25-Year-Old Man With Flank Pain, Hematuria, and Proteinuria

ANDREW SMYTH, MD,* AND VESNA D. GAROVIC, MD†

A 25-year-old nonsmoking male tire technician presented to the emergency department with a 3-week history of macroscopic hematuria and flank pain. He had previously been feeling well and was taking no regular medications; however, he had seen his primary care physician 10 days previously for left flank pain and was empirically treated for pyelonephritis with oral ciprofloxacin. On presentation, the patient was not passing clots through the urethra, denied recent trauma, and rated his flank pain as 6 on a severity scale of 10, described as constant, bilateral, nonradiating, and pleuritic with no relieving factors. He had no nausea, vomiting, diarrhea, fevers, chills, or rigors. He denied recent travel, animal contacts, occupational exposures, use of over-the-counter medications, or illegal drug use.

On examination, the patient appeared clinically well without evidence of distress, pallor, or jaundice. His temperature was 36.8°C, blood pressure was 118/72 mm Hg, pulse rate was 74/min, and oxygen saturation was 95% while breathing room air. Findings on cardiovascular and respiratory examinations were noncontributory. The abdomen was soft, nondistended, and nontender without masses or organomegaly. No costovertebral angle tenderness, suprapubic tenderness, or renal bruits were appreciated. There was no evidence of rash or musculoskeletal abnormality.

Laboratory tests yielded the following results (reference ranges provided parenthetically): a normal white blood cell count with no evidence of peripheral eosinophilia; creatinine, 1.5 mg/dL (0.9-1.4 mg/dL); C-reactive protein, 99.2 mg/L (≤8.0 mg/L); and erythrocyte sedimentation rate, 111 mm/h (0-22 mm/h). The estimated glomerular filtration rate (eGFR) was 57 mL/min per 1.73m^2 and the international normalized ratio was 1.0. Urinalysis by dipstick showed trace ketones, protein 3+, bilirubin 1+, and occult blood 3+. Initial urinalysis showed reddish urine, a protein concentration of 3100 mg/dL, and a large amount of hemoglobin. Microscopic examination showed more than 100 red blood cells per high power field, with more than 25% dysmorphic red blood cells and no evidence of urinary eosinophils. Chest radiography showed mild bilateral pleural effusions and atelectasis at the left base behind the heart. Computed tomography (CT) of the abdomen and pelvis was performed according to the renal stone protocol; findings were negative for kidney stones.

1. Which <u>one</u> of the following is the <u>most likely</u> cause of the dysmorphic red blood cells in the urine of this patient?

a. *Contrast-induced nephropathy*
b. *Urolithiasis*
c. *Flank trauma*
d. *Bladder malignancy*
e. *Glomerulonephritis*

Patients with *contrast-induced nephropathy*, defined as acute renal failure that develops within 48 hours of exposure to intravenous radiographic contrast medium,[1] present with an elevated creatinine level. This condition is unlikely in our patient who received no intravenous contrast medium during CT of the abdomen and pelvis. Urolithiasis and trauma are common causes of flank pain with hematuria but generally cause postglomerular bleeding resulting in macroscopic hematuria with morphologically normal (not dysmorphic) red blood cells. These 2 conditions were ruled out on the basis of the CT findings (unenhanced CT has been reported to have a specificity of 96% and sensitivity of 97% in diagnosing urolithiasis[2]) and the lack of a history of a recent trauma, respectively. Bladder malignancies commonly present with painless hematuria and with morphologically normal red blood cells in male smokers older than 60 years. These malignancies have been associated with prolonged exposure to arylamines and polyaromatic hydrocarbons, commonly found in the rubber and plastic industries.

Glomerulonephritides present with an active urinary sediment (>5 red and white blood cells per high power field and/or ≥1 cellular cast), with or without renal insufficiency. Dysmorphic red blood cells are seen in glomerular disorders that cause blebs, budding, and segmental loss of the red blood cell membrane, resulting in the variable morphology of red blood cells in urine. Glomerulonephritis would be the most likely cause of the high proportion (>25%) of dysmorphic red blood cells in the urine of this patient.

