A 69-year-old man presented to the emergency department (ED) with new-onset dysuria, urinary frequency and urgency, and right lower quadrant abdominal pain of 5-hour duration. His medical comorbidities included benign prostatic hyperplasia, obesity, hypertension, and hyperlipidemia. He also noted nausea and 3 episodes of nonbloody, nonbilious emesis. For the past week, he reported severe colicky right flank pain, which he attributed to musculoskeletal pain, that was partially relieved by taking no more than 1 tablet of an over-the-counter nonsteroidal anti-inflammatory drug daily. He denied fever, chills, hematuria, or passage of stones in his urine.

Medications at the time of admission included aspirin, atorvastatin, metoprolol succinate, tamsulosin, and finasteride.

Emergency department vital signs revealed mild hypertension of 154/94 mm Hg but were otherwise within normal limits, with a temperature of 36.6°C and a pulse rate of 76 beats/min. On physical examination, the patient was sitting comfortably in no distress. No skin lesions were noted. There was no cervical, submandibular, or supraclavicular lymphadenopathy. He had a regular rate and rhythm without murmurs or peripheral edema on cardiac examination. Respirations were nonlabored with clear equal breath sounds. He had right flank tenderness and right lower quadrant abdominal tenderness without distension, rebound, or guarding. There were no motor or sensory abnormalities noted. In the ED, he received 1 g of acetaminophen, 4 mg of ondansetron, and 1 L of crystalloid fluid and his symptoms resolved.

Laboratory studies revealed the following (reference ranges provided parenthetically): mild leukocytosis with a leukocyte count of $9.8 \times 10^9/L$ (3.4 to 9.6) $\times 10^9/L$ with mild neutrophilia with a neutrophil count of $6.93 \times 10^9/L$ (1.56 to 6.45) $\times 10^9/L$, mild normocytic anemia with a hemoglobin level of 13.1 g/dL (13.2 to 16.6 g/dL) and a mean corpuscular volume of 91.1 fl (78.2 to 97.9 fl), a creatinine level of 4.86 mg/dL (0.74 to 1.35 mg/dL) elevated from baseline 1.08 mg/dL 3 months ago, a blood urea nitrogen level of 77 mg/dL (8 to 24 mg/dL), a creatinine clearance estimated using the Cockcroft-Gault formula of 29 mL/min (97 to 137 mL/min), and an estimated glomerular filtration rate measured using the Modification of Diet in Renal Disease equation of $<15$ mL/min per body surface area ($>60$ mL/min per body surface area). Urinalysis revealed a urine osmolality of 406 mOsm/kg (150 to 1150 mOsm/kg) and proteinuria with a protein level of 169 mg/dL ($<26$ mg/dL) with an estimated 24-hour urine protein level of 3666 mg/24 h but with the actual 24-hour urine total protein level of 592 mg/24 h; there were no nitrites, leukocyte esterase, glucose, red blood cells, white blood cells, or casts. The serum albumin level was 4.7 g/dL (3.5 to 5.0 g/dL). These were all within normal limits 3 months ago.

1. Which one of the following is the next best step to evaluate acute kidney injury (AKI) in this patient?
   a. Check urine sodium and creatinine excretion
   b. Check urine eosinophils
   c. Perform kidney ultrasound with Doppler
   d. Perform kidney biopsy
   e. Perform noncontrast computed tomography (CT) of the abdomen and pelvis

