57-Year-Old Woman With Fatigue and Dyspnea

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A 57-year-old woman presented to the emergency department with progressive fatigue, oliguria, and dyspnea. Three weeks before presentation, she experienced worsening fatigue and shortness of breath. Her symptoms were associated with watery diarrhea and poor dietary intake. She also reported weight loss and decreased urinary output with no gross hematuria. Her medical history was notable for systolic heart failure of unclear etiology and unknown duration with an ejection fraction of 37% and essential hypertension. Medications included lisinopril and furosemide. She was a former smoker. Her family history was unremarkable.

On presentation, the patient was afebrile, pulse rate was 77 beats/min, blood pressure was 118/77 mm Hg, respiratory rate was 16 breaths/min, and oxygen saturation was 95% while breathing room air. Physical examination revealed a fatigued-appearing woman with clear breath sounds bilaterally, jugular venous pressure elevated to 15 cm H_2O, and lower extremity edema.

Laboratory evaluation yielded the following (reference ranges provided parenthetically): hemoglobin, 13.3 g/dL (11.6 to 15.0 g/dL); platelet count, 366 × 10^9/L (157 to 371 × 10^9/L); leukocytes, 7.7 × 10^9/L (3.4 to 9.6 × 10^9/L); creatinine, 9.22 mg/dL (0.59 to 1.04 mg/dL; her baseline creatinine level was 0.54 mg/dL 5 months previously); potassium, 4.9 mmol/L (3.6 to 5.2 mmol/L); calcium, 8.9 mg/dL (8.6 to 10.0 mg/dL); bicarbonate, 17 mmol/L (22 to 29 mmol/L); anion gap, 21 (7 to 15); osmolar gap, 5 mOsm/kg (<10 mOsm/kg); albumin, 3.0 g/dL (3.5 to 5.0 g/dL); alanine aminotransferase 12 U/L (7 to 45 U/L); aspartate aminotransferase, 9 U/L (8 to 43 U/L); and alkaline phosphatase, 102 U/L (35 to 104 U/L). Urinalysis revealed a protein to osmolality ratio of 4.88 (<4.22); predicted urinary protein level of 3001 mg/24 h; white blood cell count of 4 to 10 cells per high-power field; red blood cell count of 3 to 10 cells per high-power field; and no casts.

Electrocardiography revealed low-voltage QRS complexes in all leads and right axis deviation. Chest radiography revealed an enlarged cardiac silhouette with no consolidations or effusions. Computed tomography (CT) of the abdomen and pelvis revealed no hydronephrosis or urolithiasis.

1. **Which *one* of the following is the *most likely* cause of the patient's acute kidney injury?**
   a. Glomerular disease
   b. Unilateral renal vein thrombosis
   c. Pyelonephritis
   d. Ethylene glycol toxicity
   e. Hypovolemia

The patient has a stage 3 acute kidney injury based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[1] In addition, she has proteinuria (urinary protein level >3000 mg/24 h), making glomerular disease the most likely explanation for her presentation. Unilateral renal vein thrombosis is unlikely because it usually presents as new-onset flank or abdominal pain and gross hematuria, none of which were seen in this patient. Similarly, in most cases, the serum creatinine level is only elevated in bilateral renal vein thrombosis (not unilateral). Pyelonephritis is also unlikely given the lack of fever and leukocytosis and the presence of severe proteinuria. Although the patient has an anion gap, she did not have an osmolar gap, making

See end of article for correct answers to questions.

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ethylene glycol consumption doubtful. A hypovolemic state would also be unlikely given the degree of acute kidney injury and physical examination findings of elevated jugular venous pressure and lower extremity edema.

The patient remained oliguric and was given intravenous furosemide, 120 mg, which produced a urinary output of 700 mL. Repeated assessment after diuresis revealed normal blood pressure, absence of orthostatic symptoms, and persistence of lower extremity edema and elevated jugular venous pressure.

2. **Which *one* of the following tests would be *most helpful* as the next step in patient evaluation?**
   a. Hepatitis C viral (HCV) testing
   b. Autoimmune panel
   c. Kidney biopsy
   d. Streptococcal antibody profile
   e. Echocardiography

Although HCV-associated membranous nephropathy can cause decline in kidney function and proteinuria, this condition is typically seen in patients with chronic and advanced HCV infection. Given the patient's normal aspartate aminotransferase and alanine aminotransferase levels and the absence of hepatic steatosis on CT imaging, HCV infection and subsequent associated membranous nephropathy is unlikely. Testing for an autoimmune disease would not be indicated in the initial evaluation and would likely result in false-positive results since the clinical history and physical examination findings do not suggest an underlying autoimmune etiology. A kidney biopsy is the best next step in view of the patient's rapidly progressive acute renal failure and suspicion for nephrotic syndrome. Indications for renal biopsy include rapid elevation in serum creatinine level, presence of red blood cell casts with an elevated serum creatinine level or proteinuria, urinary protein level of more than 1 g/d on multiple measurements with no clear etiology and more than 3 g/d in the absence of diabetes, rapid increase in proteinuria in the presence of diabetes, or presumptive acute interstitial nephritis that has not resolved with the removal of a suspected medication. A streptococcal antibody profile would not be warranted because the patient's history does not suggest recent infection with *Streptococcus*. Although she has chronic heart failure, echocardiography would not provide a definitive answer for a marked elevation in creatinine in the setting of significant proteinuria, weight loss, and unremarkable chest radiography.

