# 65-Year-Old Woman With Shortness of Breath and Dark Urine

Ming Y. Lim, MBBChir* and Eddie L. Greene, MD†

A 65-year-old previously healthy woman presented to her primary care physician with a 6-week history of increasing dyspnea, accompanied by a dry cough, fatigue, malaise, and poor appetite. Before her initial presentation and the onset of the aforementioned symptoms, she had attributed her illness to an upper respiratory tract infection. She also reported a 1-week history of passing dark urine and had been treated empirically 2 weeks previously with a 3-day course of oral trimethoprim-sulfamethoxazole for presumptive urinary tract infection. At the time of presentation, she denied any other constitutional symptoms, recent travel, medication changes (except for the trimethoprim-sulfamethoxazole), and animal or occupational exposure. Her medical history was remarkable for hypertension, hypothyroidism, diverticulosis, and peptic stricture in the gastroesophageal junction status after a balloon dilatation. Her medications included aspirin (81 mg/d), atenolol (50 mg/d), chlorthalidone (25 mg/d), lisinopril (20 mg/d), elemental iron (65 mg twice daily), levothyroxine (112 μg/d), calcium, and vitamin D tablets. The patient was a nonsmoker. Her family history was remarkable for cholangiocarcinoma in both her father and her son.

Initial laboratory studies yielded the following results (reference ranges provided parenthetically for abnormal values): hemoglobin, 8.4 g/dL (12.0-15.5 g/dL); leukocytes, 12.3 × $10^9$/L (3.5-10.5 × $10^9$/L); platelet count, 449 × $10^9$/L; prothrombin time, 12.5 s (8.3-10.8 s); serum sodium, 131 mmol/L (135-145 mmol/L); potassium, 3.9 mmol/L; creatinine, 4.8 mg/dL (0.6-1.1 mg/dL); blood urea nitrogen, 56 mg/dL (6-21 mg/dL); chloride, 95 mmol/L (100-108 mmol/L); bicarbonate, 23 mEq/L; calcium, 9.6 mg/dL; and glucose, 97 mg/dL. Findings on liver function tests were as follows: aspartate aminotransferase, 29 IU/L; alanine aminotransferase, 21 IU/L; total and direct bilirubin, 0.2 mg/dL and 0.1 mg/dL, respectively; albumin, 3.5 g/dL; and total protein, 6.6 g/dL.

Because previous serum creatinine values had been in the normal range, the patient was admitted to her local hospital for further work-up for acute renal failure. On admission she was hemodynamically stable and her vital signs were as follows: blood pressure, 134/78 mm Hg; heart rate, 70 beats/min; and respiratory rate, 22 breaths/min on room air. On physical examination, the patient was afebrile, alert, and oriented. There was mild conjunctival pallor. Cardiac examination revealed a normal $S_1$ and $S_2$ with a 2/6 holosystolic nonradiating murmur loudest at the apex, no additional rubs, and no jugular venous distension. Lungs were clear to auscultation except for bibasilar inspiratory crackles. The remainder of the physical examination findings were unremarkable. Chest radiography showed mild cardiomegaly, pulmonary venous hypertension, and small bilateral pleural effusions with bibasilar atelectasis.

A urinalysis demonstrated 4 to 10 white blood cells per high-power field (hpf) (1-10/ hpf) and 51 to 100 red blood cells (RBCs)/hpf (<3/hpf), with less than 25% noted to be dysmorphic, accompanied by occasional granular casts. The predicted urinary protein value was 3281 mg/24 hours. The urine sample was orange and cloudy.

***1. On the basis of the available clinical information, which <u>one</u> of the following is <u>least likely</u> to be a cause of this patient's acute renal failure?***

***a.*** *Glomerulonephritis*
***b.*** *Nephrotic syndrome*
***c.*** *Acute tubular necrosis*
***d.*** *Pyelonephritis*
***e.*** *Genitourinary malignancy*

The constellation of hematuria with dysmorphic RBCs, proteinuria, and cellular casts is commonly associated with glomerulonephritis, especially the presence of RBCs, which are virtually pathognomonic. However, the initial absence of substantial numbers of dysmorphic urinary RBCs in our patient does not exclude this diagnosis.

The predicted 24-hour urinary protein level was greater than 3 g. Nephrotic syndrome could be a cause; however, the patient's plasma albumin level was near normal. A 24-hour urinary protein collection should be obtained to accurately quantify urinary protein excretion.

In acute tubular necrosis, the urinalysis usually reveals muddy brown granular and epithelial cell casts as well as renal tubular epithelial cells caused by sloughing of the renal tubules in the urine. However, the absence of these urinary findings does not necessarily exclude acute tubular necrosis.

