A 47-year-old woman with a history of myeloperoxidase–anti-neutrophil cytoplasmic autoantibody (MPO-ANCA) microscopic polyangiitis (MPA) in remission, left orbital plasmacytoma in remission, and hypothyroidism presented to the hospital for 1 month of persistent bilateral flank pain. Additionally, she had 2 months of migratory joint pain and a rash that was briefly treated with hydroxychloroquine. Treatment was discontinued because of gastrointestinal upset. Upon evaluation, she also had complaints of mild sinus congestion and right ear fullness, but denied any shortness of breath, fever, chills, cough, hemoptysis, dysuria, urinary frequency and urgency, or routine use of protein pump inhibitors, nonsteroidal anti-inflammatory drugs, diuretics, herbal supplements, or illicit drugs. Home medications included pork thyroid, estradiol, and probiotics.

Vital signs revealed an oral temperature of 36.9°C, blood pressure of 113/80 mm Hg, a respiratory rate of 20 breaths/min, a heart rate of 73 beats/min, and an oxygen saturation of 98% on room air. Physical examination was positive for costovertebral angle tenderness (left more than right). Cardiac, pulmonary, and dermatological examinations were unremarkable. Her oral mucosa was moist without ulceration. There was no peripheral edema, synovitis, or tenosynovitis. Initial laboratory testing yielded the following results (reference ranges provided parenthetically): sodium level, 137 mmol/L (135 to 145 mmol/L); potassium level, 3.3 mmol/L (3.6 to 5.2 mmol/L); blood urea nitrogen level, 10 mg/dL (6 to 21 mg/dL); serum creatinine (SCr) level, 1.03 mg/dL (0.59 to 1.04 mg/dL); bicarbonate level, 27 mEq/L (22 to 29 mEq/L); hemoglobin level, 10.7 g/dL (11.6 to 15.0 g/dL); hematocrit level, 32.2 (35.5% to 44.9%); white blood cell (WBC) count, 4.8 × 10^9/L ((3.4 to 9.6) × 10^9/L); and peripheral eosinophil count, 0.06 × 10^9/L ((0.03 to 0.48) × 10^9/L. Two months before presentation, the patient’s SCr level was 0.6 mg/dL. Urinalysis was significant for 100 mg/dL of protein, moderate hemoglobin, 3 WBCs per high-power field, and 3 red blood cells per high-power field. Urinalysis was negative for bacteria, leukocyte esterase, and nitrites. Urine sodium and creatinine levels were 44 and 46 mmol/L, respectively. A 24-hour urine collection yielded 1.9 g of protein. Computed tomography (CT) urogram without and with intravenous contrast revealed multiple patchy areas of decreased enhancement in both kidneys as well as diffuse urothelial enhancement involving the collecting system and ureters (Supplemental Figure, available online at http://www.mayoclinicproceedings.org). No renal calculi or hydronephrosis was appreciated.

1. Which one of the following is the most accurate description of this patient’s kidney function?
   a. No kidney injury
   b. Acute kidney injury (AKI) stage 1
   c. Acute kidney injury stage 2
   d. Acute kidney injury stage 3
   e. Chronic kidney disease (CKD) stage 3

Although the patient’s SCr level was within normal limits, it was substantially elevated at 1.03 from 0.6 (170% from baseline). The patient had nonoliguric acute kidney injury (AKI) stage 1, defined per the Kidney Disease: Improving Global Outcomes guidelines as an acute increase in SCr level of 0.3 mg/dL or higher in 48 hours or an increase in SCr level by 150% to 200% or more from baseline or a urine output
(UOP) of less than 0.5 mL/kg per hour for 6 to 12 hours. Acute kidney injury stage 2 is an increase in SCr level of more than 200% to 300% from baseline or a UOP of less than 0.5 mL/kg per hour for more than 12 hours. Acute kidney injury stage 3 is an increase in SCr level of more than 300% from baseline, an increase in SCr level to 4 mg/dL or higher, initiation of renal replacement therapy for AKI, a UOP of less than 0.3 mL/kg per hour for more than 24 hours, or anuria (<100 mL of urine per 24 hours). The specific staging of renal injury adds valuable prognostic data. There is an increase in mortality, length of hospital stay, severity of residual CKD, and need for renal replacement therapy with increasing stages of AKI.\(^1\)

Chronic kidney disease is defined as a decreased glomerular filtration rate of less than 60 mL/min per 1.73 m\(^2\) and/or markers of kidney damage for 3 months or more. With the available data, the patient’s SCr level was 0.6 mg/dL and the estimated glomerular filtration rate was higher than 90 mL/min/BSA 2 months before making CKD unlikely. Additionally, she had new onset proteinuria compared to previous urinalyses.

