Light Chain Glomerulopathy Causing Kidney Failure in Renal Cell Carcinoma

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Abstract
Light chain deposition disease (LCDD) is a rare cause of kidney failure. It is associated with multiple myeloma and is diagnosed by the evaluation of serum and urine free light chains. Patients who are diagnosed with this disease often develop rapidly progressive renal failure. To our knowledge, it does not have any association with other malignancies aside from multiple myeloma. We present a case that highlights a novel association between renal cell carcinoma and light chain-mediated renal disease. Our patient was admitted due to acute renal failure and underwent a comprehensive diagnostic evaluation with an eventual diagnosis of light chain glomerulopathy in the setting of metastatic renal cell carcinoma.

Categories: Internal Medicine, Oncology, Hematology
Keywords: multiple myeloma, light cast chain nephropathy, light chain deposition disease, renal cell carcinoma, systemic capillary leak syndrome

Introduction
Multiple myeloma is a plasma cell cancer that can lead to kidney disease. It has been traditionally characterized by unexplained anemia, renal dysfunction, bone pain, elevated total serum protein, and hypercalcemia. The disease process generally involves a specific class of immunoglobulins, most commonly immunoglobulin G (IgG). However, it can affect any immunoglobin, including classes A, M, D, and E. These immunoglobulins all have heavy chain and/or light chain components that are often involved in the pathologic process [1,2]. Light chain renal disease, mediated through kappa and lambda, is considered significantly more common than heavy chain disease. It can lead to proteinuria and rapidly progressive renal failure. It can also occur with or without multiple myeloma [3].

Once clinical suspicion is established, diagnostic evaluation often begins with serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum immunofixation electrophoresis (SIFE), and urine immunofixation electrophoresis (UIFE) testing. These identify the presence and type of monoclonal protein as well as quantify it. Light chain analysis with measurements of kappa and lambda is also a key part of the diagnostic process for light chain glomerulopathy and/or multiple myeloma. An elevated ratio of kappa/lambda (>3.0) or a low ratio of <0.26 is supportive of the diagnosis of light chain-mediated renal disease and potentially multiple myeloma [4]. Additional serum testing that is often done is beta-2 microglobulin as it is a prognostic marker, with levels >4.0 being associated with a worse prognosis [5]. In addition to serum and urine testing, a bone marrow biopsy is required to make a comprehensive diagnosis of multiple myeloma. The span of testing includes cytogentic testing, flow cytometry, and immunohistochemistry testing. When cytogentic testing is performed, it involves the fluorescence in situ hybridization (FISH) test [6].

Renal disease often develops in patients who have multiple myeloma or light chain glomerulopathy, and it may occur during any stage of the disease. Due to the pathologic process, free light chains and immunoglobulins are produced in high levels. This can result in excretion through the kidneys and subsequent nephrotoxicity. Glomerular filtration areas can also be decreased in light chain deposition disease (LCDD). A characteristic finding in these patients is the presence of proteinuria. Other considerations in the differential diagnosis would be amyloid light-chain amyloidosis and heavy chain disease.

LCDD frequently involves rapidly progressive renal insufficiency and failure. It may also affect other organs such as the liver and heart. In addition, it may progress to multiple myeloma if it is not already present. Treatment is similar to multiple myeloma management and includes a regimen of chemotherapy, immunosuppressive therapy, and corticosteroids. Depending on the preexisting risk factors, many patients can progress to end-stage renal disease [7].

Case Presentation
The patient was a 59-year-old male who was being treated for grade 4 clear cell renal carcinoma with
metastatic disease to the perinephric fat, Gerota’s fascia, hilar lymph nodes, lungs, and liver. He was status post-palliative right nephrectomy and had completed four cycles of nivolumab/ipilimumab with notable disease progression. Subsequently, he had been enrolled in a clinical trial of selenomethionine/axitinib and was partaking in the trial at the time of his presentation. There had been multiple pauses of his trial due to adverse symptomatic reactions to the chemotherapy. His previous medical history was also significant for obstructive sleep apnea, coronary artery disease, controlled type 2 diabetes mellitus, essential hypertension, hyperlipidemia, obesity, and chronic kidney disease stage 2.

