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Case Report

When Acute Kidney Injury in the Intensive Care Unit isn't Acute Tubular Necrosis: A Case Report of Kappa Light Chain Crystalline Tubulopathy

Neal Shah[1*], Ivy Rosales[2], Rex Neal Smith[2], Jacob E. Berchuck[3], Andrew J. Yee[3], Nina Tolkoff-Rubin[1]

[1]Division of Nephrology, Massachusetts General Hospital, Boston, MA, USA

[2]Division of Pathology, Massachusetts General Hospital, Boston, MA, USA

[3]Division of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, USA

[*]**Corresponding author:** Neal Shah, Division of Nephrology, Massachusetts General Hospital, Boston, MA, USA. Email: nbshah@bwh.harvard.edu

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Abstract

Introduction: This case highlights the importance of thorough workup for acute kidney injury before assigning a diagnosis.

Case Presentation: A 68-year-old male was referred to our clinic after a recent outside hospitalization for septic knee arthritis and acute kidney injury requiring hemodialysis. He had chronic kidney disease presumed secondary to diabetes with baseline GFR 50 ml/min. He complained of fatigue and weight loss. Vital signs were normal. Exam was notable for trace ankle edema, healed right knee scar and hemodialysis catheter. Medications included amlodipine, aspirin, atorvastatin, furosemide, sevelamer and cephalexin. Creatinine clearance was 6 ml/min with urine output 2 liters/day. Urinalysis showed 1+ protein, 2+ glucose and fine granular casts. Clinical impression was ischemic acute tubular necrosis in recovery phase. However, when he didn't improve and continued requiring dialysis, further workup showed elevated serum kappa free light chains and urine Bence Jones protein. Renal biopsy showed kappa light chain crystalline tubulopathy, interstitial inflammation and extensive fibrosis. Subsequent bone marrow biopsy showed 15% kappa-restricted plasma cells. Multiple myeloma was diagnosed, and chemotherapy initiated.

Conclusion: This case describes a rare presentation of kappa light chain crystalline tubulopathy and illustrates the value of a comprehensive evaluation for acute kidney injury to enable prompt diagnosis and therapy.

Keywords: Acute Kidney Injury; Crystalline Tubulopathy; Kappa Light Chain; Multiple Myeloma

Introduction

Acute Kidney Injury (AKI) from increased production of Free Light Chains (FLC) is an important cause of morbidity and mortality in patients with multiple myeloma where early detection and treatment can significantly improve prognosis [1]. Various paraprotein and non-paraprotein related renal pathologic forms have been described both affecting the glomerulus and tubulointerstitium, cast nephropathy being the commonest [2,3]. Tubular injury from paraproteins depends on the quantity and structure of the free light chain and is rarely caused by crystallization of paraprotein resulting in proximal tubulopathy, crystal-storing histiocytosis and crystalglobulinemia [4-6]. This report describes a case of multiple myeloma causing kappa light chain crystalline tubulopathy and cast nephropathy masked under presumed diagnosis of diabetic Chronic Kidney Disease (CKD) followed by AKI attributed to sepsis induced ischemic Acute Tubular Necrosis (ATN) resulting in delayed diagnosis and treatment.

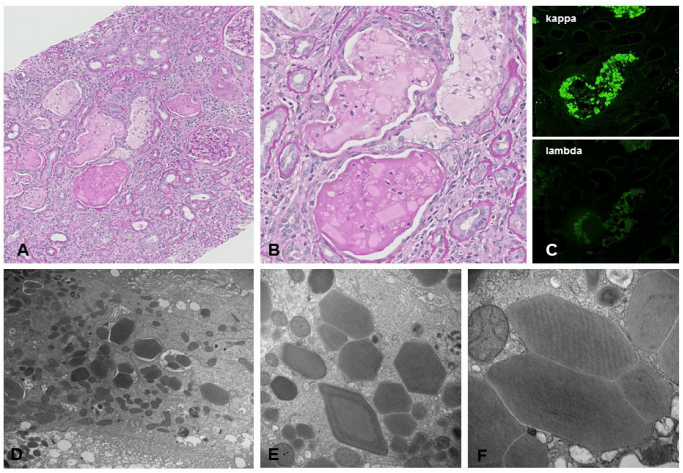
Clinical History

A 68-year-old Caucasian male was referred urgently to renal clinic after recent admission to an outside hospital where he developed AKI requiring dialysis. Patient had returned home with a plan to continue hemodialysis. Past medical history was significant for obesity, type 2 diabetes mellitus and chronic kidney disease attributed to diabetes with baseline GFR 50ml/min and

