



69-Year-Old Man With Nasal Congestion and Pre-Syncope

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See end of article for correct answers to questions.

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A 69-year-old man with a past medical history consisting only of benign prostatic hyperplasia (BPH) presented to his primary care physician complaining of pre-syncope episodes in the setting of a sinus infection lasting greater than 1 month. The patient was taking doxazosin for BPH and occasional ibuprofen for pain related to his sinus infection. He denied any new urinary symptoms such as dysuria or hematuria. He reported no changes in his dietary habits. Vital signs were blood pressure 124/76 mm Hg, pulse 84 beats/min, respiratory rate 14 breaths/min, temporal temperature 36.3 °C, height 173 cm, and weight 78.2 kg. Physical exam showed an approximately 30-g smooth and symmetrical prostate without nodules or tenderness and a normal genitourinary exam. Nasal passages were congested with yellow mucus. No bloody nasal discharge, ulcerations, or nasal crusting was appreciated. Cardiac and lung examinations were unremarkable. Orthostatic vital signs were negative. Initial laboratory work-up revealed the following (reference ranges provided parenthetically): Complete blood count with differential showed hemoglobin, 12.0 g/dL (13.2 to 16.6 g/dL); mean corpuscular volume, 90.1 fL (78.2 to 97.9 fL); platelets $196 \times 10^9/L$ (135 to $317 \times 10^9/L$); white blood cells, $7.5 \times 10^9/L$ (3.4 to $9.6 \times 10^9/L$); and eosinophils, $0.16 \times 10^9/L$ (0.03 to $0.48 \times 10^9/L$). Thyroid stimulating hormone was 2.8 mIU/L (0.3 to 4.2 mIU/L). Prostate-specific antigen was 1.9 ng/mL (0.0 to 4.0 ng/mL). Basic metabolic panel revealed sodium 137 mmol/L (135 to 145 mmol/L); potassium, 5.3 mmol/L (3.6 to 5.2 mmol/L); chloride, 99 mmol/L (98 to 107 mmol/L); bicarbonate, 26 mmol/L (22 to 26 mmol/L); blood urea nitrogen, 28 mg/dL (7 to 20 mg/dL);

creatinine, 1.74 mg/dL (0.74 to 1.35 mg/dL); and glucose, 119 mg/dL (70 to 99 mg/dL). C-reactive protein was 74.9 mg/L (≤ 8.0 mg/L). The patient's baseline creatinine was 1.1 mg/dL obtained 3 months prior. Chest x-ray and electrocardiogram were unremarkable.

1. In addition to urinalysis with microscopy, what is the next best step for evaluating this patient's kidney injury?
 - a. Computed tomography (CT) urogram
 - b. Obtain urine culture
 - c. Stop doxazosin
 - d. Stop ibuprofen
 - e. Advise patient to drink at least 2 L of liquid daily and follow-up if symptoms worsen

Obtaining urinalysis with microscopy is an essential step in evaluating the patient with unexplained renal insufficiency. Obtaining a CT urogram would be inappropriate at this time as the patient does not have any signs or symptoms of nephrolithiasis or documented hematuria. A patient without new urinary symptoms should not be evaluated with urine culture, as approximately 9% of older adult men will have a positive urine culture indicative of colonization, rather than infection.¹ Doxazosin is not typically associated with renal injury as it is hepatically metabolized and often improves renal blood flow by vasodilatory effect of competitive inhibition of α_1 -adrenergic receptors. The patient should be instructed to stop ibuprofen as 1% to 5% of patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) experience adverse renal events through vasoconstriction of afferent renal arterioles as a result of inhibition of prostaglandin synthesis by NSAIDs.² In a patient experiencing renal

injury of unknown etiology, increasing fluid intake to at least 2 L of liquid daily is a reasonable approach, as dehydration causing prerenal injury is a possible cause of this patient's kidney injury; however, the more likely explanation is NSAID-induced renal injury in this patient without known risk factors for dehydration.

The patient was advised to stop ibuprofen. He further complained of ongoing pre-syncopal episodes, particularly while at religious services where he would go from a sitting to standing position repeatedly.

