Monoclonal Light Chain Nephropathy: A Potential Diagnostic Delay

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ABSTRACT

Multiple myeloma (MM) is estimated to be diagnosed in over 20,000 people in the United States in 2014, representing only 1% of all malignancies and 10% of all blood cancers.¹ The estimated death rate, however, is 45%; in comparison, breast cancer is expected to be diagnosed in 235,000 and the death rate is 17%.² MM is characterized by a clonal proliferation of plasma cells that in most cases produces a monoclonal immunoglobulin. One difficulty in diagnosing patients with MM is that the clinical presentation can be highly variable depending on the involved organ leading to broad differential diagnoses and potential diagnostic delays. The diagnosis of MM may be suspected because of one or more of the following clinical findings that is not explained by another unrelated disease or disorder: hypercalcemia, renal failure, anemia, and bone lesions (commonly referred to by the acronym "CRAB").³ The most common symptoms reported are those related to lytic bone lesions such as unexplained backache. Renal disease associated with MM most often results from the deposition of monoclonal light chains in the kidney and can cause renal dysfunction in numerous ways.⁴ The most common histologic entities occurring in order of greatest frequency include light chain cast nephropathy (40%), light chain amyloidosis (30%), and light chain deposition disease (19%).⁴,⁵ Furthermore, diagnosis can be complicated in older patients with comorbidities such as hypertension, heart failure, or type 2 diabetes. We herein describe a 59-year-old Hispanic man presenting with nephrotic range proteinuria who was unexpectedly diagnosed with MM.

CASE PRESENTATION

A 59-year-old Spanish-speaking male with a past medical history of hypertension presented to the emergency department after being told to go to the ER by his primary care physician. He had been started on furosemide several weeks prior to admission for bilateral lower extremity edema and newly developed dyspnea on exertion. However, he denied chest pain, orthopnea, or paroxysmal nocturnal dyspnea. On review of systems, he had also experienced blurry vision for approximately one month, increased thirst, urinary frequency, and intermittent nausea without vomiting. For the past 2-3 months, he had noted frothy urine. He had no known history of diabetes, kidney or liver disease, and did not notice any changes in the color of his urine. He had

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a weight gain of approximately 8 pounds over one month. He denied over-the-counter medications or illicit drug use, but he did have a history of tobacco and heavy alcohol use. Pertinent findings on initial physical exam included blood pressure of 191/90 mm Hg, temperature of 37.3°C, absent cervical lymphadenopathy, and 3+ pitting edema of the lower extremities bilaterally. There were no significant abnormalities on auscultation or palpation of the thoracic and abdominal cavities. There was no costovertebral angle tenderness.

Laboratory values obtained at presentation showed electrolyte abnormalities including a high potassium of 5.3 mEq/L, chloride of 112 mEq/L, and a low bicarbonate of 19 mmol/L. Blood urea nitrogen and creatinine were elevated at 54 mg/dL and 4.3 mg/dL, respectively. A calcium of 9.1 mg/dL was within normal range. GFR was calculated at 14 mL/min/1.73m². There was a normal white blood cell count; however, a hemoglobin/hematocrit was low at 7.7 gm/dL and 22.7%, respectively. Glucose was not elevated. Albumin was normal. Urinalysis revealed 100 mg/dL protein with 0-2 red cells per high power fields without casts. The urine protein to creatinine ratio was 5.5 mg/g creatinine.

A chest x-ray showed no opacities or infiltrates in the lung fields, although there was evidence of an old healed left rib fracture. Renal ultrasound showed no abnormalities of either kidney, although a mildly enlarged prostate gland was found without evidence of hydronephrosis or calculi. Cardiac workup included an echocardiogram showing moderate left ventricular diastolic dysfunction, mild mitral regurgitation, mild to moderate left atrial dilatation, and left and right ventricular chamber sizes at the upper limits of normal.

Serologies ordered on hospital day 2 included anti-glomerular basement membrane, anti-neu-

trophilic cytoplasmic antibody (ANCA), complement C3 and C4, and antinuclear antibodies. All were reported within normal range. Serum total kappa and lambda light chains were also within normal range with a normal ratio. Serum
protein electrophoresis showed a pattern consistent with hypoalbuminemia suggestive of selective protein loss. Due to unexplained renal failure and proteinuria, an ultrasound-guided percutaneous needle biopsy of the left kidney was performed on hospital day 3.

