CLINICAL VIGNETTE

A Protean Case of Small Vessel Vasculitis

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A 54-year-old female with diabetes mellitus (DM) type 1 with microalbuminuria and baseline creatinine 1.1 was admitted with acute kidney injury (creatinine of 5.1 at outside lab). The urinalysis microscopy was positive for red blood cells and white blood cells, without dysmorphic cells or casts. The urinary total protein/creatinine ratio was 3.9 g/g with an albumin to creatinine of 2.9 g/g. Recent hemoglobin A1C was 6.7, but recent blood pressure (BP) had been 150-160s. Outpatient medications included ibuprofen, benazepril 80mg per day, and hydrochlorothiazide (HCTZ) 50mg per day. Medical history included osteoarthritis, diabetic retinopathy, hypertension, Hashimoto's thyroiditis, L sided hearing loss ascribed to Meniere disease, and weakly positive testing for ANA and C-ANCA (MPO, PR3 negative) in 2013. She had also been diagnosed with asthma about three years prior, though she reported poor response to bronchodilator therapy. She had no acute complaints and was surprised when she was referred to the hospital because she felt well. Renal ultrasound showed a kidney stone on the right but otherwise normal anatomy. On admission, amlodipine was given, benazepril and HCTZ were stopped. With improvement in creatinine to 4.0, she was discharged home about 36 hours later.

At the post-discharge follow-up appointment 1 week later, her home BPs were 130-140s/60s. She continued to feel well without complaints. Labs showed increased creatinine to 5.0 and positive ANCA, so she was electively admitted for possible ANCA-associated rapidly progressive glomerulonephritis. Pulse methylprednisolone was started, and she underwent kidney biopsy. About 3 days after admission, she developed shortness of breath with mild hypoxemia. CXR and chest CT showed nonspecific infiltrates and old scarring. Bronchoscopy showed normal gross anatomy, cultures, and cytology were sent. Her respiratory insufficiency worsened, and she was intubated on hospital day 6. Repeat bronchoscopy showed diffuse alveolar hemorrhage. Plasmapheresis was started after the bronchoscopy with 1 volume exchange and albumin and fresh frozen plasma as replacement fluid. Respiratory failure improved, and she was extubated on hospital day 9 after 3 plasmapheresis sessions. However that same day, metabolic acidosis worsened; she started hemodialysis and cyclophosphamide 1200mg IV. Dialysis was repeated on hospital day 11, and she continued to receive plasmapheresis. Her renal function then started to recover and plasmapheresis was stopped after 6 sessions. On hospital day 16, she was discharged home with a creatinine of 4.6 and off oxygen. The final kidney biopsy showed pauci-immune glomerulonephritis with crescents in about 25% of glomeruli, early diabetic nephropathy, and moderate chronic changes. All respiratory cultures were negative, but the cytology from the bronchoscopy showed hemosiderin-laden macrophages (suggestive of diffuse alveolar hemorrhage). Repeat ANCA before discharge was negative.

After discharge, she has felt very well with no complaints. She remains on cyclophosphamide every 2 weeks and creatinine improved to 3.5 (peak of 5.1), urine protein/creatinine ratio has decreased to 2.5, and microhematuria has resolved. ANCA remains negative and C-reactive protein has normalized.

ANCA-associated small vessel vasculitis (SVV) causes inflammation of small- to medium-sized vessels, leading to ischemic necrosis in the tissues supplied by the affected vascular beds. It is characterized by circulating antibodies, first identified in 1982, active against neutrophil granules, which have a direct role in pathogenesis of the diseases.[1] Necrotizing vascular inflammation with scant immune deposition characterizes biopsy samples.[2] The most common clinical manifestations are renal (pauci-immune crescentic GN; 80-90%), pulmonary (pulmonary hemorrhage; 50-90%), musculoskeletal (myalgias and arthralgias; 60%), upper airway and ENT (35-90%), gastrointestinal (50%), neurologic (mononeuritis multiplex; 30-50%), cutaneous (purpura caused by leukocytoclastic vasculitis; 40%), and constitutional (15-75%).[1,3,4]

Because ANCA-associated SVV can affect many different vascular beds, the clinical manifestations are highly variable. There is considerable overlap between vasculitis syndromes, making classification difficult, part of the impetus for the creation of multiple classification schemes in the literature. The Chapel Hill Consensus Conference in 1994 helped standardize the definition of vasculitis for research purposes, including delineation of microscopic polyangiitis.[5,6] The European Medicines Agency developed additional classification criteria in 2007, which expanded upon the Chapel Hill Consensus Conference and earlier classification schemes.[7] However, there are still no universally accepted clinical diagnostic criteria for these diseases.[8]

The ANCA SVVs are uncommon with an estimated annual incidence of about 2.5-5 per million for microscopic polyangiitis and 10 per million for Granulomatosis with Polyangiitis in northern European populations.[9] When their variable presentation and lack of accepted diagnostic criteria are taken into account, diagnosis can be difficult and is frequently delayed. Unfortunately, the consequences of

delayed diagnosis can be severe, including renal failure and early mortality in ANCA vasculitis.[10] The patient in this case had more common conditions that otherwise explained the clinical findings including longstanding diabetes (leading to increased creatinine and proteinuria); nephrolithiasis (leading to hematuria); use of medications, which commonly cause acute kidney injury (NSAIDS, ACE inhibitors, diuretics); asthma; and Meniere disease. A high index of suspicion was essential to arrive at the correct diagnosis and treatment.

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Submitted September 30, 2015