or survival were noted (control 50% versus plasmapheresis 64%, \( P = \text{NS} \)). Not only was this study severely underpowered and results not statistically significant, but the more severe cases were in the plasmapheresis group. However, in a subgroup analysis of dialysis-dependent patients, renal function recovered only in those receiving plasmapheresis (43% in the plasmapheresis group versus 0% in the control group). These studies led the Scientific Advisors of the International Myeloma Foundation to formally endorse its use.

Finally, the third, and the largest, randomized study involving 97 patients with newly diagnosed myeloma failed to show any benefit. In this study, dialysis at baseline was less common than the previous studies, occurring in only 36% of control and 26% of plasmapheresis-receiving patients. Renal diagnosis was not confirmed in the vast majority of these patients, since biopsies were rarely performed. The results showed 69% of the controls and 58% of the plasmapheresis-receiving patients gave a composite outcome, which included death, dialysis dependence, and estimated GFR <30 ml min\(^{-1}\) 1.73 m\(^{-2}\) at 6 months. Results were not statistically significant. Plasmapheresis appeared to be ineffective in myeloma patients with undifferentiated RF.

Using the results of these three studies, a treatment plan was initiated for our patient. First, because of the high mortality rate of the peritoneal dialysis patients in Zucchelli’s study, HD was used as renal replacement therapy. The decision to start plasmapheresis was more difficult. Because our patient was dialysis dependent, recovery of renal function without plasmapheresis would be less likely, based on Johnson’s study. On the other hand, Clark’s study clearly showed no difference in the composite outcome. We ultimately decided to start plasmapheresis as our patient was more similar to those in Zucchelli and Johnson’s studies whose renal diagnosis had been confirmed. In addition, by using monoclonal protein (IgA and later sFLC) as markers of therapy, our patient was insured more effective therapy and ended up receiving more exchanges than patients in Clark’s study. In the end however, the results of our patient were consistent with those of Clark’s study, since estimated GFR of our patient was only 26 ml min\(^{-1}\) 1.73 m\(^{-2}\).

In summary, we present the case of a man with RF, secondary to MCN, in a patient with relapsed MM who was treated with plasmapheresis. This case illustrates several important points when deciding on the appropriate treatments for these patients. Having a biopsyConfirmed renal diagnosis lent more support for use of plasmapheresis. In addition, goal-directed therapy targeting the monoclonal protein may produce better outcome. The most important question, however, remains as to how we interpret the results. If our patient were enrolled in Clark’s study, he would have been...
labeled a treatment failure, yet he would have been a success in Zucchelli and Johnson’s studies. While having an estimated GFR < 30 ml min⁻¹ 1.73 m⁻² has its disadvantages, it is certainly a superior alternative to dialysis. Our patient has remained dialysis-free. He was therefore able to receive the latest myeloma therapy at the recommended doses, which has extended his lifespan. In this case, by Clark’s criteria, he would be deemed a treatment failure; his outcome was in fact a great victory in terms of quality and years of life.

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