The patient was admitted to our institution with a working diagnosis of glomerulonephritis and began taking high-dose pulse methylprednisolone. Autoimmune serologic tests were conducted.

*Resident in Internal Medicine, Mayo School of Graduate Medical Education, Mayo Clinic, Rochester, MN.
†Adviser to resident and Consultant in Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

See end of article for correct answers to questions.

Individual reprints of this article are not available. Address correspondence to Vesna D. Garovic, MD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (garovic.vesna@mayo.edu).

2. Which one of the following is the most likely cause of renal disorder in this patient?

a. IgA nephropathy
b. Wegener granulomatosis
c. Acute interstitial nephritis
d. Lupus nephritis
e. Postinfectious glomerulonephritis

IgA nephropathy, the most common cause of primary glomerulonephritis in the West, occurs because of deposition of IgA in the glomerulus. Gross hematuria after upper respiratory tract infection is the most common presentation. Our patient presented with proteinuria, active urinary sediment, and renal insufficiency. However, the laboratory findings consistent with a systemic inflammatory response (ie, elevated C-reactive protein concentration and erythrocyte sedimentation rate), along with radiographic evidence of a pulmonary process, were suggestive of a more systemic disease.

Wegener granulomatosis, a systemic vasculitis predominantly affecting medium and small arteries, most frequently involves the respiratory tract and kidneys. The absence of respiratory symptoms, joint pains, and vasculitic rash argued against this diagnosis.

Acute interstitial nephritis is an allergic-type reaction, most often induced by drug therapy; its onset may range from several days to several weeks after exposure to the offending agent. Patients typically present with rash, fever, or eosinophilia. Laboratory manifestations include acute renal insufficiency, proteinuria (total protein excretion <1.0 g/24 h), and presence of white and red blood cells and white blood cell casts in the urine sediment. A diagnosis of acute interstitial nephritis was ruled unlikely on the basis of urinalysis findings, pulmonary involvement, and absence of rash, fever, and eosinophilia/eosinophiluria. Although ciprofloxacin has been reported to be associated with acute interstitial nephritis,[3] the patient's symptoms preceded its introduction.

Lupus nephritis is a common finding in cases of systemic lupus erythematosus (SLE) and presents with active urinary sediment, typically consisting of hematuria, pyuria, cellular (particularly red blood cell) casts, and proteinuria, with or without altered renal function. Our patient presented with an active urinary sediment and signs of serositis (pleural effusion), commonly present in SLE.

Postinfectious glomerulonephritis is induced by infection with specific strains of group A β-hemolytic streptococci, and renal manifestations are most commonly preceded by symptoms of either pharyngitis or skin infection (impetigo), with a latent period from infection to hematuria of 10 and 21 days, respectively. Our patient denied a history of either upper respiratory tract or skin infection.

Serologic findings were positive for antinuclear antibody (ANA) (>12 U [≤1 U]) and anti-double-stranded DNA (anti-dsDNA) (115 IU [negative <25 IU, weakly positive 25-59 IU, positive 60-200 IU, strongly positive >200 IU]) but negative for proteinase 3 and antistreptolysin, which are implicated in Wegener granulomatosis and postinfectious glomerulonephritis, respectively. Proteinuria (total protein excretion, 12 g/24 h) was revealed on 24-hour urine collection. Given the presence of 4 classification criteria for SLE (pleural effusion, total protein excretion >0.5 g/24 h, and positive anti-dsDNA and ANA titers), the diagnosis of SLE was most likely.[4]

3. Which one of the following is the most appropriate next step?

a. *Kidney biopsy*
b. *Initiation of angiotensin-converting enzyme (ACE) inhibitor treatment*
c. *Continuation of long-term, high-dose corticosteroid treatment*
d. *Initiation of hydroxychloroquine treatment*
e. *Intravenous cyclophosphamide every other month with oral prednisone*

A precise diagnosis is critical in choosing optimal therapy because therapy varies depending on the type and severity of renal injury. Kidney biopsy is required to characterize renal involvement and to determine the degree of irreversible changes that may predict long-term renal prognosis and likelihood of response to treatment.

