Kidney Injury in Multiple Myeloma: A Kidney Biopsy Teaching Case

Itunu Owoyemi, Sanjeev Sethi, and Nelson Leung

Myeloma-related kidney disease has several manifestations; the 2 most common histologic diagnoses are myeloma cast nephropathy and acute tubular necrosis. We describe a case of different kidney pathologies occurring concomitantly in a patient found to have immunoglobulin Aκ multiple myeloma. A White woman in her 70s presented with an 8-month history of back pain and was found to have nephrotic-range proteinuria and acute kidney injury. Serum calcium level was 12.6 mg/dL. Kidney biopsy showed κ light chain only proliferative glomerulonephritis with monoclonal immunoglobulin deposits, light chain proximal tubulopathy with κ light chain deposits, mild tubular atrophy, and interstitial fibrosis. Free κ light chain ratio was >1,000 mg/dL and free κ light chain level was 4,670 mg/dL. Within a week following treatment of hypercalcemia and initiation of chemotherapy, her acute kidney injury and hypercalcemia resolved. This case highlights the many kidney manifestations of multiple myeloma and that prompt management targeting these manifestations, including hypercalcemia, can improve clinical outcomes.

INTRODUCTION

Multiple myeloma is a hematologic malignancy characterized by abnormal proliferation of plasma cells producing monoclonal immunoglobulins. This leads to the presence of a serum monoclonal spike (M-spike) of >3 g/dL or >10% clonal plasma cells in the bone marrow and at least 1 of the myeloma-defining events commonly known as CRAB (increased calcium level, renal [kidney] injury, anemia, and bone lesion or biomarkers of malignancy such as clonal bone marrow) plasma cell percentage ≥ 60%, involved: uninvolved serum free light chain ratio ≥ 100 and >1 focal lesion on magnetic resonance imaging studies. Up to 40% of individuals with newly diagnosed multiple myeloma have significantly reduced kidney function, with 10% to 15% requiring dialysis and ~1% progressing to end-stage disease.

Several pathologic manifestations of myeloma-related kidney disease have been reported and there is increasing evidence that the different kidney biopsy findings in multiple myeloma can have prognostic implications. We report a unique case of myeloma-related kidney injury in a patient with several manifestations.

CASE REPORT

Clinical History and Initial Laboratory Data

A White woman in her 70s presented with an 8-month history of back pain. She had a medical history of breast cancer approximately 20 years before presentation, which was treated with lumpectomy and tamoxifen. She also had a history of actinic keratosis but otherwise was at her active baseline functional status until her back pain progressively worsened. Her workup was significant for anemia, elevated serum creatinine level of 1.3 mg/dL, and proteinuria with protein excretion of 9 g in a 24-hour urine collection. She was also found to have L4 compression fracture on x-ray imaging of her spine but not definitive for osteolytic lesions. She underwent kidney biopsy and was subsequently referred to Mayo Clinic for further evaluation of her biopsy findings.

On presentation, blood pressure was 111/41 mm Hg. The patient appeared fatigued, with pedal edema (1+). She was found to have moderate hypercalcemia with a corrected calcium level of 12.6 mg/dL, prompting hospital admission. Details of her workup are outlined in Table 1. She underwent a skeletal computed tomographic survey that showed generalized osteopenia and innumerable osteolytic lesions throughout the visualized skeleton, compatible with multiple myeloma. She had a free light chain ratio > 1,000 and free κ light chain level was 4,670 mg/dL. All immunoglobulins were suppressed except for immunoglobulin Aκ (IgA), which was reported as 1,140 mg/dL. A bone marrow biopsy was done and showed 95% monotypic κ light chain–restricted light chains. Congo red staining on bone marrow biopsy and fat aspirate was negative for amyloid deposition.

Kidney Biopsy

Kidney biopsy slides were retrieved from the outside hospital and reported to show proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMD) with κ light chain deposition in mesangial and capillary walls, crystalglobulinemia, light chain proximal tubulopathy with κ light chain deposits, mild tubular atrophy, and interstitial fibrosis.

Diagnosis

Based on the patient’s clinical presentation and laboratory workup, a diagnosis of IgAκ multiple myeloma was made.