Examination of the renal biopsy specimen revealed diffuse acute glomerular and tubular injury with abundant atypical casts consistent with λ light chain cast nephropathy. Congo stain was only focally positive in the interstitial compartment, suggesting light chain (AL) amyloidosis. Given the concern for dysproteinemia, serum protein electrophoresis and free light chain testing were obtained and revealed a significantly elevated λ free light chain level of 446 mg/dL (0.57 to 2.63 mg/dL). Urinary protein electrophoresis revealed an M spike of 546 mg/24 h with immunofixation identifying the M spike as monoclonal IgA-λ.

3. **Given the information obtained thus far, which *one* of the following is the *most likely* diagnosis in this patient?**
   a. Cryoglobulinemia
   b. Monoclonal gammopathy of renal significance
   c. Waldenström macroglobulinemia
   d. Multiple myeloma (MM)
   e. AL amyloidosis

Cryoglobulinemia most commonly presents as membranoproliferative glomerulonephritis and not light chain cast deposits. Monoclonal gammopathy of renal significance (MGRS) represents a group of disorders that are caused by nonmalignant or premalignant plasma cells that secrete monoclonal immunoglobulins. By definition, MGRS does not meet diagnostic criteria for multiple myeloma; MGRS typically presents as progressive kidney failure, and diffuse acute tubular injury is not seen. Waldenström macroglobulinemia is a

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lymphoplasmacytic lymphoma that presents with anemia, thrombocytopenia, lymphadenopathy, splenomegaly, and neuropathy. Renal involvement is rare. Multiple myeloma was highly suspected as it is the main cause of light chain cast nephropathy and a subset of patients also has concomitant amyloid involvement of the kidney. Renal disease occurs due to the overproduction of λ or κ light chains by abnormal plasma cells that occlude tubular lumens of nephrons and create the characteristics seen on pathology. Although Congo red staining of the renal biopsy specimen was positive in this patient, it was very focal, so it is unlikely that AL amyloidosis alone would be the cause of her renal dysfunction. In addition, the type of her proteinuria was predominantly monoclonal immunoglobulin seen in MM, as opposed to albuminuria commonly seen in AL amyloidosis. Further work-up confirmed the diagnosis.

Bone marrow biopsy revealed 30% λ light chain–restricted plasma cells, confirming the diagnosis of MM. Skeletal survey identified lytic lesions in the C7 and T1 vertebral bodies. Systemic AL amyloidosis was also confirmed with fat pad aspiration. Suspicion for cardiac amyloid was high because of the low-voltage QRS complexes seen on electrocardiography and the enlarged cardiac silhouette on chest radiography. Repeated transthoracic echocardiography revealed concentric left ventricular hypertrophy with elevated filling pressure, abnormal strain with apical sparing, and a small pericardial effusion. Similarly, the change in the patient's bowel movements was also suspected to be due to amyloid intestinal deposition; however, it was not confirmed.

4. **In addition to chemotherapy, which *one* of the following should be considered as an addition to the *initial* treatment of this patient?**
   a. Elotuzumab
   b. Plasmapheresis
   c. Stem cell transplant
   d. Radiation therapy
   e. Ultrafiltration

Elotuzumab is an antitumor monoclonal antibody that can be used in a few selected patients with MM. However, it is not approved as a first-line therapy and has not been studied for light chain cast nephropathy. Chemotherapy regimens that include high-dose corticosteroids remain the first-line therapy for MM because it targets the light chain–producing plasma cells. Some institutions consider adding plasmapheresis in selected patients to enhance the removal of existing nephrotoxic free light chains in the circulation. However, this therapy is not widely available, and further randomized controlled trials are needed to solidify its role.[2] Stem cell transplant is not used for initial treatment but may be a potential long-term treatment option in MM. In the context of MM, radiation therapy is used in solitary extramedullary plasmacytomas. Ultrafiltration would not be beneficial in removing light chain–producing plasma cells or alleviating the patient's kidney injury.

For our patient, 4 sessions of emergent plasmapheresis were able to reduce her burden of λ light chain immunoglobulins from 446 mg/dL to 37.9 mg/dL. Cyclophosphamide, bortezomib, and dexamethasone therapy was also initiated.