The biopsy sample contained 16 glomeruli. By light microscopy, the majority of the glomeruli revealed global nodular mesangial matrix expansion and hypercellularity with resultant capillary wall compression (Figure 1a). Moderate to severe interstitial fibrosis and tubular atrophy were also noted. Congo red staining was negative for amyloid. Immunofluorescence microscopy showed striking positivity exclusively for kappa light chains (3+) in a prominent diffuse global linear pattern in tubular and glomerular basement membranes and in arterial walls (Figure 1b). Other immunoreactants including heavy chain immunoglobulins and lambda light chains were negative (Figure 1c). Myeloma casts were not identified. Ultrastructural studies showed powdery deposits along the subendothelial side of the glomerular and tubular basement membranes (not shown). The biopsy results were consistent with light chain deposition disease (LCDD), kappa light chain type.

The unexpected findings of the renal biopsy were immediately relayed to the consulting nephrologist. Repeat serum electrophoresis results on hospital day 5 were still negative for an M spike with low protein of 5.9 gm/dL. A free serum kappa and lambda light chain measurement (hospital day 6) showed a highly elevated ratio of 32 (normal 0.26-1.65). A bone marrow biopsy was also performed and demonstrated mild hypercellularity with 20-30% of the cellularity comprised of CD138-positive plasma cells. The peripheral blood smear did not show obvious rouleaux formation. Flow cytometric studies confirmed an abnormal plasma cell population with kappa light chain restriction. Additionally, a fluorescence in-situ hybridization panel (FISH) for multiple myeloma revealed rearrangements and translocations within the IgH gene loci.

On hospital day 8, a 24-hour urine collection showed 9.9 g of protein and detected a small free kappa monoclonal protein by immunofixation electrophoresis (not quantified). Radiographic skeletal survey revealed an intramedullary lytic lesion of up to 2 cm in the left humerus. No other lytic lesions were identified. The results of the studies were consistent with the diagnosis of multiple myeloma and the patient was started on an appropriate chemotherapy regimen.

**DISCUSSION**

Clonal proliferations of plasma cells are unique from other neoplasms and malignancies in that not only can mass effect cause local destruction, but also, depending on the clone, the secretion of immunoglobulin results in a wide range of symptomatic presentations. Manifestations in the kidney most commonly include myeloma cast nephropathy, amyloidosis, and monoclonal immunoglobulin deposition disease with the resulting renal dysfunction often preceding the diagnosis of MM. Typically, these distinct entities are caused by the manufacturing of abnormal light chains, although heavy chains alone or rarely both heavy and light chains are known to occur. The criteria for MM, however, requires myeloma-related organ or tissue impairment (ROTI), presence of clonal plasma cells in the bone marrow (or a plasmacytoma), and a monoclonal protein in the patient’s serum or urine. The latter is usually first detected on a screening test based on migration patterns of proteins by gel electrophoresis. The appearance of a “spike” on a densitometer tracing of the separated proteins is thus designated as an “M-spike” for monoclonal. Subsequent typing is performed to
determine the class of immunoglobulin by immunofixation. Patients who do not meet the criteria for MM may fall into the category of asymptomatic myeloma also known as “smoldering myeloma,” monoclonal gammopathy of undetermined significance or “MGUS,” solitary plasmacytoma of bone, or nonesecretory myeloma. For a patient who already has signs of end organ damage as in our case, the initial work-up may not reveal the underlying disorder and becomes a diagnostic challenge.

It is unknown whether all of the patient’s symptoms at presentation could be explained by the plasma cell clone. Indeed, the majority of patients classically present with bone pain or are found with pathologic fractures. MM can involve the neurological system and cause visual disturbances, retinopathy, or neuropathy. Up to 50% of patients have direct and indirect kidney dysfunction. Far fewer patients have direct pathology that is identified possibly due to a diagnosis of MM being made by other criteria and avoidance of invasive procedures. Of the renal impairments, both light chain amyloidosis and light chain deposition disease present with nephrotic syndrome while myeloma cast nephropathy (light chain cast nephropathy) typically causes acute renal failure. Nephrotic syndrome classically involves edema, massive proteinuria of over 3.5 grams per day, hypoalbuminemia (<3 grams/dL), and increased lipids in serum and urine. Not all patients with nephrotic range proteinuria have nephrotic syndrome and the differential diagnosis of nephrotic range proteinuria can be challenging in a patient with co-morbid conditions including hypertension, heart failure, or diabetes. However, the proteins that are typically lost are small proteins such as albumin and light chains in normal kappa to lambda ratios of approximately 2:1, respectively. In patients with long standing diabetes who present with nephrotic range proteinuria, it is not uncommon for physicians to conclude diabetic nephropathy based on just the clinical presentation. Although renal biopsy is not indicated in adults with nephrotic syndrome from an obvious cause such as diabetic nephropathy, glomerular diseases including focal glomerulosclerosis, membranous nephropathy, and minimal change disease must be ruled out by renal biopsy due to their different treatment options and prognoses. Adequate tissue must be collected and examined by light, immunofluorescence, and electron microscopy in order to discern immune deposits that are characteristic to the specific diseases. In the case of minimal change disease, alterations of cellular structures are visible only by the high magnification of an electron microscope. Although a renal biopsy carries some risk of bleeding, most experienced medical centers routinely perform percutaneous needle core biopsies under ultrasound guidance and monitor patients for a period of time to avoid such complications. In this case, the findings from the renal biopsy led to a more thorough investigation for a lymphoproliferative disorder.