He presented initially to the emergency department with complaints of poor oral intake, nausea, vomiting, bilateral lower extremity swelling, intermittent chest pain, and back pain. In addition to the increased swelling in his legs, he also noted a 10-kilogram weight gain in the past three months. He further reported that he had been having diarrhea for one week leading up to his admission. On initial presentation to the emergency department, he was found to be hyponatremic (130 mEq/L), hyperkalemic (5.7 mEq/L), with a corresponding high anion gap metabolic acidosis (HCO$_3$: 17 mEq/L, anion gap: 17 mEq/L). The patient received insulin with dextrose, and 1-liter normal saline (NS) and was subsequently admitted to the oncology ward. On admission, his vitals were stable and notably, his blood pressure was 120/86 mmHg. Additionally, his chemotherapy was held. CT studies showed moderate-to-large volume ascites along with increased carcinomatosis compared to previous scans. It also showed a pulmonary embolism (Figure 1), which prompted the initiation of therapeutic anticoagulation with heparin.
On day two of admission, his serum potassium level increased to 6.3 mEq/L and he was treated with insulin, dextrose, furosemide, and an NS bolus, with potassium reduction to 4.0 mEq/L. Notably, a late-morning cortisol was obtained and was found to be 21.9 µg/dL and adrenocorticotropic hormone (ACTH) levels were 45 pg/mL. Later that day, he developed asymptomatic hypotension (systolic pressures between 60-70 mmHg, diastolic pressures between 50-60 mmHg) but spontaneously somewhat recovered (systolic pressures between 90-100 mmHg, diastolic pressures between 50-60 mmHg). The patient was subsequently started on midodrine at doses of 10 mg three times per day. He additionally received a total of 4 liters of NS as well as intravenous albumin with no change in his blood pressure.

Given the persisting combination of hypotension, hyponatremia, and hyperkalemia, a trans-tubular potassium gradient (TTKG) was calculated, which was noted to be 4.0. Due to the low TTKG, plasma...
aldosterone and renin levels were obtained. Aldosterone levels returned at 4.8 ng/dL and plasma renin levels were significantly elevated at 180 ng/dL/h. Notably, the patient had been taking an angiotensin-converting enzyme (ACE) inhibitor medication up until the day of admission. On day three of admission, his creatinine trended up to 2.6 from 1.7 mg/dL. Given his recurrent hypotension and ongoing evidence of acute kidney injury, he was transferred to the medical intensive care unit (ICU) for escalating care and closer monitoring.

On transfer to the ICU, his potassium was 5.9 mEq/L and his creatinine further increased to 3.3 mg/dL. Point-of-care ultrasound (POCUS) demonstrated small and collapsible inferior vena cava (IVC), suggesting a significant degree of volume depletion. In addition, the patient had persistent low urine output (<150 cc per 24 hours). Given his presentation, hypoaldosteronism was considered, and he was started on hydrocortisone at 50 mg every six hours and subsequently on fludrocortisone at 0.1 mg daily. Unfortunately, the patient’s hypotension and urine output did not significantly improve on these regimens.

Due to ongoing ascites, a paracentesis was performed with 1 liter of fluid being removed. The fluid showed a lactate dehydrogenase (LDH) level of 1446, as well as a fluid/serum LDH ratio of 5.3 and a fluid/serum protein ratio of 0.6, all suggestive of a malignant effusion later confirmed by cytology. His potassium and creatinine continued to trend upwards on day four of admission (6.6 mg/dL and 3.4 mg/dL respectively) although his EKG remained unremarkable. He was started on Kayexalate and also received another 1-liter bolus of NS along with early morning cortisol was 15 µg/dL. On day seven of admission, he received 100 grams of albumin as his hypotension did not resolve with NS resuscitation. Notably, his urine output had remained low throughout his admission course despite volume repletion efforts with crystalloids and colloids. Corticotropin testing was initiated and resulted in an increase in cortisol by 8 µg/dL, suggesting an etiology other than adrenal insufficiency. Furthermore, the patient’s urine sodium (17 mEq/L) and urine potassium (47.9 mEq/L) were not suggestive of hypoaldosteronism. The patient remained borderline hypotensive, but given his overall stability and lack of symptoms, he was transferred back to the medical ward.