Pyelonephritis can present with hematuria and could be a consideration if the patient's recent history of a urinary tract infection was inadequately treated. Given the absence of pyuria, fever, and/or flank pain, this would be the least likely cause for acute renal failure in this patient.

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

See end of article for correct answers to questions.

Individual reprints of this article are not available. Address correspondence to Eddie L. Greene, MD, Division of Nephrology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (greene.eddie@mayo.edu).

Genitourinary malignancies can present with painless hematuria, and the patient's anemia might also raise the suspicion for this possibility. Malignancies involving the renal pelvis or ureter can cause obstruction of the ureter or ureteropelvic junction; however, pain may be minimal or absent because they are usually slowly developing obstructive lesions. Urinary tract obstruction can lead to hydronephrosis and eventually renal failure, which was a possibility in our patient.

The patient underwent ultrasonography of her renal system to rule out postobstructive causes of acute renal failure. Ultrasonographic findings were negative for hydronephrosis, and both kidneys were of normal size. Findings on computed tomography of her abdomen and pelvis without contrast agent were unremarkable.

***2. Given the clinical presentation, laboratory findings, and radiologic evaluation, which <u>one</u> of the following would be the <u>most appropriate</u> diagnostic test to perform next?***

***a.*** *Erythrocyte sedimentation rate (ESR)*
***b.*** *Autoimmune serologies*
***c.*** *Renal biopsy*
***d.*** *Echocardiography*
***e.*** *Serum and urine protein electrophoresis (SPEP and UPEP)*

Although ESRs are acute phase reactants and can act as sensitive markers of an inflammatory process, they are not specific to any particular disease. Furthermore, ESRs can be falsely elevated in anemic patients.

In addition to acute renal failure, our patient had nonspecific constitutional symptoms of fatigue, malaise, and anorexia, which might suggest a systemic inflammatory process, such as vasculitis. To make the diagnosis, serologic studies investigating an autoimmune process would be most helpful in this instance because they can facilitate a quicker diagnosis and also assist in guiding initial therapy.

The renal biopsy can also be helpful in narrowing the differential diagnosis and in determining the degree of disease severity, activity, and/or chronicity, which can help guide therapy. Renal biopsy would be appropriate if autoimmune serologies were not diagnostic or readily available.

The patient's history of exertional dyspnea, a holosystolic murmur, and chest radiographic findings would be suggestive of a valvular process, which can precipitate pulmonary edema. Echocardiography would be helpful to evaluate for cardiac and/or valvular dysfunction. In our patient, it was surmised that the volume overload was most likely caused by her acute renal failure and accompanying oliguria.

In patients presenting with anemia and acute renal failure, SPEP and UPEP can be useful diagnostic tests to exclude multiple myeloma or light-chain disease. As our patient had normal levels of calcium and total protein, this diagnosis is less likely, and therefore the SPEP and UPEP would not be the most appropriate diagnostic tests to perform next.

Autoimmune serologic tests were performed; however, while awaiting results, it was noted that the patient's renal function progressively deteriorated and was subsequently accompanied by anuria. A temporary dialysis catheter was placed in the right internal jugular vein to initiate renal replacement therapy with hemodialysis. The decision was made to proceed with an ultrasonography-guided renal biopsy to obtain a definitive nephropathologic diagnosis.

The patient's serologic findings were strongly positive for anti–glomerular basement membrane (anti-GBM) antibodies (>8.0 U [<1.0 U]) but negative for antinuclear antibodies, myeloperoxidase antibodies, and antiproteinase 3 antibodies. Hepatitis B and C serologies were negative, and total complement, C3, and C4 levels were normal.

***3. Given the serologic findings, which <u>one</u> of the following is <u>most likely</u> to be identified on renal biopsy in this patient?***

***a.*** *Loss of podocyte foot processes on electron microscopy*
***b.*** *Diffuse cellular proliferation and hump-shaped subepithelial deposits within the glomerulus on light microscopy*
***c.*** *Linear deposition of IgG antibodies along the GBM on immunofluorescence microscopy*
***d.*** *Granular deposits of IgG and C3 within the glomerulus on immunofluorescence microscopy*
***e.*** *Increased mesangial expansion and deposition of IgA antibodies in the glomerulus on immunofluorescence microscopy*

The loss of glomerular podocyte foot processes observed on electron microscopy is characteristic of diseases such as minimal change disease (MCD) and/or focal segmental glomerulosclerosis (FSGS). In both diseases there is loss of the normal charge barrier accompanied by selective leakage of albumin and other proteins, resulting in varying levels of proteinuria. Patients with MCD rarely present with acute renal failure, and those with FSGS do not typically present with severe hematuria. Therefore, both MCD and FSGS were unlikely and did not fit clinically with the initial presentation in our patient.