Clinical Follow-up

After hydration and treatment for hypercalcemia, the patient underwent 6 sessions of plasmapheresis, and
cyclophosphamide, bortezomib, and dexamethasone (CyBorD) chemotherapy. She was also started on intravenous zoledronic acid for the osteolytic bone disease, with improvement in kidney function. Within a week of initiating treatment, her serum creatinine level had decreased to 1.08 mg/dL from 1.8 mg/dL, and corrected calcium level was down to 9.1 mg/dL. At her last follow-up, kidney function had returned to baseline with a serum creatinine level of 0.85 mg/dL and calcium level remained within normal limits, as depicted in Table 1.

The patient completed 6 cycles of CyBorD and sustained a very good partial hematologic response.

**DISCUSSION**

This case report highlights the importance of early diagnosis and prompt treatment of plasma cell disorders. Our patient had presented with back pain, and work-up of proteinuria on urinalysis led to the kidney biopsy findings. Her initial skeletal survey did not show the osteolytic lesions. This is not uncommon because computed tomographic skeletal survey has been shown to be more sensitive with detection of osteolytic lesions.6

Although cast nephropathy has been reported as the most common finding in multiple myeloma, this case showed several other pathologies that have been reported with different prognostic implication, as outlined in Table 2. Figure 1A showed light chain only PGNMID, which is associated with a high detection rate of pathogenic clonal disorder and response of antimalyeloma agents; recurrent disease is extremely common in patients with PGNMID who undergo kidney transplantation for end-stage kidney disease.4

The patient’s kidney biopsy also revealed crystalglobulinemia, as shown in Fig 1B, which results from extracellular deposition of large monoclonal immunoglobulin

| Pathology | Description |
|-----------|-------------|
| PGNMID | Light chain only PGNMID seen in this case is rare. Case series suggests characterization by a high detection rate of pathogenic clonal disorder and response to antimalyeloma agents. Recurrence post–kidney transplantation is extremely common.4 |
| LCPT | Cytoplasmic inclusion of monoclonal light chain within proximal tubular cells, which can be crystalline or noncrystalline. Crystalline is associated with severe tubular injury and Fanconi syndrome. Noncrystalline LCPT, as seen in this case, is rare, with less likelihood of tubular injury suggested possibly due to physiologic trafficking of light chains.5 |
| Crystalglobulinemia | This results from extracellular deposition of large monoclonal immunoglobulin crystals within systemic vascular lumens, including renal arteries and glomerular capillaries. They can occlude vascular lamina, mimicking thrombotic microangiopathy, or incite arterial wall inflammation, producing vasculitis.7 |
| Other myeloma-related kidney diseases (not present in this case) | Common: myeloma cast nephropathy, acute tubular necrosis, AL amyloidosis, monoclonal immunoglobulin deposition disease Less common: cryoglobulinemic glomerulonephritis, immunotactoid glomerulonephritis, fibrillary glomerulosclerosis Rare: plasma cell infiltration, extramedullary hematopoiesis, membranous nephropathy, C3 nephropathy, IgA nephropathy, anti–glomerular basement membrane disease |

Note: Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: CyBorD, cyclophosphamide, bortezomib, dexamethasone; IgA, immunoglobulin A.

| Table 1. Laboratory Values Before and After Treatment of Multiple Myeloma |
|-----------------|-----------------|-----------------|
|                  | At Presentation | After 6 Cycles of CyBorD | Reference Range |
| Hemoglobin, g/dL | 9.3             | 12.7             | 11.6-15.0       |
| Calcium (corrected), mg/dL | 12.6             | 9.2             | 8.8-10.2       |
| Creatinine, mg/dL | 1.8             | 0.85             | 0.5-1.1        |
| Lactate dehydrogenase, U/L | 172             | 122-222         |                |
| Albumin, g/dL | 2.6             | 4.2             | 3.5-5.0        |
| M Spike (IgA κ) |                  |                  |                |
| α1-Globulin     | 0.3             | 0.3             |                |
| α2-Globulin     | 1.3             | 0.8             |                |
| IgG, mg/dL      | 169             | 213‡            | 767-1590       |
| IgA, mg/dL      | 1140            | 9‡              | 61-356         |
| IgM, mg/dL      | 8               | 8‡              | 37-286         |
| Free light chains |                |                  |                |
| κ, mg/dL        | 4670            | 0.63            | 0.3300-1.94    |
| λ, mg/dL        | 0.748           | 0.17            | 0.5700-2.63    |
| Free light chain ratio | >1,000 | 3.71 | 0.2600-1.65 |
| Urine 24-h protein, mg/24 h | 9,410 | 143 | <229 |

