65-Year-Old Woman With Intermittent Fevers, Lower Extremity Paresthesia, Weight Loss, and Malaise

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A 65-year-old woman presented to the emergency department with a 6-month history of intermittent fevers, symmetric bilateral lower extremity paresthesia, a 15-kg weight loss, and malaise. Before the onset of these symptoms, the patient had hypertension that was managed successfully with lifestyle intervention, and her medical history was otherwise unremarkable. She reported several recent falls due to lower extremity paresthesias without related trauma and low-grade fever several times per week.

On physical examination, the patient appeared comfortable and in no acute distress. Her vital signs included the following: temperature, 37.3°C; heart rate, 110 beats/min; respiratory rate, 18 breaths/min; blood pressure, 156/78 mm Hg; and oxygen saturation, 100% while the patient breathed room air. Her lungs were clear to auscultation, and no peripheral edema was noted. No additional heart sounds including murmurs or rubs were present. Dermatologic examination revealed no abnormalities. Findings on neurologic examination were consistent with mild symmetric loss of distal lower extremity light touch and pinprick sensation along the L5 through S1 sensory dermatome distributions with preserved motor function and normal Achilles and patellar reflexes. The reminder of her physical examination findings were unremarkable.

Laboratory studies (reference ranges provided parenthetically) on admission revealed an elevated C-reactive protein level (172.4 mg/L [≤8.0 mg/L]) and an elevated erythrocyte sedimentation rate (143 mm/1 h [0-29 mm/1 h]) without leukocytosis (white blood cell [WBC] count, 9.8×10^9/L [$3.5\text{-}10.5\times10^9$/L]). The WBC differential was normal. An electrolyte panel revealed a sodium level of 134 mmol/L (135-145 mmol/L), potassium value of 4.8 mmol/L (3.6-5.2 mmol/L), fasting glucose concentration of 78 mg/dL (70-100 mg/dL), serum urea nitrogen level of 47 mg/dL (6-21 mg/dL), creatinine level of 2.7 mg/dL (0.6-1.1 mg/dL), and albumin value of 3.0 g/dL (3.5-5.0 g/dL).

Urinalysis revealed the following: osmolality, 300 mOsm/kg (150-1150 mOsm/kg); pH, 5.8 (4.5-8.0); glucose, 17 mg/dL (0-15 mg/dL); and protein, 104 mg/dL (<22 mg/dL). Findings on urine microscopy included 21 to 30 red blood cells (RBCs) per high-power field (hpf) (<3/hpf), 4 to 10 WBCs/hpf (1-10/hpf), greater than 25% dysmorphic RBCs (<25%), and occasional RBC casts. A 24-hour urine collection yielded 1468 mg of protein (<167 mg/24 h).

1. In view of the patient's urinalysis results and additional information obtained thus far, which *one* of the following is the *most likely* underlying renal process?

a. Prerenal azotemia
b. Acute tubular necrosis (ATN)
c. Glomerulonephritis
d. Nephrotic syndrome
e. Acute interstitial nephritis (AIN)

Classically, prerenal azotemia is the result of renal hypoperfusion whereby glomerular filtration is reduced. Prerenal azotemia is often the result of intravascular volume depletion, the effects of which are reversible with resolution of the underlying renal hypoperfusion. The urinary sediment is bland in prerenal azotemia, and the presence of dysmorphic RBCs and RBC casts, as seen in our patient, would indicate an alternative diagnosis.

Acute tubular necrosis is a common cause of acute kidney injury in hospitalized patients. It can be the result of prolonged or profound ischemic injury to the kidney as seen in sepsis as well as exposure to nephrotoxins. Urinalysis findings supportive of ATN include the presence of granular or "muddy brown" casts and renal epithelial cells on urine microscopy.

See end of article for correct answers to questions.

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Neither of these findings was noted in our patient. Of note, the classic conception of prerenal azotemia and ATN in acute kidney injury has been challenged recently, and additional study is needed to develop terminology that better describes the underlying pathophysiologic processes.[1]

Our patient's urinalysis results are most suggestive of an underlying glomerulonephritis. Glomerular injury secondary to ongoing glomerulonephritis results in spillage of RBCs into the urinary space and formation of RBC casts. If seen on urine microscopy, RBC casts are highly specific for glomerular injury. As spilled RBCs traverse the course of the nephron, they are subjected to both mechanical and osmotic stressors. This process often results in abnormal-appearing, or dysmorphic, RBCs on urine microscopy.[2] In addition to RBC casts, the finding of a substantial percentage of dysmorphic RBCs on urine microscopy is highly specific for glomerulonephritis.