serum creatinine 1.4mg/dL 3 months ago. Past surgical history was remarkable for right knee arthroplasty done two years ago. He presented to an outside hospital with knee pain and fever and was diagnosed with right knee septic arthritis. A prolonged hospital course was significant for MSSA bacteremia and septic shock resulting in AKI requiring hemodialysis. He was treated with surgical irrigation and drainage of his knee and antibiotics, and discharged to rehabilitation for few weeks prior to returning home. A 6-week cephalexin course was recommended. During his clinic appointment, patient complained of fatigue, decrease appetite and recent weight loss of 60 pounds over past 2 months. Physical exam was notable for mild bilateral leg edema, right knee surgical scar and right internal jugular tunneled hemodialysis catheter. Vital signs were within normal limits. Last dialysis session was 2 days prior. Initial chemistry showed serum potassium level of 4.7mmol/L, BUN 49mg/dL and creatinine 8.9mg/dL. Urinalysis was significant for 2+ glucose and 1+ protein with some fine granular casts on sediment. Right knee X-ray showed no evidence of residual infection. A 12-hour urine specimen contained 950ml of urine and was interpreted as post-ATN diuretic phase of recovery. Calculated creatinine clearance was 6ml/min. Medications included amlodipine, aspirin, atorvastatin, furosemide, sevelamer and cephalexin. Anticipating recovery from ATN over next few weeks, the plan was to monitor his renal function closely at his dialysis center. At his follow up visit, his urine output remained excellent with close to 2 liters daily, but pre-dialysis creatinine levels remained high around 8mg/dL. On further work-up, patient was found to have a microalbumin/creatinine ratio of 104mg/g and protein/creatinine ratio 2110mg/g. Serum kappa free light chains were 3326mg/L, kappa lambda ratio was elevated at 113.54 with positive urine kappa Bence Jones protein by immunofixation.

Kidney Biopsy

A kidney biopsy showed diffuse interstitial fibrosis and tubular atrophy and a marked and extensive interstitial infiltrate (Figure 1A) comprised of lymphocytes, plasma cells and neutrophils. There was diffuse tubular injury with tubular ectasia, casts with admixed crystalline structures (Figure 1B), pale vacuolated cytoplasm in other proximal tubules and focal attenuated epithelium. There was severe arteriosclerosis and arteriolosclerosis. The glomeruli showed mild mesangial matrix expansion with no evident mesangial or endocapillary hypercellularity. The glomerular capillary walls did not show duplication. Global glomerulosclerosis was mild (7%). Immunofluorescence microscopy showed mild to moderate granular staining for IgA (1-3+) in the mesangium, with no significant staining for IgG, IgM, C3, kappa or lambda. The casts and crystalline structures showed widespread and intense staining for kappa and were negative for lambda (Figure 1C). Electron microscopy showed crystals within tubular epithelial cells (Figure 1D) occurring as polygonal structures (Figure 1E), some with striations (Figure 1F). Rare mesangial, intramembranous and subendothelial electron dense deposits were present, possibly related to IgA. The glomerular basement membranes showed a mean thickness of 862 nm. These findings were consistent with kappa light chain crystalline tubulopathy, against a background of marked and active interstitial nephritis and tubulointerstitial scarring. The tubulointerstitial disease was likely from severe tubular injury from both crystal formation and light chain injury and deposition. A drug-associated interstitial nephritis was also in the differential diagnosis. The IgA deposition in this case could be from an idiopathic IgA nephropathy or a *Staphylococcus*-associated IgA glomerulonephritis. The thickened glomerular basement membranes supported a diagnosis of early diabetic glomerulopathy.



Figures 1(A-F): (A): The kidney biopsy showed diffuse interstitial inflammation and tubular injury with casts against a background of interstitial fibrosis. **(B):** Dilated tubules showed casts and crystals within the lumen. **(C):** Casts and crystals showed staining for kappa light chain and were negative for lambda light chain by immunofluorescence microscopy. Electron microscopy showed crystals within tubular epithelial cells **(D)** of varying polygonal shapes **(E)** and occasional striations **(F).**