As mentioned in the case presentation, light microscopic examination showed a pattern of nodular mesangial expansion identical to that seen in diabetic nephropathy. Also known as Kimmelstiel-Wilson nodules, these globular acellular accumulations of periodic acid-Schiff (PAS) stain positive material distort the normal glomerular architecture and are a sign of irreversible renal damage due to chronic hyperglycemia. However, in light of the fact that the patient did not have a history of hyperglycemia, the characteristic nodules were unlikely due to undiagnosed diabetes. Furthermore, Congo red staining was negative, making renal amyloidosis an unlikely diagnosis which also must be considered in the differential of mesangial nodularity. The evaluation of immunoglobulin deposition patterns is a standard in renal biopsy studies. By direct immunofluorescence methods, a panel of fluorescein labeled antibodies to immunoglobulins revealed bright diffuse staining
of kappa light chains in glomerular basement membrane elements as well as tubules and arteri-ies. In contrast, lambda light chains and other immunoglobulins (IgA, IgG, IgM) were negative. Electron microscopic examination showed characteristic powdery deposits lining the base-ment membranes as opposed to fibrils which stain with congo red, as would be seen in cases of amyloidosis.⁶

The nature of the plasma cell clone and corre-sponding secreted light chain determines a unique effect on the kidney and other organs. While either kappa or lambda light chains may be involved in any of the renal diseases, lambda light chains are involved in the majority of renal amyloidosis and kappa light chains are most of-ten the type found in deposition disease and cast nephropathy.⁶,⁸ Experimental models have shown that if the patient serum containing amy-loid causing light chains or light chains from cast nephropathy are injected into mice, these path-ologic light chains are able to reproduce the same renal disease as the patient.¹⁵

An echocardiogram did not support congestive heart failure as a reason for the patient’s dyspne-a; rather, the edema was felt to be related to the massive loss of protein due to renal causes. The degree of proteinuria as determined by a urine protein to creatinine ratio in our case was high enough to prompt a renal biopsy. However, the absence of an M-spike on serum protein electro-phoresis may have delayed a somewhat in-vasive procedure if the patient had a known history of diabetes. Furthermore, the measurement of both bound and unbound light chains with re-spect to heavy chain (i.e. the total amount of free chain) was in the normal range leading the diag-nosis away from a disorder of plasma cells. The light chains are often too quickly excreted due to their small size and are at levels below the detect-ion ability of a screening serum protein electro-phoresis.¹⁶ These light chains in the urine are also known as Bence-Jones proteins. It is impor-tant to recognize that in one of every five cases of myeloma, the plasma cells only secrete light chains and therefore utilization of serum free light chain assay or urine protein electrophoresis is necessary.⁵,⁸ Rarely in 3% of cases a plasma cell clone is found and end-organ damage is demonstrated, yet a monoclonal protein cannot be detected despite thorough testing of urine and serum. In these instances, a diagnosis of non-secretory myeloma is given. A 24-hour urine sample indeed confirmed nephrotic range pro-teinuria of over 9 grams. From this cumulative sample, only a small monoclonal kappa light chain was identified which was under the limits of detection by serum electrophoresis. The serum free light chain assay was markedly ab-normal with an elevated kappa to lambda ratio. However, had it not been for the rapid verbal communication of the biopsy results to the con-sulting nephrologist, these laboratory values and the ensuing work-up of the bone marrow would have been delayed or possibly not or-dered to the detriment of the patient.

Although the television dramas depicting medical mysteries can be solved nearly in 45 minutes, the real life drama of patients waiting for diagno-sis while suffering from their undiagnosed malady is excruciating. Our patient had an unexpect-ed but important manifestation of nephrotic range proteinuria that expedited the diagnosis of MM. With a thorough understanding of the availability and limitations of laboratory testing, the delay in diagnosis can be reduced and appro-priate treatment can be initiated to potentially ward off a fatal disease.

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**LEARNING POINTS**

1. Renal disease associated with multiple myeloma can cause nephrotic syndrome.
2. The differential diagnosis of nephrotic syndrome is broad and can be challenging, especially in older patients with comorbid conditions such as hypertension, heart failure, or type 2 diabetes.

3. Clinical vigilance and prompt communication are needed for the timely evaluation that is essential to the treatment and prognosis of this disease.

REFERENCES