Note: Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; creatinine in mg/dL to μmol/L, ×88.4.

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| Table 2. Patterns of Myeloma Related Injury and Description |
|-----------------|-------------|
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crystals within systemic vascular lumens, including renal arteries and glomerular capillaries. The monoclonal immunoglobulin crystals can occlude the vascular lumen, mimicking a thrombus, or incite arterial wall inflammation, producing vasculitis.\(^7,8\) Light chain proximal tubulopathy was identified in the same biopsy as depicted in Fig 1C, showing proximal tubules with noncrystalline trichrome weakly red intracellular protein reabsorption granules. Light chain proximal tubulopathy can occur as a result of cytoplasmic inclusions of monoclonal light chain within proximal tubular cells that can be crystalline or noncrystalline. Crystalline depositions are more likely to have severe tubular injury and be associated with Fanconi syndrome, whereas noncrystalline form, as seen in this case, has been associated with physiologic trafficking of light chains.\(^5\)

Important factors in the cause of acute kidney injury in this case were hypercalcemia and hemodynamic-mediated acute kidney injury in the setting of hypoalbuminemia and volume depletion. Hypercalcemia in multiple myeloma can occur as a result of dysregulated bone turnover, leading to the secretion of osteoclast-activating and osteoblast-inhibiting factors.\(^7\) Hypercalcemia can lead to vasoconstriction of the renal blood vessels, which in turn reduces blood flow in the kidney. It can also cause activation of the calcium-sensing receptor in the thick ascending limb of Henle, inhibiting the sodium-potassium co-transporter, thereby exacerbating natriuresis and volume depletion.\(^9\)

Management of hypercalcemia in multiple myeloma is outlined in Table 3.\(^11\) Our patient was treated with intravenous zoledronic acid as her kidney function improved. Bisphosphonates play an important role in supportive care for patients with myeloma with osteoporosis and lytic bone lesions.\(^12\) Although higher doses of pamidronate have rarely been associated with collapsing focal segmental glomerulosclerosis,\(^13\) a lower dose of 60 mg initiated if glomerular filtration rate is <30 mL/min per body surface area will treat the hypercalcemia by inhibiting bone resorption and is less associated with kidney injury. Steroids are used in the treatment of hypercalcemia because they have direct tumorlytic effects and also cause a reduction in tumor production of locally active cytokines, resulting in inhibition of osteoclast resorption.\(^14\)

**Table 3. Management of Multiple Myeloma–Induced Hypercalcemia**

| Stage of Hypercalcemia | Treatment |
|------------------------|-----------|
| Mild hypercalcemia (serum calcium < 12 mg/dL) | Isotonic Fluids + Dexamethasone |
| Moderate to severe hypercalcemia (serum calcium ≥ 12 to 14 mg/dL) | Isotonic fluids + corticosteroids + bisphosphonates* |
| Extremely severe hypercalcemia (eg, serum calcium > 18 mg/dL) | Hemodialysis + measures outlined above |

Data from Rajkumar et al.\(^11\)

*Avoid intravenous zoledronic acid if creatinine clearance < 30 mL/min.
Myeloma-related kidney disease has been shown to be a poor prognostic factor. However, recovery of kidney injury and hematologic response are the strongest markers associated with patient survival. Hematologic response is also the strongest factor associated with major kidney response.15

In summary, we report a case of multiple myeloma–related kidney disease with multiple manifestations on kidney biopsy. Poor prognosis can be reversible with restoration of kidney function, highlighting the need for prompt identification and treatment of acute kidney injury in patients with multiple myeloma.16,17

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