The nephrotic syndrome includes proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia.[3] Nephrotic-range proteinuria is defined as more than 3.5 g of total urinary protein per day. In addition, some investigators suggest that the serum albumin should be less than 2.5 g/dL. Our patient met neither of these criteria and had no peripheral edema on physical examination. Often caused by medications, autoinflammatory conditions, or infection, AIN is characterized by findings of an inflammatory infiltrate within the renal interstitium on renal biopsy. Acute interstitial nephritis classically manifests as acute kidney injury with associated rash, fever, and eosinophilia. Few patients, however, present with all of the classic findings. Urinalysis findings supportive of a diagnosis of AIN include eosinophiluria and WBC casts, as well as variable numbers of WBCs and RBCs. The utility of urinary eosinophils in this regard, however, has recently been called into question.[4] The lack of a history supporting an inciting agent and the absence of rash, eosinophilia, eosinophiluria, or WBC casts makes AIN less likely in this case.

Retroperitoneal ultrasonography revealed normal-sized kidneys with normal cortical thickness and echogenicity. No masses, hydronephrosis, or dilation in the collecting system was noted. Following admission, the patient's urinary output remained between 1 and 2 L/24 h. Chest radiography yielded normal results, with no evidence of pulmonary infiltrates.

2. Which *one* of the following diagnostic tests would *best* aid in determining the etiology of the patient's glomerulonephritis?

a. Serum IgA level
b. Complement C5 level
c. Hemoglobin A_{1c} concentration
d. Proteinase 3 (PR3) and myeloperoxidase (MPO) antibody tests
e. Antistreptolysin antibody test

IgA nephropathy is recognized as the most common cause of chronic glomerular disease worldwide. Although some investigators tout the utility of serum galactose-deficient IgA1 levels in the evaluation of suspected IgA nephropathy,[5] kidney biopsy remains the criterion standard diagnostic test. Serum IgA levels do not aid in the evaluation of a patient suspected to have IgA nephropathy or in determining the cause of this patient's glomerulonephritis.

Hypocomplementemia is associated with several causes of glomerulonephritis including lupus nephritis, mixed cryoglobulinemia, membranoproliferative glomerulonephritis, and infection-related glomerulonephritis. Immune complexes associated with these conditions result in complement activation and fixation, thereby decreasing total complement, C3, and C4 levels. Normal total complement, C3, and C4 levels, however, would support a cause of glomerulonephritis not associated with immune-complex formation, such as pauci-immune glomerulonephritis. Although total complement, C3, and C4 levels would be useful in the evaluation of glomerulonephritis, C5 levels would not aid in the evaluation of this patient.

Poor glycemic control is associated with gradually progressive diabetic nephropathy. Our patient had a normal fasting glucose level and no history of diabetes mellitus, making diabetic nephropathy unlikely. Hemoglobin A_{1c} testing would be of little utility in this setting.

Proteinase 3 and MPO antibody tests should be obtained in this setting because these factors accompany antineutrophil cytoplasmic antibody (ANCA)—associated glomerulonephritis and would assist in evaluation.

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Poststreptococcal glomerulonephritis is associated with autoantibody production, including antistreptolysin antibodies, and is a common cause of glomerulonephritis. In this patient with no recent history of pharyngitis, soft tissue infection, or other group A streptococcal exposure, antistreptolysin antibody testing would not be helpful.

Complement levels were measured and were normal: C3 serum complement, 113 mg/dL (75-175 mg/dL), and C4 serum complement, 25 mg/dL (14-40 mg/dL). The MPO, anti–glomerular basement membrane (GBM), anti–double-stranded DNA, and antinuclear antibody titers were additionally unremarkable. Of note, indirect immunofluorescence cytoplasmic ANCA (c-ANCA) testing was positive at 1:64. Indirect immunofluorescence for perinuclear ANCA (p-ANCA) was negative. Testing for PR3 antibody was strongly positive (>8.0 U [<0.4 U]).