This patient’s more than 300% increase in creatinine level met the Kidney Disease: Improving Global Outcomes definition of...
stage 3 AKI. Evaluation of AKI is important to determine often reversible etiologies, which are classified as prerenal (from decreased kidney perfusion pressure), intrinsic renal (from renal vasculitis, glomerulonephritis, or tubulointerstitial nephritis), or postrenal (from obstruction of urinary flow). In this case, checking urine sodium and creatinine excretion was not indicated because this patient still made urine and these tests are helpful only in oliguric patients not receiving diuretics to distinguish prerenal from intrinsic renal etiologies of AKI.1 Similarly, the low sensitivity of urine eosinophils were not helpful as the triad of fever, rash, and eosinophilia occurs in only 7% of patients with interstitial nephritis.2 Initial renal ultrasound is associated with lower radiation exposure than CT without any difference in the diagnosis and complication of nephrolithiasis or return ED visits and hospitalizations, thus making ultrasound the preferred initial step in evaluation. This patient’s kidney ultrasound revealed bilateral parenchymal hyperechogenicity concerning for pyelonephritis, but no hydronephrosis. His history of colicky unilateral flank pain and dysuria were consistent with ureterolithiasis. The absence of hematuria after a week of flank pain was consistent with later presentation, as documented by 1 retrospective study of more than 450 patients with CT-revealed acute ureterolithiasis, which suggested the absence of hematuria in one-third of cases 3 to 4 days after the onset of flank pain in contrast to the presence of hematuria on the first day of flank pain in 95% cases.3 Subsequently, a noncontrast CT of the abdomen and pelvis revealed moderate right hydronephrosis, which was not present on imaging 3 months ago, but no ureterolithiasis, definite cause of obstruction, or left hydronephrosis was seen. Additionally, although long-standing benign prostatic hyperplasia could lead to overflow incontinence, CT did not reveal bladder changes suggestive of chronic outlet obstruction or bilateral hydronephrosis. Postrenal obstructive AKI secondary to a recently passed kidney stone would be consistent with this patient’s symptomatology and unilateral hydronephrosis. Kidney biopsy would be considered after serological testing for glomerulonephritis.

This patient’s significant degree of kidney injury and proteinuria were also of concern for intrinsic kidney injury, which prompted serological testing for glomerulonephritis. Serum antinuclear, glomerular basement membrane IgG, myeloperoxidase, proteinase 3, hepatitis B surface antigen, hepatitis C, and human immunodeficiency virus antigen and antibodies were negative, and complement C3 and C4 levels were normal. Monoclonal gammopathy screening was positive for a small kappa monoclonal spike in the gamma globulin region, abnormally elevated serum kappa free light chain (FLC) levels of 907 mg/dL (0.33 to 1.94 mg/dL) and a FLC ratio of 692 (0.26 to 1.65) with an IgG level of 491 mg/dL (767 to 1590 mg/dL), an IgA level of 44 mg/dL (61 to 356 mg/dL), and an IgM level of 7 mg/dL (37 to 286 mg/dL), which was concerning for a new kappa light chain multiple myeloma (MM) causing light chain cast nephropathy (LCCN). Other less likely causes of monoclonal gammopathy included disorders of monoclonal protein structure, such as amyloidosis, light chain deposition disease, or cryoglobulinemia, and malignant neoplasms of plasma or B cells, such as macroglobulinemia, plasmacytoma, and B-cell lymphoma. According to the American Society for Apheresis, myeloma cast nephropathy is a category II indication for plasmapheresis (second-line therapy), so this patient underwent plasmapheresis with monitoring of his serum FLC level in an attempt to remove nephrotoxic FLC and salvage kidney function.

2. Which one of the following is the next best test to diagnose suspected new MM in this patient?
   a. Bone marrow biopsy
   b. Whole-body low-dose noncontrast CT scan (skeletal survey)
   c. 24-Hour urine monoclonal protein study
   d. Kidney biopsy
   e. Serum plasma cell assessment

This patient’s monoclonal gammopathy was indicative of a plasma cell proliferative
disorder, most likely MM. As part of this diagnosis, the International Myeloma Working Group requires a biopsy revealing either clonal plasma cells of 10% or more in bone marrow or a plasmacytoma in bone or extra-medullary sites, with kappa/lambda light chain restriction to establish clonality. This patient’s bone marrow biopsy revealed 50% kappa light chain restricted plasma cells, and Congo red staining was negative for amyloidosis. The diagnosis of active MM is made when in addition to biopsy, end-organ damage is attributed to MM using the acronym CRAB, which stands for increased serum calcium level of greater than 11 mg/dL (this patient’s calcium level was normal), renal insufficiency with a creatinine clearance of less than 40 mL/min (this patient met criteria for renal insufficiency), anemia with a hemoglobin level of less than 10 g/dL (this patient’s anemia did not meet criteria), and bone lytic lesions.