The appearance of diffuse cellular proliferation and hump-shaped subepithelial deposits in the glomerulus on light microscopy is usually observed in patients with membranous glomerulonephritis, one of the most common causes of nephrotic syndrome in adults. However, similar to FSGS, membranous glomerulonephritis does not usually present with severe hematuria and would therefore be an unusual finding in our patient.

The immunofluorescence pattern of linear IgG antibody deposition along the GBM is characteristic of anti-GBM dis-

ease (Goodpasture syndrome), which would be the most likely finding in this patient with positive anti-GBM antibodies and her clinical presentation.

Granular deposition of IgG and C3 in the glomerulus is suggestive of postinfectious glomerulonephritis, which would fit the clinical history of our patient. However, it is associated with low complement levels and would be unlikely in our patient with normal complement levels and positive anti-GBM antibodies.

Mesangial deposition of IgA antibodies on immunofluorescence microscopy occurs in IgA nephropathy (Berger disease) and is the most common cause of glomerulonephritis globally. The hematuria in IgA nephropathy commonly occurs during a viral illness, which would fit the clinical history of our patient. However, given the positive anti-GBM antibodies, this diagnosis would be less likely in our patient.

The patient's renal biopsy revealed an aggressive and severe crescentic glomerulonephritis with extensive necrotizing lesions on light microscopy. Specifically noted were rupture of the Bowman capsule and periglomerular inflammation in many glomeruli. Significant tubulointerstitial disease was also present based on findings of a cellular infiltrate (mononuclear cells, neutrophils, and eosinophils), RBC casts, and accompanying tubular atrophy. Glomerular immunofluorescence studies demonstrated linear staining for anti-IgG along the GBM, confirming the diagnosis of anti-GBM antibody–mediated glomerulonephritis. Intravenous pulse methylprednisolone (1000 mg/d) was initiated.

***4. In addition to high-dose corticosteroids, which <u>one</u> of the following is the <u>most appropriate</u> treatment regimen?***

***a.*** *Methotrexate and plasmapheresis*
***b.*** *Methotrexate and intravenous immunoglobulin*
***c.*** *Tacrolimus and plasmapheresis*
***d.*** *Cyclophosphamide and plasmapheresis*
***e.*** *Cyclophosphamide and intravenous immunoglobulin*

To date, methotrexate and tacrolimus have had limited or minimal role(s) in the management of anti-GBM disease. The primary treatment modality for anti-GBM disease has been plasmapheresis combined with prednisone and cyclophosphamide. The rationale for this approach is that plasmapheresis rapidly removes the circulating pathogenic antibodies, cyclophosphamide prevents further antibody production, and corticosteroids act as anti-inflammatory agents.

Intravenous immunoglobulin may be used to partially replenish antibody levels if patients develop a severe infection while undergoing plasmapheresis. Because our patient had no clinical evidence of ongoing infection, intravenous immunoglobulin therapy was not indicated.

The patient was transferred to our institution for initiation of plasmapheresis. On her transfer here, she began receiving oral cyclophosphamide therapy at 2 mg/kg daily. Plasmapheresis was initiated with plans for daily therapy for 14 days.

***5. While undergoing this treatment modality, which <u>one</u> of the following medications should be <u>withheld</u>?***

***a.*** *Aspirin*
***b.*** *Levothyroxine*
***c.*** *Chlorthalidone*
***d.*** *Elemental iron*
***e.*** *Lisinopril*

Aspirin, levothyroxine, chlorthalidone, and elemental iron can be safely administered in patients undergoing plasmapheresis. However, because plasmapheresis is nonselective, these medications should not be administered immediately before plasmapheresis. Instead, these medications should have their dosing times changed and administered after plasmapheresis.

In patients receiving angiotensin-converting enzyme (ACE) inhibitors, symptoms of severe hypotension, flushing, and abdominal cramping have been reported during plasmapheresis. Blood contact with the negatively charged plastic of the plasmapheresis kit has been shown to result in the production of bradykinin.[1] Physiologically, bradykinin is rapidly degraded by kininase. However, in the presence of ACE inhibitors, kininase activity is blocked, resulting in high levels of bradykinin and related adverse effects of severe hypotension, facial flushing, and abdominal pain. One study of 299 consecutive patients undergoing plasmapheresis showed that all 14 patients (100%) receiving ACE inhibitors at the time of plasmapheresis reported these symptoms.[2] In contrast, only 20 (7%) of 285 patients not receiving ACE inhibitors reported these symptoms. Thus, ACE inhibitors should ideally be withheld in patients undergoing plasmapheresis.