5. **When discussing prognosis with this patient, which *one* of the following statements is *true*?**
   a. There is little correlation between the patient's initial significant renal dysfunction and her survival
   b. Recovery of the patient's kidney function will not affect her overall survival
   c. Despite chemotherapy and plasmapheresis, the patient may still have progression to end-stage renal disease (ESRD)
   d. If ESRD develops, it will exclude the patient from autologous stem cell transplant
   e. The coexistence of the patient's AL amyloidosis will not affect her overall prognosis

Studies have suggested that there is a correlation between the severity of kidney damage and patient survival; patients who

have adequate renal recovery often have improved survival.[3,4] Despite prompt initiation of therapy, a percentage of patients may never recover renal function and will have progression to ESRD.[5] Kidney dysfunction or ESRD is not a contraindication to autologous stem cell transplant.[6] Given the patient's age and lack of nonhematologic comorbidities, she may be a stem cell transplant candidate. However, studies have suggested that the coexistence of MM and amyloidosis often results in a worse prognosis due to multiorgan deposition of amyloid.[7]

Our patient remained oliguric during hospitalization, and the nephrology service advised starting dialysis. The patient was eventually discharged from the hospital and continued to follow up with the hematology and nephrology departments as an outpatient. Unfortunately, her kidney function never recovered and she became dialysis dependent.

DISCUSSION

Multiple myeloma is a hematologic malignancy characterized by a neoplastic proliferation of plasma cells that produce a monoclonal immunoglobulin. It classically presents with hypercalcemia, renal insufficiency, anemia, and bone pain from lytic bone lesions, as well as other features such as constitutional symptoms and recurrent infection. Multiple myeloma should always be suspected when any of these features are present.

Renal injury with a serum creatinine level of greater than 1.3 mg/dL is seen in about 50% of patients with diagnosed MM, while more than 20% of cases are classified as having a severe renal injury with a serum creatinine of greater than 2.0 mg/dL. More than 80% of cases have proteinuria (consisting most commonly of light chains). However, only 15% to 25% of patients have development of glomerular disease.[8] Renal injury most often occurs due to circulating fragments of immunoglobulins and free light chains that lodge in the tubules of the nephron, resulting in cast nephropathy. Intact immunoglobulins typically do not cross the glomeruli. Light chain cast nephropathy is commonly seen in MM, with one study reporting up to 33% of patients with MM having pathologic evidence of light chain casts on kidney biopsy.[9] This number could potentially be higher as many patients with evidence of light chains in the urine begin therapy without ever undergoing a kidney biopsy.

The International Myeloma Working Group considers acute renal failure from light chain cast nephropathy a myeloma-defining event and is the most common renal pathology seen in patients with MM. Rarely, light chain cast nephropathy has also been associated with Waldenström macroglobulinemia, chronic lymphocytic leukemia, and certain types of lymphomas. Diagnosis is confirmed with histologic evaluation or presumed based on the assumption of significantly elevated serum free light chain levels (>150 mg/dL) in patients previously diagnosed with MM. Patients who have an unexplained acute kidney injury with free light chain levels of less than 50 mg/dL should undergo kidney biopsy to rule out other causes of renal failure per recommendations of the International Myeloma Working Group criteria. Urinary albumin excretion can provide additional information when confirming the diagnosis. One study found that urinary albumin excretion was consistently less than 25% in patients with a confirmed diagnosis of light chain cast nephropathy.[2,10]

Multiple myeloma–induced light chain cast nephropathy requires immediate diagnosis as well as early institution of therapy to prevent irreversible kidney damage and restore renal function. When assessing a patient with suspected light chain cast nephropathy, initial evaluation begins with the assessment of volume status. Typically, these patients are volume depleted due to poor oral intake as well as hypercalcemia-related diuresis. If there are signs of volume deficits, steps should be taken to correct them. Hypercalcemia is also concurrently seen in these patients and should be

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managed appropriately. To prevent any further kidney damage, nephrotoxic agents should be avoided.

Further management as illustrated in this case includes the initiation of urgent chemotherapy with or without plasmapheresis. The role of antimyeloma therapy is to eliminate the source of the abnormal light chain–producing plasma cells. A common first-line regimen includes bortezomib, lenalidomide, and dexamethasone. However, lenalidomide is usually avoided in patients with renal dysfunction. Cyclophosphamide, bortezomib, and dexamethasone is the regimen of choice in such patients. Unlike plasmapheresis, chemotherapy does not address the serum free light chains already produced and found in the circulation. Plasmapheresis allows for rapid reduction of serum free light chains, which has been reported to lead to improvement of renal function and resulted in improved overall survival in some studies.[11] Overall, with directed and supportive therapies, reported rates of improvement in kidney function range between 50% and 80%.[3] However, there is the possibility that patients will never recover renal function and will have progression to ESRD, as seen in our patient.

Finally, AL amyloidosis should always be considered in patients with MM because 12% to 15% of patients with myeloma have development of clinical amyloidosis at some point during the course of the disease. Common organs of amyloid involvement include the kidney, liver, and heart. The following symptoms should raise suspicion for amyloidosis: severe nonischemic cardiomyopathy in a nonhypertensive patient, new-onset arrhythmias, unexplained hepatomegaly, macroglossia, periorbital purpura, peripheral neuropathy, nonselective proteinuria, glomerular disease, and gastrointestinal changes such as diarrhea or constipation.[12] Diagnosis requires histologic confirmation with Congo red staining as well as visualization of apple-green birefringence under polarized light. Treatment of AL amyloidosis with concurrent MM is similar to that for patients with MM without AL amyloidosis. However, outcomes are worse due to underlying concomitant cardiac and renal dysfunction.[7]

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Correct Answers: 1. a. 2. c. 3. d. 4. b. 5. c