In addition to laboratory assessment, a renal biopsy was performed. On light microscopy, segmental fibrinoid necrosis of the small- to medium-sized arteries was visualized (Supplemental Figure, A, available online at http://www.mayoclinicproceedings) with associated cellular crescent formation involving glomeruli (Supplemental Figure, B). Immunofluorescence revealed segmental staining with fibrinogen, suggesting fibrinoid necrosis and/or crescentic change, which was supported by electron microscopy. Immunofluorescence was negative for any substantial deposition of C3, C1q, IgG, IgA, IgM, or κ or λ light chains. No immune complex or paraprotein-related deposits were noted. The pathologic findings were consistent with pauci-immune rapidly progressive crescentic glomerulonephritis.

3. Which *one* of the following diagnoses is *most likely* in this patient?

a. Microscopic polyangiitis (MPA)
b. Granulomatosis with polyangiitis (GPA)
c. Anti-GBM antibody (Goodpasture) disease
d. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
e. Polyarteritis nodosa (PAN)

Microscopic polyangiitis is a necrotizing vasculitis primarily affecting small vessels without the presence of granulomas or notable immune complex formation, most commonly associated with the presence of p-ANCA and MPO antibodies. Although MPA is commonly associated with renal vasculitis, the presence of c-ANCA and PR3 antibodies indicates that an alternative diagnosis is more likely.

Granulomatosis with polyangiitis, formerly known as Wegener granulomatosis, is a necrotizing granulomatous vasculitis of small- to medium-sized vessels commonly affecting the upper and lower airways, frequently with notable renal involvement. Granulomatosis with polyangiitis is commonly associated with the presence of c-ANCA and PR3 antibodies, as seen in our patient.

Anti-GBM antibody disease often manifests with rapidly progressive crescentic glomerulonephritis, frequently associated with pulmonary involvement. To establish this diagnosis, one would expect the presence of anti-GBM antibodies, either in the blood or on histopathologic studies with immunofluorescence. Neither of these findings were seen in our patient.

Eosinophilic granulomatosis with polyangiitis is characterized by eosinophil-rich necrotizing granulomatous inflammation of small- to medium-sized arteries and can present with a rapidly progressive pauci-immune glomerulonephritis. Eosinophilic granulomatosis with polyangiitis is more often associated with the presence of MPO antibodies and p-ANCA positivity, as compared with the PR3 antibodies and c-ANCA positivity in this case.

PAN is a systemic vasculitis, often with renal, gastrointestinal, cutaneous, muscular, or peripheral nerve involvement. PAN often spares the lungs and is not associated with ANCA. PAN rarely presents with glomerular involvement on histopathology because it primarily involves medium-sized muscular arteries. The presence of c-ANCA and PR3 antibodies, as well as glomerular involvement on histopathology, as in the case of our patient, argues strongly against a diagnosis of PAN.

After completion of the renal biopsy, the patient continued to note lower extremity paresthesia.

4. Based on the patient's clinical presentation, which *one* of the following is the *most appropriate* initial treatment regimen for remission induction?

a. High-dose intravenous (IV) glucocorticoids
b. High-dose IV glucocorticoids with methotrexate
c. High-dose IV glucocorticoids with mycophenolate mofetil
d. High-dose IV glucocorticoids with rituximab
e. Plasma exchange

Glucocorticoids alone should not be used for remission induction. Glucocorticoids plus methotrexate can be used for remission induction in patients with mild disease, but such therapy would not be recommended in our patient who has more severe disease. Corticosteroid therapy with mycophenolate mofetil has shown promise in inducing remission in patients with MPO-positive ANCA-associated vasculitis (AAV) but not in patients with PR3 antibodies.

Of the options presented, high-dose IV glucocorticoids with rituximab would be the best initial treatment regimen. Rituximab, a monoclonal antibody against B lymphocyte—expressed CD20, has been found in recent randomized controlled studies, including the Rituximab in ANCA-Associated Vasculitis (RAVE) trial,[6] to be comparable to cyclophosphamide therapy for induction of remission while having potential superiority in inducing remission in relapsing disease. In the setting of severe AAV, plasma exchange can be considered as an adjunct to immunosuppressive therapy for remission induction, especially for those presenting with diffuse alveolar hemorrhage or severe renal impairment necessitating hemodialysis. Plasma exchange would not be used as monotherapy, however.

Our patient was treated initially with IV methylprednisolone and an IV rituximab infusion (375 mg/m^2 body surface area). After several days of IV methylprednisolone treatment, the patient was transitioned to oral prednisone (60 mg/d). On hospital discharge, 3 subsequent weekly rituximab infusions were scheduled, with an anticipated several-month course of corticosteroid therapy.