2. What next step would reduce this patient's risk for orthostasis?

- Referral to neurology for autonomic dysfunction testing
- Stop doxazosin and initiate tamsulosin
- Initiate finasteride
- Apply compression stockings and abdominal binder
- Increase salt and water intake

The patient has not yet tried modification of their medications and nonpharmacologic measures, such as compression stockings and dietary changes to help resolve orthostasis. Thus, referral to a neurologic specialist for autonomic dysfunction to elucidate the cause of his episodes of orthostasis is inappropriate at this time. Stopping doxazosin and initiating alternate therapy would be the best first approach. Doxazosin is less selective for prostate α_1 -adrenergic receptors and therefore is more likely to cause hypotension than tamsulosin. Finasteride is not as effective in treating the symptoms of BPH as α_1 -adrenergic blockade and adding finasteride to doxazosin would be unlikely to improve the orthostatic side effects,³ making stopping doxazosin and initiating tamsulosin the superior option. Patients with orthostatic hypotension benefit from compression stockings and abdominal binders,⁴ and this could be trialed if modification of medical therapy does not lead to improvement in pre-syncopal episodes. Increasing salt and water in the diet would be inappropriate in this patient with unexplained renal insufficiency.

Urinalysis showed protein/osmolality ratio of 1.14 (<0.42) predicting a proteinuria of 1 g over 24 hours, and >100 red blood cells (RBCs) (0-3) with no dysmorphic RBCs. Three weeks later, the patient returned for re-evaluation. His sinus infection had not resolved. He had not developed any new urinary symptoms. Repeat urinalysis showed worsening proteinuria and 51 to 100 RBCs without dysmorphic RBCs, casts, or eosinophils. Repeat basic metabolic panel showed creatinine of 2.60 mg/dL. Hemoglobin had decreased from 12.0 g/dL to 9.7 g/dL. A retroperitoneal ultrasound was obtained with unremarkable findings. A non-contrast CT scan of the head obtained for pre-syncope evaluation showed polypoid mucosal thickening in the bilateral maxillary sinuses. A 24-hour Holter monitor was unremarkable. The patient declined echocardiogram due to cost.

3. What test will best establish this patient's diagnosis and determine therapy?

- Antinuclear antibody and anti-double-stranded DNA antibodies
- Complement levels (CH50, C3, C4)
- Antineutrophil cytoplasmic antibodies (ANCA) panel
- Renal biopsy
- HIV, hepatitis B and C serology

Given this patient's rapidly progressing renal failure over the course of 3 weeks, with evidence of hematuria and significant proteinuria, concern is high for rapidly progressive glomerulonephritis (RPGN). As eosinophilia was not present on urinalysis or complete blood count with differential, the patient's acute kidney injury (AKI) is inconsistent with acute interstitial nephritis. As a result, serology studies are an important part of the initial workup. Antinuclear antibody and anti-double-stranded DNA antibodies would be useful for identifying lupus nephritis, but would be unlikely to be positive in a patient without other features of systemic lupus erythematosus. Similarly, complement levels (specifically CH50, C3, and C4) would be appropriate for helping to identify post-streptococcal glomerulonephritis or lupus nephritis; however, this

would be insufficient to establish a diagnosis in this patient without other features suspicious for these diagnoses. Sinus involvement in this patient with RPGN is concerning for ANCA-associated vasculitis. As a result, an ANCA panel could help both support the diagnosis of ANCA-associated vasculitis and identify the subtype of ANCA-associated vasculitis. All of the above serologies should be obtained as part of the initial workup of a patient with RPGN, but given the severity of RPGN, a renal biopsy is the most critical test to obtain in a timely manner to establish the diagnosis in this patient. Thus, renal biopsy should be pursued to establish the diagnosis of ANCA-associated vasculitis with RPGN and begin treatment.⁵ Finally, HIV and hepatitis viral serologies should be obtained in patients with glomerulonephritis; however, a biopsy would be more appropriate to establish the diagnosis in this patient with a clinical syndrome more consistent with ANCA-associated vasculitis.