We discussed the evaluation of AKI with the patient, explaining the subtle yet significant elevation in her SCr level. She was agreeable to further diagnostic tests and treatments for her condition.

2. Which one of the following is the most appropriate next step in the characterization of renal injury?
   a. Renal ultrasound
   b. Retrograde pyelogram
   c. Urine eosinophils
   d. Anti-neutrophil cytoplasmic autoantibody (ANCA) panel
   e. Urine sediment examination

   Renal ultrasound and retrograde pyelogram are imaging options that can rule out urinary obstruction. Renal ultrasound is preferred for this indication because of the lack of radiation exposure, easy availability, and low cost. Retrograde pyelograms are invasive and hold possible complications including urinary tract infections and bladder perforation. Nevertheless, ordering further imaging would be unnecessary as a previous CT urogram did not detect nephrolithiasis or hydronephrosis.

   Testing for urine eosinophils has an insignificant role in characterizing AKI given its lack of sensitivity and specificity for the diagnosis of acute interstitial nephritis (AIN).\(^2\) Eosinophiluria may be present in numerous diseases beyond AIN, such as urogenital infections, atheroembolic renal disease, acute tubular necrosis (ATN), rapidly progressive glomerulonephritis, and malignant tumor of bladder.

   The ANCA panel would be a reasonable test to pursue because of her medical history of MPA. Rising ANCA titers have been modestly associated with future vasculitic relapses.\(^3,4\) We noticed that the patient’s MPO antibody titers were increasing over the past 7 years (from 1.5 to >8.0; normal, <0.4). However, an ANCA panel by itself would not be the first step in providing a broad work-up required to evaluate for other causes of AKI, which include pre-renal and intrinsic renal parenchymal damage.

   Urine sediment examination is the most appropriate next step as it provides key information about the etiology of AKI. It allows clinicians to analyze cellular morphology, assess tubular integrity, and identify the presence of casts and crystals.\(^5\) Despite careful assessment of volume status, UOP, and fractional excretion of sodium/urea, the diagnosis of pre-renal AKI or ATN can be challenging to make. Manual urine microscopy is helpful in making this distinction and allowing for appropriate prognostication and guidance of therapy. An active urinary sediment would warrant further diagnostics and rapid treatment.

   The patient’s urinary sediment contained mixed cellular casts predominantly composed of red blood cells and a few WBCs. Renal tubular epithelial cells were also present, which may indicate the presence of concurrent ATN. The patient’s fractional excretion of sodium was 0.7%, which initially supported pre-renal as the etiology
of AKI. However, a low fractional excretion of sodium can also be seen in acute glomerulonephritis and contrast-induced nephropathy. Therefore, this highlights the superiority of urine sediment analysis over a simple laboratory value in distinction between pre-renal and intrinsic AKI.

Other unremarkable laboratory investigations included blood cultures, urine culture, IgG4 level, hepatitis B (core, surface antigen, and surface antibody) and C antibodies, proteinase 3 level, c-ANCA, cryoglobulins, serum protein electrophoresis without the presence of a monoclonal protein on immunofixation, antinuclear antibody, rheumatoid factor, and anti–cyclic citrullinated peptide. Although κ and λ free light chain concentrations were elevated at 5.33 mg/dL (0.33 to 1.94 mg/dL) and 3.54 mg/dL (0.57 to 2.63 mg/dL), respectively, the κ/λ ratio was 1.51 (0.26 to 1.65).

The next step in diagnostic evaluation was renal biopsy, as there was a high suspicion of systemic disease with renal involvement as evidenced by new onset proteinuria, hematuria, and an active urinary sediment. The biopsy consisted of 3 cores of cortex with up to 20 glomeruli. Glomerular findings included segmental tuft hypercellularity with focal glomerular basement membrane breaks, focal necrosis, cellular/fibrocellular crescents, and segmental/global sclerosis. Additionally, there was diffuse moderate acute tubular injury with isometric cytoplasmic vacuolization. Lastly, there was mild to moderate tubulointerstitial fibrosis, mild arteriolar hyalinosis, and moderate arteriosclerosis. There were no neutrophils, eosinophils, or crystals in the tubulointerstitium. Immunofluorescence examination did not reveal any significant staining for IgM, IgG, IgA, C3, κ, or λ. There was no subepithelial, intramembranous, or subendothelial immune complex deposition on electron microscopy.