5. Which *one* of the following laboratory studies should be obtained *before* initiation of rituximab therapy?

a. RBC thiopurine methyltransferase (TPMT) level
b. Iothalamate clearance
c. *Mycobacterium tuberculosis* interferon-γ release assay
d. Antibodies for endemic fungi (*Coccidioides, Histoplasma, Blastomyces*)
e. Hepatitis B serologies

Red blood cell TPMT levels should be obtained before administration of thiopurine drugs including azathioprine. Patients with reduced enzyme activity are at risk for adverse effects including bone morrow toxicity. Although measuring TPMT levels may aid in choosing future maintenance immunosuppression, it is not necessary before rituximab initiation. Evaluation of iothalamate clearance allows for an accurate assessment of glomerular filtration rate but would be of little utility because rituximab is dosed on the basis of body surface area, not glomerular filtration rate.

Systematic testing for organisms such as *M tuberculosis* and endemic fungi before rituximab initiation is not routinely performed. All patients, however, should be evaluated for evidence of ongoing infection before initiation of rituximab. Patients treated with rituximab have been found to be at increased risk for reactivation of hepatitis B.[7] Consequences of hepatitis B reactivation including fulminant liver failure and death have been reported in patients treated with rituximab. The US Food and Drug Administration currently recommends screening all patients for hepatitis B before initiation of rituximab.

On hospital discharge, follow-up with an outpatient nephrologist was scheduled to monitor the therapeutic response to rituximab and determine the duration of glucocorticoid therapy.

DISCUSSION

Several vasculitides are encompassed within the broader category of AAV including granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), and microscopic polyangiitis. These diseases are characterized by small-vessel necrotizing inflammation and autoantibodies to

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neutrophil cytoplasmic components including PR3 and MPO. ANCA-associated vasculitis has an annual incidence of approximately 20 per million and considerable mortality risk, estimated to approach 25% at 5 years.[8] Renal involvement is common, with severe impairment associated with poor outcomes.

Pauci-immune necrotizing glomerulonephritis describes the relative absence of immune deposits observed on histologic review using electron microscopy or immunofluorescence. Although aspects of our patient's case are consistent with GPA, some would argue that the term *GPA* should be reserved for those with granulomatous inflammation seen on histopathologic examination. Others have noted that grouping patients by antigenic specificity of ANCA may be more prognostically valuable than the traditional classification of GPA and MPA, with increased relapse rates seen in patients with PR3 antibodies but greater mortality with MPO antibody–driven disease.[9] Because ANCA positivity is not 100% specific for vasculitis, correlation among clinical, laboratory, and pathologic findings is necessary to confidently diagnose AAV.

One unusual aspect of our patient's clinical presentation was her lower extremity paresthesia. The distal and symmetric loss of light touch and pinprick sensation appeared consistent with mononeuritis multiplex, a disease well recognized for its relationship with concomitant vasculitis. In the setting of vasculitic neuropathies, treatment is directed toward the underlying vasculitis.

Because ANCA-associated vasculitides may be associated with rapidly progressive glomerulonephritis, initiation of empirical treatment should be instituted, especially if a delay in renal biopsy is anticipated. Rapidly progressive glomerulonephritis–directed empirical therapy consists of high-dose corticosteroids. Plasma exchange can be considered if there is concomitant pulmonary hemorrhage requiring ventilatory support or in the setting of severe renal involvement (creatinine concentration >5.0 mg/dL or need for dialysis), although the role of this therapy is controversial. Once the diagnosis of ANCA-associated renal vasculitis is confirmed, either cyclophosphamide or rituximab is then initiated for remission induction. Direct comparison of induction regimens containing either cyclophosphamide or rituximab for ANCA-associated renal vasculitis yielded similar rates of sustained remission at 82% and 76%, respectively.[10]

After successful initiation of induction therapy, outpatient follow-up is crucial to monitor pharmacological efficacy, identify adverse effects, and determine the duration of glucocorticoid therapy. Because several months of glucocorticoid therapy are usually needed to abate systemic symptoms, antibiotic prophylaxis is a necessary adjunct to prevent opportunistic infections including *Pneumocystis* pneumonia.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

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CORRECT ANSWERS: 1. c. 2. d. 3. b. 4. d. 5. e