ACE inhibitors, considered a mainstay treatment of hypertension in patients with proteinuric renal insufficiency, are often initiated for their antiproteinuric effect in normotensive patients. Although ACE inhibitors may have a role in the management of proteinuria, the next step should be to focus on diagnosis and treatment.

Corticosteroids are effective immunosuppressive agents used in high doses as intravenous pulse regimens to induce rapid immunosuppression. When used as long-term therapy, prednisone is used with corticosteroid-sparing agents, such as cyclophosphamide, mycophenolate, azathioprine, and tacrolimus, to minimize the array of associated adverse effects.

Hydroxychloroquine treatment, most useful for skin and musculoskeletal SLE manifestations, is not the drug of choice for central nervous system and kidney involvement. Cyclophosphamide combined with low-dose prednisone has been associated with high remission rates and lower rates of persistent nephrotic syndrome than oral prednisone alone.[5] However, because of its toxicity and adverse effects (eg, infertility) in patients with lupus nephritis, cyclophosphamide is initiated only after a kidney biopsy has shown a potential benefit of treatment.

Kidney biopsy was performed under ultrasonographic guidance and showed membranous nephropathy and class V lupus nephritis (2004 classification of the International

Society of Nephrology and Renal Pathology Society[6]). Immunofluorescence showed extensive positive staining for complements, immunoglobulins, and κ and λ light chains.

At 48 hours after kidney biopsy, the patient became short of breath at rest, without cough or chest pain. His temperature was 36.8°C, blood pressure was 130/84 mm Hg, heart rate was 86/min, and oxygen saturation was 92% while breathing room air. Breath sounds were absent in the right lower zone, but the rest of the lung fields were clear to auscultation. Heart sounds were normal with no evidence of elevated jugular venous pressure or peripheral edema. Electrocardiographic results were normal. A follow-up chest radiograph showed an interval increase to a moderate-sized pleural effusion on the right side with volume loss in the right lower lobe.

4. ***Which <u>one</u> of the following conditions is the <u>most likely</u> cause of hypoxia in this patient****?*

a. *Pneumonia*
b. *Pulmonary edema*
c. *Pneumothorax*
d. *Pulmonary embolism*
e. *Acute respiratory distress syndrome*

Pneumonia is characterized by fever, a cough that may be productive of sputum, and evidence of infiltrate on chest radiography. The patient was afebrile and denied cough; despite the volume loss affecting the right lower zone, the chest radiograph showed no convincing evidence of consolidation.

Pulmonary edema frequently presents with shortness of breath and evidence of vascular congestion on chest radiography. Typical clinical findings include elevation of jugular venous pressure, S_3 and/or S_4 gallop, crackles on lung examination, and peripheral edema. In this patient, electrocardiography showed no evidence of abnormalities, and cardiac examination revealed no murmurs; these findings, along with absence of clinical and radiographic evidence, made pulmonary edema less likely.

Pneumothorax is characterized by the sudden onset of dyspnea, pleuritic chest pain, and hypoxia. In our patient, breath sounds were absent over affected areas, with hyperresonance on percussion. Progression to tension pneumothorax is associated with hemodynamic instability and evidence of mediastinal shift. This diagnosis was excluded on the basis of the pulmonary examination findings and the lack of the characteristic radiographic finding of a white visceral pleural line, separated from the parietal pleura by an avascular gas collection.

Pulmonary embolism is characterized by dyspnea, pleuritic chest pain, cough, and hemoptysis. Tachypnea, tachycardia, an accentuated pulmonary component of S_2, and S_4 gallop are also typical. Our patient presented with pleuritic chest pain and developed hypoxia, in the setting of nephrotic syndrome, which is considered a risk factor for a hypercoagulable state; the presumptive diagnosis of pulmonary embolism was entertained.