3. On the basis of the imaging, laboratory, and biopsy findings, which one of the following is the most likely diagnosis?
   a. Acute pyelonephritis
   b. Immunoglobulin G4–related disease
   c. Acute interstitial nephritis
   d. Myeloma cast nephropathy
   e. Pauci-immune crescentic glomerulonephritis

Acute pyelonephritis was considered because of heterogeneous parenchymal echogenicity on CT and flank pain. However, the criterion standard for confirming a diagnosis of pyelonephritis is a urine culture, which was negative for bacterial growth. Additionally, the patient was afebrile with no evidence of leukocytosis. Despite the overall low suspicion of pyelonephritis, ceftriaxone 1 g every 24 hours was initiated for empirical treatment while waiting for the urine culture result. Renal biopsy was completed after a no growth in urine culture.

Immunoglobulin G4–related disease is a systemic disease with infiltration of polyclonal lymphocytes and plasma cells, storiform fibrosis, and obliterative phlebitis. It was considered in the diagnostic evaluation, particularly in the setting of the patient’s history of orbital plasmocytoma. Immunoglobulin G4 renal disease manifests as tubulointerstitial nephritis with significant immunoglobulin deposits and moderate tissue eosinophilia. Immunofluorescence on kidney biopsy was negative for IgG4, and light microscopy did not exhibit any eosinophils. Immunoglobulin G4 disease is associated with low complement level, peripheral eosinophilia, and elevated serum IgG4 level. Our patient had a normal eosinophil count and serum IgG4 level.

Acute interstitial nephritis was a reasonable diagnostic consideration because of the presence of mixed cellular casts. Renal tubular epithelial cells, though most commonly associated with ATN, have been observed in up to 86% of AIN cases. The patient did not display the classic triad of fever, rash, and eosinophilia that can be associated with AIN, although this triad is seen only in a minority of cases. However, the diagnosis could not be ruled out before analyzing the urine sediment and kidney biopsy findings.

Acute interstitial nephritis is most commonly attributed to medications followed by autoimmune diseases. The patient
was not taking any medications or supplements that would lead to AIN. Lastly, renal biopsy remains the criterion standard for the diagnosis of AIN and, in this case, did not present the typical findings of eosinophils, plasma cells, and lymphocytic infiltrates in the peritubular areas of the interstitium. Myeloma cast nephropathy was an unlikely diagnosis because of negative serum protein electrophoresis, lack of a monoclonal protein on immunofixation, normal serum free light chain ratio, and absence of tubular casts on renal biopsy.

On the basis of the renal biopsy findings and the patient’s known history of MPA, pauci-immune focally necrotizing and crescentic glomerulonephritis secondary to MPA was the final diagnosis. The patient’s SCr level continued to rise, peaking at 1.26 mg/dL.

4. Which one of the following is the most efficacious induction regimen for this patient’s diagnosis?
   a. Glucocorticoids and rituximab
   b. Mycophenolate mofetil
   c. Methotrexate
   d. Azathioprine
   e. Therapeutic plasma exchange

In patients with mild or moderate renal involvement with no diffuse pulmonary hemorrhage, recommended induction therapies include high-dose glucocorticoids followed by intravenous pulse cyclophosphamide or rituximab. The initial high doses of intravenous glucocorticoids are eventually tapered to daily oral prednisone with subsequent taper over 6 months. Although a cyclophosphamide-based induction regimen is frequently used, it carries significant cumulative dose-dependent adverse effects such as leukopenia, infections, hemorrhagic cystitis, and malignancy. Rituximab, an anti-CD20 monoclonal antibody, is an equally efficacious alternative option. The Rituximab versus Cyclophosphamide for ANCA-associated Vasculitis and Rituximab versus Cyclophosphamide in ANCA-associated Renal Vasculitis trials found that rituximab was noninferior to cyclophosphamide in inducing remission. Mycophenolate mofetil and methotrexate have been found to induce remission in less severe cases, but can be associated with higher disease relapse rates. Azathioprine has no role in induction therapy. Therapeutic plasma exchange has been used in severe disease manifested by severe renal failure with or without diffuse pulmonary hemorrhage. However, the Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis trial did not find a significant reduction in the incidence of death or end-stage renal disease with adjunctive therapeutic plasma exchange when added to standard of care.

The patient received intravenous methylprednisolone 1000 mg for 3 days followed by oral prednisone (1 mg/kg) for 1 month. A slow taper of prednisone, per the Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis trial protocol, was initiated afterward. Additionally, she received intravenous rituximab 375 mg/m² once weekly for 4 doses. The patient tolerated the treatment with no significant adverse effects. At 2-month follow-up, her SCr level improved to 0.85 mg/dL. The protein-to-creatinine ratio decreased to 0.56. Urinalysis revealed resolution of hematuria. Her bilateral flank pain resolved completely.