Clinical Follow Up

Due to possibility of cefalexin-induced interstitial nephritis, he was switched to doxycycline. He was referred to oncology and underwent a bone marrow biopsy which showed 15% kappa-restricted plasma cells consistent with multiple myeloma. Skeletal survey showed no lytic lesions. Serum calcium levels were within normal limits and hemoglobin ranged between 11-12g/dL. FISH and cytogenetics were not performed due to an inadequate number of plasma cells in the sample. He was initiated on chemotherapy with lenalidomide, bortezomib and dexamethasone. Lenalidomide dose was adjusted for renal dysfunction. After 3 cycles, serum free kappa light chain level decreased to 711mg/L, kappa/lambda ratio 48 and

spot urine protein/creatinine ratio 410mg/g. His pre-dialysis serum creatinine levels improved to 4-5mg/dL and creatinine clearance improved to 15ml/min. Urine output remained approximately 2 liters daily. His dialysis schedule was reduced gradually to twice weekly 3.5- hour sessions each without any fluid removal. Patient subjectively started feeling well, improved appetite and gained his weight back. Unfortunately, he required admission for vancomycin resistant enterococcal bacteremia suspected from his dialysis catheter which was removed. His creatinine clearance stabilized at 18-20ml/min, and he came off dialysis.

Discussion

Unlike intact immunoglobulins, Free Light Chains (FLC) are low molecular weight proteins freely filtered at the glomerulus and subsequently catabolized by proximal tubules via clathrin dependent endocytosis by megalin/ cubilin receptor system with minimal excretion in urine [7]. In patients with multiple myeloma (excess FLC production) and renal dysfunction (reduced FLC excretion), risk of light chain deposition increases, and the type of tubular injury depends on physiochemical properties of FLCs [8]. Common renal tubular injuries described are cast nephropathy, Fanconi syndrome, proximal tubulopathy and interstitial fibrosis. Several cases of proximal tubulopathy from light chains have been reported but only few have shown propensity for crystalline formation [5,9,10]. Earlier studies have shown that monoclonal light chains coprecipitate with Tamm-Horsfall (TH) glycoprotein in the distal tubules which in turn binds to the Complementarity Determining Region (CDR) domain of FLC [11,12]. Decourt et al. analyzed the light chain structure and properties of one patient with Fanconi syndrome associated with myeloma casts and crystalline proximal tubule inclusions [13]. The light chain is composed of a Vk1 subgroup, which is found in high frequency in cases of Fanconi syndrome. This Vk1 subgroup is derived from a 08/018 germline gene that is normally rearranged for the Jk4 segment. It also bears peculiar features including residue substitutions in the CDR1 and an unusual conformation of the k1 domain. These features were postulated to alter catabolism of the protein after internalization in tubules resulting in dysfunction. Larsen et al. studied 13 cases of light chain proximal tubulopathy of which 3 had crystals and found that protease-resistant variable domain tended to have a lower affinity for Tamm Horsfall protein resulting in spontaneously crystal formation [14]. Stokes et al. reported 40 cases of crystal light chain, all kappa restricted which is the commonest type [15]. Very few are lambda-restricted [16].

Clinically, our patient was diagnosed with kappa light chain myeloma based on bone marrow involvement, markedly elevated serum free kappa light chain, and renal dysfunction. Glucosuria in urine could have been from Fanconi syndrome, however patient also had diabetes. While 10-20% of patients with myeloma associated renal failure end up needing dialysis, this prognosis worsens to >80% in those presenting at an advanced stage with cast nephropathy [17,18]. Early diagnosis is therefore imperative to improve outcomes by initiating early chemotherapy. The decision to treat is motivated by the multiple myeloma diagnosis as well as the use of plasma cell-directed therapy in monoclonal gammopathy of renal significance [19]. Median survival time in general has been shown to be better in crystalline proximal tubulopathy as compared to non-crystalline tubulopathy [15]. Chemotherapy regimen of choice for multiple myeloma is determined by patient's risk classification and clinical status [20]. While no specific literature has tested the regimen of choice for crystalline tubulopathy forms due to its rare occurrence, our patient received therapy with a standard induction regimen of lenalidomide, bortezomib and dexamethasone and responded well to it with decrease in light chain burden, improvement in renal function and being able to come off dialysis. We believe that an early diagnosis and treatment opportunity was missed due to presumptive diagnosis of diabetic CKD and ischemic ATN due to sepsis respectively.

Conclusion

In conclusion, we report a rare case of kappa light chain multiple myeloma associated crystalline tubulopathy with interstitial inflammation and fibrosis. Our case also demonstrates the importance of maintaining high vigilance for early diagnosis and treatment in such cases which can significantly improve prognosis.

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