After 3 days of pulse methylprednisolone, the patient was transitioned to oral prednisone (60 mg/d). Plasmapheresis was stopped prematurely after 8 days of treatment because of possible acute cardiac-related disturbances. The patient received maintenance immunosuppressive therapy and continued maintenance dialysis throughout her hospital stay. She was discharged to the care of her local nephrologist for outpatient dialysis and management of her anti-GBM disease. At the time of discharge, in addition to immunosuppressive therapy, the patient received oral trimethoprim-sulfamethoxazole as prophylaxis for *Pneumocystis* pneumonia, oral mesna for prevention of hemorrhagic cystitis, calcium and vitamin D supplementation for prophylaxis against corticosteroid-induced osteoporosis, fluconazole for fungal infection prophylaxis, and omeprazole for gastritis prophylaxis.

Because of a limited response to therapy, cyclophosphamide was discontinued after 2 months while prednisone was slowly tapered until discontinuation. At follow-up 4 months later, the patient remained dependent on dialysis.

## DISCUSSION

Anti-GBM disease is a rare disorder with an estimated incidence of about 1 patient per million population. It is due to an autoimmune response to the noncollagenous domain (NC1) of the α3 chain of type IV collagen,[3] a major component of the GBM.

Most patients present with the combination of rapidly progressive glomerulonephritis and pulmonary hemorrhage, although 30% to 40% of patients present with isolated renal involvement, as in our patient.[4] Rarely, pulmonary involvement predominates in the setting of a normal initial level of serum creatinine,[5] reminding the clinician that anti-GBM disease should also be considered in any patient presenting with alveolar hemorrhage.

The diagnosis is usually made via detection of anti-GBM antibodies in the serum using a direct enzyme-linked immunoassay. Although the presence of anti-GBM antibodies is sufficient to initiate treatment, a renal biopsy is usually recommended because it allows a careful assessment of the extent and severity of glomerular and tubular injury, both of which may help to guide therapy.

Left untreated, patients with anti-GBM disease have a poor outcome, with increased morbidity and/or mortality linked to renal failure or pulmonary hemorrhage. The introduction of combined treatment with corticosteroids, cyclophosphamide, and plasmapheresis in the 1970s changed the approach to therapy and altered what had previously been poor outcomes in patients with the disease.[6] At least 1 randomized controlled trial of 17 patients compared outcomes in patients treated with prednisone and cyclophosphamide alone, or in combination with plasmapheresis.[7] In this study, the rate of clearance of anti-GBM antibody was substantially increased in patients receiving plasmapheresis, suggesting a trend toward better outcome in patients receiving corticosteroids, cytotoxic therapy, and plasmapheresis. According to the American Society for Apheresis, plasmapheresis is currently considered a standard and accepted primary treatment modality for anti-GBM disease (category I indication).[8]

It may be worth considering the initiation of empiric therapy with intravenous pulse methylprednisolone if clinical suspicion is high, particularly if there is a delay in obtaining anti-GBM levels and/or interpreting the renal biopsy. Starting empiric therapy will not necessarily alter the histologic abnormalities observed in the renal biopsy.

The duration of treatment is based on clearance of anti-GBM antibody. Plasmapheresis is usually successful in reducing anti-GBM antibody levels to near normal limits within 2 weeks of treatment but can be continued for longer if anti-GBM antibodies are still detectable. Serial measurement of anti-GBM antibody should be performed weekly during plasmapheresis, and then every 2 weeks, until they are negative on 2 occasions. After remission, maintenance immunosuppressive medications should be continued for at least 2 months and then slowly tapered until discontinuation. Periodically, anti-GBM levels should be monitored to confirm that remission is maintained.

Relapse is rare but has been reported.[9] Relapses are more likely in patients who are also positive for antineutrophil cytoplasmic antibodies, in whom vasculitis and not the anti-GBM disease is reactivated.[10]

With current therapeutic strategies, the 1-year survival rate for anti-GBM disease is around 77%, with a wide range from 65% to 100%, depending on the severity of disease and renal function on presentation.[11] However, renal recovery is less common and depends on renal function at the initiation of therapy. In a British study of 71 patients with anti-GBM disease,[11] those who presented with a serum creatinine concentration of less than 5.7 mg/dL had a 95% chance of retaining independent renal function at 1-year follow-up. This percentage dropped to 82% in patients who presented with a serum creatinine concentration of more than 5.7 mg/dL but who did not require dialysis immediately. In patients requiring immediate dialysis on presentation, 8% or fewer regained enough renal function to be independent of dialysis at 1 year. These data highlight the importance of making an early diagnosis and starting aggressive treatment because renal function recovery and outcome are tightly linked to renal function at the start of treatment.

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