5. Which one of the following is the most appropriate maintenance regimen for this patient’s diagnosis?
   a. Rituximab
   b. Trimethoprim-sulfamethoxazole
   c. Cyclophosphamide
   d. Hydroxychloroquine
   e. Bortezomib

In addition to azathioprine, methotrexate, and mycophenolate mofetil for maintenance of remission, rituximab is often preferred because of its ability to better prevent disease relapse. The MAINRITSAN trial evaluated rituximab vs azathioprine as remission maintenance therapy for ANCA-associated vasculitis (AAV). Rituximab resulted in higher sustained remission at month 28 than did azathioprine with a similar rate of adverse events.
Trimethoprim-sulfamethoxazole is indicated for the prophylaxis of *Pneumocystis jirovecii* pneumonia in patients receiving immunosuppressive agents. Maintenance cyclophosphamide is not recommended because of the aforementioned toxicities. There is a lack of data via placebo-controlled trials to support the use of hydroxychloroquine or bortezomib for the treatment of AAV.

Our patient will be receiving rituximab for maintenance therapy every 6 months.

**DISCUSSION**

In summary, this patient with a history of MPA, orbital plasmacytoma, and hypothyroidism presented to our facility with a chief complaint of bilateral flank pain and previous migratory joint pain with intermittent rashes. She was found to have nonoliguric AKI stage 1 associated with proteinuria, hematuria, and active urine sediment. The renal biopsy revealed that her AKI was due to relapse of vasculitis.

This case highlights the diagnostic approach and management of patients with AKI secondary to AAV. In our patient, the initial recognition of AKI in the setting of a "normal" SCr level and new onset proteinuria prompted our attention in initiating a thorough work-up and aggressive follow-up treatment. It is important to note the increasing trends in SCr, particularly in patients with lower muscle mass. An AKI may still exist while the SCr level may deceptively appear normal. Beginning with noninvasive tests such as urinalysis, urine electrolytes, and urine sediment analysis provides critical information to pursue additional diagnostic procedures. Manual urine microscopy has fallen out of favor because of technological advances in urine analysis, perceived burden of time, and possible interobserver variability. However, as found in this case, it was a vital diagnostic tool that allowed us to further characterize AKI in real time, promptly perform a renal biopsy, and initiate life- and organ-saving treatment. If intrinsic renal injury was not identified early on the urine sediment, it is possible that the patient would have progressed to AKI stage 3, potentially requiring renal replacement therapy. As part of this diagnostic work-up, it was equally important to rule out other causes of AKI such as prerenal or obstructive causes by taking a meticulous history and performing renal imaging. Ultimately, the renal biopsy was critical in making the diagnosis of glomerulonephritis secondary to microscopic polyangiitis.

Anti-neutrophil cytoplasmic autoantibody–associated vasculitis is a heterogeneous inflammatory disease affecting small- to medium-sized blood vessels. Severe AAV causes significant organ compromise, which includes diffuse alveolar hemorrhage, glomerulonephritis, mononeuritis multiplex, sensorineural deafness, scleritis, or gangrene. Nonsevere disease includes sinonasal involvement, pulmonary nodules, tracheobronchial disease, and arthritis. Most patients eventually progress to severe disease, oftentimes initially presenting in the fulminant form. The most common severe sequelae of AAV is renal involvement, with up to 30% of patients progressing to end-stage renal disease. Rarely, vasculitis of the periureteral blood vessels can lead to ureteral abnormalities, which was seen on CT in our patient.

Anti-neutrophil cytoplasmic autoantibody–associated vasculitis is subdivided into MPA, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and renal-limited vasculitis with pauci-immune necrotizing glomerulonephritis alone with no evidence for systemic vasculitis. Classifying the specific AAV with serologies (MPO-ANCA, proteinase 3–ANCA, and ANCA-negative) and pathological entity is helpful in predicting the prognosis and response to treatment. When suspicion is high for AAV on the basis of history taking and physical examination, it is critical to obtain a diagnosis with tissue biopsy because positive outcomes depend on the rapid initiation of effective treatment. The mainstay of treatment in patients with AAV is induction therapy with high-dose glucocorticoids and either cyclophosphamide or rituximab. We highlight the efficacy of rituximab in the induction and maintenance of AAV over conventional immunosuppressants. Our patient responded favorably to treatment, with her...
laboratory results presenting evidence of renal recovery. Lastly, it is important for patients to adhere to therapy to decrease rates of disease relapse. Frontiers for the treatment of AAV are constantly expanding as more clinical trials study the utility of potential immunomodulators.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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REFERENCES

CORRECT ANSWERS: 1. b. 2. e. 3. e. 4. a. 5. a