The patient’s renal function continued to worsen in the setting of worsening lower extremity edema and low urine output. A urine protein:creatinine ratio had been obtained earlier in the admission and found to be 0.42 mg/dL (urine protein: 123 mg/dL; urine creatinine: 292.7 mg/dL). Prior to transfer to the ward, an SPEP and SIFE were obtained to evaluate his ongoing kidney disease; this demonstrated an elevated IgA lambda monoclonal peak suggestive of multiple myeloma. UPEP and UIFE showed a monoclonal IgA heavy chain with an associated lambda light chain and the presence of Bence Jones protein. Serum and urine kappa lambda light chains were subsequently performed. Kappa free light chains were elevated at 32.10 mg/L (3.30-19.40 mg/L) with lambda free light chains at 361.50 mg/L (5.70-26.30 mg/L), a ratio of 0.09 (0.26-1.65). Urine kappa was elevated at 161.59 mg/L (0.00-32.90) and lambda was elevated at 740.51 mg/L (0.00-32.90). After an extensive goals-of-care discussion, the patient opted to undergo a bone marrow biopsy. Initial attempts at the bedside procedure failed due to the body habitus and extensive edema. A repeat attempt was made with CT guidance and was successful. The results demonstrated 5-7% plasma cells with CD138 immunohistochemistry; concurrent flow cytometry revealed a 0.03% population of lambda-monotypic plasma cells suggestive of a plasma cell neoplasm. The FISH study showed monosomy 13 at 26%, with the normal range being <4%. Fibroblast growth factor receptor 3 (FGFR3)/immunoglobulin heavy locus (IgH) dual fusion of 34% was also noted, with the normal range being <1% (Table 1).
| Probe | Normal range | Result (% abnormal nuclei) |
|-------|--------------|---------------------------|
| CKS1B/p18 [1q21/1p32] | Gain of CKS1B: <1.5%, loss of p18: <5.6% | Normal |
| TAS2R1/CEP9/CEP15 [5p15.31/9cen/15cen] | Gain of 5: <1%, gain of 9: <1.2%, gain of 15: <1% | Normal |
| D13S319/13q34 [13q14.3/13q34] | 13q deletion: <4.4%, monosomy 13: <4% | Monosomy 13 (26%) |
| IgH [14q32.3] | IgH rearrangement: <1% | Breakapart rearrangement (26%) |
| p53/CEP10 [17p13.1/10cen] | Loss of p53: <3.7% | Normal |
| FGFR3/IgH [4p16.3/14q32.3] | Dual fusion: <1% | Dual fusion (34%) |
| CCND1 XT/IgH [11q13/14q32.3] | Dual fusion: <1% | No fusion |
| IgH/MAF [14q32.3/16q23] | Dual fusion: <1% | No fusion, a copy loss of MAF (24%) |

**TABLE 1: Fluorescence in situ hybridization (FISH) studies**

FISH studies were performed on CD138-positive enriched plasma cells using the multi-probe panel set listed in the table above.

It was also noted that the patient had gained approximately 20 kilograms in weight during the admission, likely due to third spacing from the fluid resuscitation. He was unresponsive to intravenous furosemide boluses and oral metolazone. He then had a tunneled dialysis catheter placed to undergo dialysis due to extensive hypervolemia refractory to diuresis. His creatinine continued to increase to 7 mg/dL by day 18 of admission and he had reoccurring asymptomatic hypotension. After further discussion, he opted to be discharged to hospice care at home on day 19 of admission.

**Discussion**

This case highlighted an unusual presentation of light chain glomerulopathy, particularly in the setting of an unrelated preexisting malignancy. In the context of metastatic renal cancer, worsened renal function can be expected during the latter stages of a patient’s illness due to various potential etiologies. In our patient, the initial admitting presentation was consistent with presumable prerenal acute kidney injury due to hypovolemia as a result of gastrointestinal losses. The hypotension and electrolyte abnormalities were also explainable with his presentation. However, despite adequate volume resuscitation, the patient’s condition continued to worsen and he required ICU admission. The combination of his symptoms, physical examination findings, low albumin levels, and electrolyte abnormalities led to the consideration of systemic capillary leak syndrome as a potential diagnosis. However, the patient’s hematocrit had dropped whereas capillary leak syndrome generally involves hemoconcentration. Hypoaldosteronism was also considered as a potential diagnosis, which would explain the hypotension and lab abnormalities. The patient’s elevated aldosterone level and lower renin levels as well as the low TTKG were relatively consistent with hypoaldosteronism. However, subsequent evaluation of the urine electrolytes and the patient’s history of taking an ACE inhibitor prior to presentation did not align with hypoaldosteronism.

The worsening renal function prompted an SPEP, UPEP, and SIFE. Given the abnormalities, a kappa and lambda light chain test was obtained. The positive results were suggestive of IgA myeloma with potential LCDD or light chain glomerulopathy. However, the bone marrow biopsy was not fully consistent with a diagnosis of multiple myeloma given the percentage of plasma cells. Given the highly elevated serum and urine lambda light chains, the diagnosis was consistent with light chain glomerulopathy or LCDD in the glomerulus.

This patient’s renal failure diagnostic evaluation was difficult due to the overlap in his clinical and laboratory findings. Once a diagnosis had been made, a renal biopsy was required to confirm it. However, given the patient’s worsened clinical status and evolving goals of care, the biopsy was deferred. In addition, further direct treatment was also not initiated as it was also not consistent with the patient’s goals of care.

**Conclusions**

LCDD and/or multiple myeloma should be considered in the differential diagnosis of patients who present with worsening renal disease, even in the setting of other known malignancies. The presentation of multiple myeloma or light chain glomerulopathy can sometimes be ambiguous and nonspecific. Physicians may defer diagnostic evaluation in the absence of other pertinent findings, such as high serum total protein, nephrotic range proteinuria, or hypercalcemia. Nonetheless, multiple myeloma and/or light chain...
glomerulopathy diagnostic testing is generally performed for nonspecific kidney disease. This case highlights the fact that it should not be ignored as a potential etiology of renal disease even in those with a preexisting unrelated malignancy. It also illustrates the first case in the literature that reveals an association between renal cell carcinoma and light chain glomerulopathy.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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