Acute respiratory distress syndrome causes hypoxia and is associated with a wide number of conditions, including sepsis, aspiration of gastric contents, pneumonia, burns, blood transfusions, and transfusion-related acute lung injury. Characteristic bilateral lung infiltrates were not evident on chest radiography. Our patient had no history of relevant comorbidities and had no evidence of hemodynamic instability or postbiopsy hemorrhage that could predispose him to acute respiratory distress syndrome.

Arterial blood gas analysis showed a pH of 7.36, a P_{O_2} of 70 mm Hg, a P_{CO_2} of 40 mm Hg, and an elevated calculated alveolar-arterial oxygen gradient of 32 mm Hg (normal, age-adjusted gradient, 8 mm Hg). The patient's clinical presentation and laboratory findings were consistent with pulmonary embolism. Magnetic resonance imaging of the chest with intravenous gadolinium showed a large occlusive embolus in the pulmonary artery supplying the right lower lobe. Concomitant intravenous heparin and oral warfarin anticoagulation therapies were initiated.

5. ***Which <u>one</u> of the following did <u>not</u> contribute to a hypercoagulable state in this patient with SLE?***

a. *Factor V Leiden*
b. *Recent invasive procedure (eg, kidney biopsy)*
c. *Nephrotic syndrome*
d. *Antiphospholipid antibodies*
e. *Occult malignancy*

Factor V Leiden, the most common cause of inherited thrombophilia in white people (reported prevalence, 5%), brings about a hypercoagulable state by increasing the generation of thrombin and decreasing the anticoagulant activity of activated protein C. The most common presentation is deep venous thrombosis, with or without pulmonary embolism, or recurrent pregnancy loss.

Surgical procedures, especially those involving the hip, pelvis, or knee, increase the risk of venous thromboembolic disease, mainly because of either decreased activity or prolonged immobilization. After renal biopsy, patients must be inactive for only 6 hours on average, not long enough to increase the risk of thromboembolism.

In nephrotic syndrome, protein loss is associated with urinary loss of antithrombin III, a vitamin K–independent glycoprotein that inhibits thrombin and other coagulation factors, thereby modulating the coagulation cascade. Its deficiency is associated with a hypercoagulable state. However, not all patients with nephrotic syndrome develop pulmonary embolism; almost half of patients with SLE have 1 of the antiphospholipid antibodies, which may further exacerbate the hypercoagulable state. Because this patient showed clinical features suggestive of antiphospho-

lipid syndrome (eg, venous and arterial thromboses), testing for lupus anticoagulant and anticardiolipin antibodies was performed.

A thrombotic event may herald an occult malignancy, but this diagnosis was considered unlikely in our patient because he was young and did not smoke and because physical examination and laboratory tests yielded no evidence of occult malignancy.

Evaluation for a hypercoagulable state was remarkable for a prolonged partial thromboplastin time, indicating inhibition within the coagulation cascade. The addition of hexagonal phase phospholipid marginally shortened the clotting time, providing evidence for lupus anticoagulant. Anticardiolipin antibody assays were negative.

Intravenous heparin and oral warfarin were continued until the patient's international normalized ratio reached a therapeutic range (2.0-3.0), at which time heparin was discontinued. After completing a 3-day course of high-dose intravenous methylprednisolone, the patient was switched to 60 mg/d of prednisone with trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia because it has been reported to be superior to aerosolized pentamidine.[7]

The patient began taking 500 mg of mycophenolate twice daily; the dosage was later increased to 1 g twice daily. The patient received 5 mg/d of lisinopril for its antiproteinuric effect, but this medication was discontinued when his creatinine level increased to 2.0 mg/dL, with an eGFR of 41 mL/min per 1.73m^2. One week after dismissal, the patient showed marked symptomatic improvement and improved atelectasis and effusions on chest radiographs. At 6-month follow-up, our patient's kidney function had substantially improved, with a creatinine level of 1.0 mg/dL and an eGFR of more than 60 mL/min per 1.73m^2. He still had nephrotic-range proteinuria (total protein excretion, 3.9 g/24 h), which, in patients with membranous nephropathy, may persist for months after clinical remission has been achieved because of subepithelial complexes that are hard to remove.