Renal biopsy showed a focal segmental necrotizing and crescentic glomerulonephritis consistent with pauci-immune vasculitis. Three of 11 glomeruli obtained on biopsy were globally sclerotic. Serologies returned with positive perinuclear-ANCA and positive myeloperoxidase antibody at greater than 8 (positive ≥ 1 U, negative < 0.4 U). A diagnosis of microscopic polyangiitis was made. The patient continued to make adequate amounts of urine and electrolytes were unremarkable despite creatinine rising to a peak of 2.68 mg/dL.

4. What is the best initial therapy for this patient's condition?

- a. Glucocorticoids and rituximab or cyclophosphamide
- b. Therapeutic plasma exchange
- c. Hemodialysis
- d. Intravenous immunoglobulin
- e. Methotrexate

Initial management of RPGN in patients with ANCA-associated vasculitis is directed

at immunosuppression with glucocorticoids and a steroid-sparing agent to induce remission of the disease process and to prepare for immunosuppression longer term without steroids.⁵ First, the disease should be classified based on severity. Mild cases without evidence of end-organ damage (eg, rising creatinine, progressive neuropathy, neurologic impairment, gastrointestinal bleeding, or carditis) benefit from glucocorticoids alone or glucocorticoids in conjunction with methotrexate. Moderate cases with evidence of end-organ damage, such as this patient, benefit from glucocorticoids and rituximab or cyclophosphamide. The most severe cases with concomitant anti-glomerular basement membrane, end-organ failure, or pulmonary hemorrhage may benefit from therapeutic plasma exchange, although this strategy is controversial. Notably, a recent clinical trial did not show mortality benefit or reduction in the development of end-stage renal disease (ESRD).^{5,6} Hemodialysis in patients with RPGN is indicated based on standard indications for dialysis such as severe electrolyte abnormalities. The patient did not meet criteria for therapeutic plasma exchange or hemodialysis. Intravenous immunoglobulin is not indicated in the treatment of ANCA-associated vasculitis. The combination of glucocorticoids and methotrexate would be sufficient for mild cases but methotrexate alone is generally not sufficient for the initial treatment of ANCA-associated vasculitis.

The patient was given 2 g of methylprednisolone intravenously followed by oral prednisone 60 mg daily, and began induction therapy with rituximab 375 mg/m² for 4 weeks. Proteinuria and hematuria resolved 3 months after his initial presentation. Sinus congestion and pre-syncopal episodes also resolved at follow-up. The pre-syncopal episodes were believed to be multifactorial with doxazosin, anemia, and chronic illness each contributing, supported by the fact that the patient's episodes resolved with treatment of the underlying vasculitis and discontinuation of doxazosin. Pre-syncope is an

uncommon presentation of ANCA-associated vasculitis but warrants comprehensive workup.

5. What infectious prophylaxis does this patient need?

- a. Penicillin
- b. Fluoroquinolone
- c. Valacyclovir
- d. Trimethoprim-sulfamethoxazole
- e. Fluconazole

Penicillin antibiotic prophylaxis is occasionally used in asplenic or hyposplenic patients who are at high risk for severe infections or history of sepsis caused by encapsulated bacteria. Fluoroquinolones are the alternative option for those asplenic patients at high risk for severe infection with encapsulated bacteria and allergic to penicillins. Valacyclovir prophylaxis is recommended for patients requiring hematopoietic cell transplantation or acute leukemia induction chemotherapy.⁷ Pneumocystis pneumonia (PCP) prophylaxis with trimethoprim-sulfamethoxazole is critical in a patient anticipated to be on glucocorticoids and another immunosuppressive agent for greater than 1 month due to the high mortality rate associated with this infection. The US Food and Drug Administration recommends patients receiving rituximab for maintenance therapy of ANCA-associated vasculitis should also receive PCP prophylaxis during treatment and for at least 6 months following the last rituximab infusion.⁸ Fluconazole prophylaxis is indicated for the prevention of *Candida* infections in patients with hematologic malignancies.⁷

The patient was concurrently started on PCP prophylaxis. A slow prednisone taper was begun and the patient remained in remission on rituximab at 1-year follow-up with stable creatinine at 2.7 mg/dL and C-reactive protein less than 3.0 mg/L.