A skeletal survey was not indicated for the diagnosis of MM, but ordered for complete work-up of lytic lesions and fractures secondary to myeloma. Importantly, because bones were of primary interest, CT was performed without contrast. Fortunately, he did not report a history of bone pain or fractures, and his skeletal survey revealed only symmetric soft tissue marrow changes in the femurs and proximal humeri without lytic lesions or fractures. Additionally, resolution of his right hydronephrosis was seen. A 24-hour urine monoclonal protein study and immunofixation were not indicated for the diagnosis of MM but ordered to assist in diagnosing LCCN. This patient’s urine protein electrophoresis exhibited an IgG kappa light chain monoclonal spike of 239 mg/dL in the gamma fraction with a collected 24-hour urine protein level of 592 mg/24 hours and a normal urine albumin level of 17.7 mg/dL (<30 mg/dL). Given bland urine sediment, low urinary albumin excretion, and elevated serum FLC level, this patient was indeed presumed to have LCCN and did not need an immediate kidney biopsy to differentiate between amyloidosis and direct plasma cell infiltration of the kidney. Serum plasma cell assessment, which uses flow cytometry to detect plasma cells with CD38 and CD138 and then differentiates normal polyclonal CD19-positive plasma cells from neoplastic monoclonal CD19-negative plasma cells, suggests plasma cell involvement in peripheral blood in most patients with MM but is not diagnostic of MM as per above criteria.

This patient’s bone marrow biopsy revealing 50% kappa light chain restricted plasma cells and acute renal failure with a creatinine clearance estimated using the Cockcroft-Gault formula of 29 mL/min (97 to 137 mL/min) met criteria for the diagnosis of new IgG kappa light chain MM. Risk stratification suggested an Eastern Cooperative Oncology Group (ECOG) performance status of 1, a platelet count of 153 × 10^9/L ((135 to 317) × 10^9/L), a β2-microglobulin level of 10.80 mg/mL (1.21 to 2.70 mg/mL), a lactate dehydrogenase level of 223 U/L (122 to 222 U/L), and a serum calcium level of 9.1 mg/dL (8.8 to 10.2 mg/dL). Bone marrow flow cytometric immunophenotyping revealed diploid monotypic CD19-negative plasma cells expressing CD38 and CD138. Plasma cell fluorescence in situ hybridization identified t(11;14).

According to the Mayo Stratification of Myeloma and Risk-adapted Therapy, this patient’s t(11;14) is a standard risk genetic translocation; however, t(4;14), t(14;16), and t(14:20) are high-risk translocations. Monosomy, particularly 13, not diploidy, is associated with poorer prognosis, whereas trisomies are favorable prognostic factors. Patient factors such as an ECOG performance status of 3 to 4, low serum albumin level less than 3.0 g/dL, and age 70 years or older have as much prognostic value as disease-related factors in predicting poor

3. Which one of the following predicts a poorer prognosis for this patient?
   a. t(11;14)
   b. Diploid monotypic plasma cells
   c. Serum albumin level of 4.7 g/dL
   d. Eastern Cooperative Oncology Group performance status of 1
   e. β2-Microglobulin level of 10.80 μg/mL
In this patient's case, an elevated β2-microglobulin level of 10.80 μg/mL and lactate dehydrogenase level above the upper limit of normal was associated with poorer prognosis and placed him at stage III, the highest stage, of the Revised International Staging System (R-ISS), which has a median overall survival of 43 months and a progression-free survival of 29 months. In the severe setting of his acute kidney injury, an expedited management response was favored in an attempt to recover his renal function.

4. A chemotherapy regimen containing which one of the following is most appropriate for this patient to begin immediately?
   a. Cyclophosphamide
   b. Lenalidomide
   c. Daratumumab
   d. Carfilzomib
   e. Ixazomib

The initial treatment of newly diagnosed MM considers risk stratification, patient comorbidities, and eligibility for autologous hematopoietic cell transplantation (HCT). Given this patient’s relatively younger age and good functioning ECOG performance status of 1, he was considered a candidate for HCT, which can be performed in patients with all stages of kidney disease and prolongs survival as compared with chemotherapy alone. Given this patient’s high-risk R-ISS stage III status and severe renal impairment, quadruple therapy with cyclophosphamide, the anti-CD38 antibody daratumumab, bortezomib, and dexamethasone (Dara-VRd). This patient’s ongoing plasmapheresis would remove the anti-CD38 antibody; therefore, triple therapy with cyclophosphamide, bortezomib, and dexamethasone was immediately begun with the intention to initiate daratumumab after completion of plasmapheresis. For transplant-eligible patients, neither of the proteasome inhibitors carfilzomib and ixazomib is used off-label in place of bortezomib.