DISCUSSION

Clinically evident renal disease may be present in up to 75% of patients with SLE, commonly presenting soon after diagnosis (6-36 months).

Lupus nephritis occurs as a consequence of immune complex–mediated glomerular disease consisting of DNA-anti-DNA deposits; the pattern of glomerular injury depends on the site of formation and degree of deposition. On the basis of clinicopathology, lupus nephritis has been categorized into 6 classes.[8]

Patients with lupus nephritis classes I and II (with predominantly mesangial involvement) have excellent renal prognoses and require no specific therapy. Patients with classes III and IV (focal and diffuse proliferative glomerulonephritis) are treated with immunosuppressive therapy consisting of corticosteroids in combination with cyclophosphamide. Alternative medications, less toxic than cyclophosphamide, may be considered, such as mycophenolate,[5] azathioprine, tacrolimus, cyclosporine, and rituximab.[9] In patients with membranous lupus nephritis who were treated with immunosuppressive therapy, the 10-year kidney survival rate has been reported to be as high as 93%.[10] The benefits of immunosuppressive therapy must be carefully balanced against toxicity. Once remission is achieved, high-dose induction therapy is followed by a less toxic maintenance regimen. Patients with class VI lupus nephritis show extensive sclerotic changes and are therefore usually not considered for immunosuppressive therapy.

Other nonimmunologic therapies include ACE inhibitors or angiotensin II receptor blockers for their antihypertensive and antiproteinuric effects that may slow progression to end-stage renal disease, lipid-lowering agents, and long-term anticoagulation therapy for patients with a history of thromboembolism.

Prompt diagnosis and initiation of treatment have been associated with improved outcome regardless of histologic subtype.[11]

REFERENCES

1. Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents [editorial]. *N Engl J Med*. 1994;331(21):1449-1450.

2. Smith RC, Verga M, McCarthy S, Rosenfield AT. Diagnosis of acute flank pain: value of unenhanced helical CT. *AJR*. 1996;166(1):97-101.

3. Mannaerts L, Van der Wurff AA, Wolfhagen FH. Intersitial nephritis attributed to treatment with piperacillin-tazobactam and with ciprofloxacin [in Dutch]. *Ned Tigdschr Geneeskd*. 2006;150(14):804-807.

4. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25(11):1271-1277.

5. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*. 2005; 353(21):2219-2228.

6. Weening JJ, D'Agati VD, Schwartz MM, et al; International Society of Nephrology and Renal Pathology Society Working Group on the Classification of Lupus Nephritis. The classification of glomerulonephritis in systemic lupus erythematosus revisited [published correction appears in *Kidney Int*. 2004;65(3):1132]. *Kidney Int.* 2004;65(2):521-530.

7. Kimura M, Tanaka S, Ishikawa A, Endo H, Hirohata S, Kondo H. Comparison of trimethoprim-sulfamethoxazole and aerosolized pentadmidine for primary prophylaxis of *Pneumocystis jiroveci* pneumonia in immunocompromised patients with connective tissue disease. *Rheumatol Int.* 2008 May;28(7):673-676. Epub 2007 Dec 14.

8. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited [published correction appears in *J Am Soc Nephrol*. 2004;15(3):835-836]. *J Am Soc Nephrol*. 2004;15(2):241-250.

9. Thatayatikom A,White AJ. Rituximab: a promising therapy in systemic lupus erythematosus. *Autoimmun Rev*. 2006 Jan;5(1):18-24. Epub 2005 Jun 13.

10. Pasquali S, Banfi G, Zucchelli A, Moroni G, Ponticelli C, Zucchelli P. Lupus membranous nephropathy: long-term outcome. *Clin Nephrol.* 1993; 39(4):175-182.

11. Faurschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *J Rheumatol*. 2006;33(8):1563-1569.

Correct answers: 1. *e*, 2. *d*, 3. *a*, 4. *d*, 5. *b*