DISCUSSION

The 2012 Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for Acute Kidney Injury (AKI) defined AKI as a rise in the serum creatinine concentration

or an abnormal urinalysis that has developed within hours to days. Consensus criteria for AKI include an increase in serum creatinine by \geq to 0.3 mg/dL relative to a known baseline value within 48 hours, or an increase to \geq to 1.5 times the known or presumed baseline value within 7 days, or a decrease in urine volume to \leq 3 mL/kg over 6 hours.⁹ According to the US Renal Data System, 21.1% of people age 60 years or older have an estimated glomerular filtration rate \leq 60%, and 4% of Medicare patients aged older than 66 years have had at least 1 AKI hospitalization.¹⁰ As a result, it is critical for the internist to know the common causes of kidney dysfunction in older adults, as well as rare causes that necessitate specialist involvement or targeted therapies.

The differential of worsening renal function in the older adult most commonly includes medication, obstructive uropathy, hypertensive nephropathy, and diabetic nephropathy. Urinalysis is critical when attempting to differentiate common causes of worsening renal function. In patients with microscopic or macroscopic hematuria, mild proteinuria, and red cell casts with worsening renal function, RPGN should be suspected. RPGN will cause ESRD in a matter of weeks to months that represents a medical emergency requiring prompt diagnosis and treatment. Three etiologies of RPGN must be considered. First is anti-glomerular basement membrane disease which is characterized by pulmonary and renal involvement due to auto-antibodies against basement membranes in these organs. Second is the immune-complex glomerulonephritides such as post-streptococcal glomerulonephritis, lupus nephritis, immunoglobulin A nephropathy, and cryoglobulinemia. Third, as in this case, is pauci-immune glomerulonephritis which is seen in association with small-vessel vasculitis, such as ANCA-associated vasculitis.

ANCA-associated vasculitis should be considered in the patient presenting with RPGN. It has an estimated prevalence of 0.01% and ANCAAs are positive in approximately 82% to 94% of diagnosed patients.¹¹

Antineutrophil cytoplasmic antibody-associated vasculitis is a systemic

multiorgan disease of small blood vessels commonly presenting with renal involvement. Other symptoms of ANCA-associated vasculitis include rhinosinusitis (as seen in this patient), peripheral neuropathy, fatigue, fever, weight loss, eye pain, or foreign body sensation. Ear, nose, and throat manifestations are more common in patients with granulomatosis with polyangiitis (90% of patients) than microscopic polyangiitis (35% of patients).¹² Cutaneous manifestations are common with half of patients showing purpura with focal necrosis and ulceration. The clinician must maintain a high index of suspicion for other organ involvement and take care not to miss comorbid conditions that can arise from ANCA-associated vasculitis including peripheral neuropathy and ocular involvement (eg, scleritis, episcleritis) to determine the aggressiveness of immunosuppressive treatment. A careful physical and neurologic examination is required of the patient with suspected ANCA-associated vasculitis. The time course of an affected patient is variable, ranging from days to weeks and months.

Imaging findings are variable, but CT of the sinuses can reveal mucosal thickening and bone destruction in the ANCA-associated vasculitides. Computed tomography of the chest most commonly reveals pulmonary nodules and ground glass opacities.¹² Common laboratory abnormalities beyond a rise in serum creatinine include a generalized inflammatory pattern with thrombocytosis, leukocytosis, normocytic and normochromic anemia, and elevated erythrocyte sedimentation rate and C-reactive protein.⁵

To establish the diagnosis of ANCA-associated vasculitis, biopsy of the affected organ is preferred; however, empiric treatment can be performed in the severely ill patient. Empiric treatment could be initiated for the patient with destructive rhinosinusitis or alveolar hemorrhage. The goal of treatment with immunosuppression with corticosteroids combined with either rituximab or cyclophosphamide is to induce remission and prevent relapse. Plasma exchange therapy is reserved for patients with the most

severe cases, particularly with concomitant anti-glomerular basement membrane antibody, end-organ failure, or pulmonary hemorrhage; although this strategy may not provide mortality benefit or reduction in the number of patients developing ESRD.^{5,6} Patients on immunosuppression should always be started on appropriate infectious prophylaxis for their treatment plan.

Potential Competing Interests: The authors report no competing interests.

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Correct Answers: 1. d. 2. b. 3. d. 4. a. 5. d.