5. Given this patient’s chemotherapy regimen, which one of the following is the next best step?
   a. Brain magnetic resonance imaging
   b. Heparin bridging to warfarin therapy
   c. Stem cell collection
   d. Dialysis
   e. Acyclovir therapy

Patients receiving proteasome inhibitors, such as bortezomib, are at an increased risk of posterior reversible leukoencephalopathy syndrome including confusion, seizures, hypertension, and visual disturbances, for which brain magnetic resonance imaging is diagnostic; however, a baseline scan is not needed when initiating treatment. Notably, more than 10% of patients receiving lenalidomide develop thrombosis, so antithrombotic prophylaxis will be needed for this patient upon changing regimens to Dara-VRd after his renal function improves. Light chain cast nephropathy is an indication for plasmapheresis, which this patient received, but not dialysis because this patient is not at end-stage renal disease. Generally, 4 cycles of induction chemotherapy are given before autologous stem cell collection in HCT-eligible patients. Use of bortezomib is associated with an increased risk of herpes zoster reactivation and Pneumocystis infection; therefore, antimicrobial prophylaxis with acyclovir and trimethoprim-sulfamethoxazole was initiated in this patient. Additionally, patients with MM are at an increased risk of deadly bacterial infections, particularly during the first 3 months of therapy; therefore, this patient received levofloxacin prophylactically. Furthermore, allopurinol was given for the prevention of tumor lysis syndrome (TLS).
in this patient because although MM itself presents low risk (<1%) for TLS, bortezomib also increases the risk of TLS, particularly in patients with high tumor burden before treatment.

**DISCUSSION**

We report the case of a 69-year-old man who presented with ureterolithiasis and was found to have the Kidney Disease: Improving Global Outcomes stage 3 AKI secondary to new R-ISS stage III IgG kappa light chain MM. This patient’s initial presentation with dysuria, right flank pain, corresponding unilateral hydronephrosis, and AKI was thought to be of obstructive postrenal etiology due to a kidney stone. However, the sustained severity of his renal insufficiency after presumably passing the kidney stone raised concern for an intrinsic renal etiology, which prompted further work-up for glomerulonephritis. Subsequently, an elevated serum monoclonal FLC level was found with a ratio of 692, which can be elevated in AKI as FLC is renally excreted but the ratio is usually less than 3.9. Acute kidney injury with a creatinine level of 2 mg/dL or greater is present in 20% of newly diagnosed MM, and kidney disease is one of the most common complications of MM.10 The likely mechanism of this patient’s severe AKI by kappa monoclonal proteins over the rapid course of 3 months without albuminuria was intratubular cast formation leading to LCCN. Although the risk of LCCN is directly associated with the level of urinary FLC, these are not regularly measured because of the high intra-individual variation. Rather, the level of urinary FLC is estimated with a 24-hour urine protein electrophoresis and measurement of serum FLC level because LCCN is not associated with a low serum FLC level of less than 500 mg/dL. The management of LCCN focuses on the prompt treatment of the underlying MM with antimyeloma therapy, particularly bortezomib.

The major diagnostic criterion for active MM is plasma cells on bone marrow biopsy or plasmacytoma at bony or extramedullary sites accompanied by end-organ damage at 1 or more sites in CRAB (an acronym of hypercalcemia, renal insufficiency, anemia, or bone lytic lesions).4 This patient’s bone marrow biopsy revealing 50% kappa light chain restricted plasma cells and acute renal failure with a creatinine clearance of 29 mL/min (97 to 137 mL/min) met diagnostic criteria for active MM.

Given this patient’s relatively good baseline functional status, he was considered a candidate for autologous HCT and received cyclophosphamide, bortezomib, and dexamethasone with later initiation of daratumumab after plasmapheresis was complete, which led to a reduction in his serum FLC level and stabilization of his creatinine level. Although MM is incurable, treatment may salvage his kidney function at which time he could switch to Dara-VRd. After HCT, he will likely require lifelong bortezomib until progression or inability to tolerate adverse effects, most notably, peripheral neuropathy.11 Other toxic effects of bortezomib include herpes zoster reactivation, cytopenia, gastrointestinal distress, new-onset heart failure, and rarely posterior reversible leukoencephalopathy syndrome. Importantly for this patient, bortezomib-based therapy was indicated in LCCN to salvage kidney function by reducing light chain production as fast as possible. In patients presenting with stage 3 AKI and found to have a new diagnosis of MM, such as the one reported herein, bortezomib-based quadruple therapy of cyclophosphamide, daratumumab, bortezomib, and dexamethasone has exhibited a higher probability of positive renal response.

**POTENTIAL COMPETING INTERESTS**

The authors report no competing interests.

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Correct Answers: 1. c, 2. a, 3. e, 4. a, 5. e