CLINICAL VIGNETTE

Finding the Unifying Diagnosis: When Hoofbeats are a Zebra

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Presentation

A 76-year-old female with a past medical history of Crohn's disease, chronic obstructive pulmonary disease (COPD), heart failure with preserved ejection fraction, obesity, hypertension, hypothyroidism, and a 38 pack-year smoking history was hospitalized with a chief complaint of weakness, dizziness, and blurred vision.

Nine months prior, she presented to her primary care physician (PCP) with dyspnea on exertion (DOE). A transthoracic echocardiogram (TTE) revealed diastolic dysfunction with normal pulmonary pressures. At the time, she was non-compliant with her COPD treatment. Despite instruction by her PCP, she did not restart her inhalers and her exertional dyspnea continued.

Three months prior, she presented to her PCP with 10 days of sinus congestion. She reported fatigue, hearing loss, ear pain, tinnitus, and continued DOE. She was treated with amoxicillin-clavulanate for acute bacterial sinusitis and when her symptoms did not improve, she was treated with courses of levofloxacin and doxycycline in addition to intra-nasal glucocorticoids and antihistamines. Her DOE was treated with furosemide and she was repeatedly encouraged to adhere to her inhalers.

Three weeks prior, she was admitted to the hospital with near syncope thought to be due to sepsis. She complained of DOE, sinus congestion, ear pain, hearing loss, and lethargy. Physical exam revealed bilateral conductive hearing loss and opacification of the tympanic membranes. A chest radiograph was concerning for pneumonia with bilateral upper lobe linear and ground glass opacities, more pronounced on the right. Computed tomography (CT) of the sinuses revealed mucosal thickening of the paranasal sinuses with an air-fluid level, aerated secretions in the left sphenoid sinus, and new bilateral mastoid and middle ear effusions (Figure 1). She was treated with intravenous antibiotics for acute bacterial sinusitis, otomastoiditis, and community acquired pneumonia. When her intermittent hypoxemia did not improve with antibiotics, she was treated for a heart failure exacerbation with furosemide. Despite broad-spectrum antibiotics, her leukocytosis persisted around 15 x $10^3/\mu l$ and the otolaryngology service was consulted. The consulting team recommended an extended course (14 days) of antibiotics, prednisone 40mg daily for 5 days, and outpatient myringotomy.

After discharge, her ear pain improved but she continued to endorse dyspnea. Her PCP prescribed furosemide and encouraged compliance with her COPD regimen. A sleep study was ordered given the nocturnal hypoxia during hospitalization.

She was admitted to the case hospitalization two weeks later with weakness, dizziness, and blurred vision.

Assessment

On admission, the patient was tachycardic to 108 beats per minute with an oxygen saturation of 93 percent on room air and a temperature of 99.3 degrees Fahrenheit. Her blood pressure was 141/72 mmHg and her respiratory rate was 16 breaths per minute. Physical exam was significant for left pupillary anisocoria, right nasolabial fold weakness, and 4/5 strength in the left upper and lower extremities with normal sensation. Magnetic resonance imaging of the brain revealed an acute infarct of the left thalamus and midbrain. Laboratory studies were significant for a leukocytosis of 15.9 x $10^3/\mu l$ with neutrophilic predominance and pyuria. Chest radiograph showed a 2.6 cm nodular, mass-like density at the right lung base with perihilar airway thickening and architectural distortion of the right upper lobe. She was treated with empiric antibiotics for a urinary tract infection and right upper lobe pneumonia. Further work-up of acute stroke, including an echocardiogram, was unrevealing.

Later in her hospitalization, she developed fevers, altered mental status, and leukocytosis that were unresponsive to empiric antibiotics. Chest CT showed multifocal consolidations and mediastinal lymph node enlargement. Evaluation for infection with blood, urine, and respiratory cultures was negative, including fungal and acid-fast stains. Inflammatory markers were elevated (ESR 54 mm/hr, CRP 17.8 mg/dL). An endoscopic bronchial ultrasound with biopsy of a mediastinal lymph node revealed multi-nucleated giant cells and negative cultures. Despite empiric antibiotics and supportive treatment, her hypoxemic respiratory failure progressed to require intubation. In the setting of hypotension, she developed an acute kidney injury. Nephrology was consulted when her renal function failed to recover and a urinalysis revealed 2+ hematuria and proteinuria. This prompted further rheumatologic workup, revealing a positive anti-neutrophil cytoplasmic antibody with a perinuclear staining pattern (p-ANCA, titer 1:320), positive anti-neutrophil cytoplasmic antibody with a cytoplasmic pattern (c-ANCA, titer of 1:80), and a positive myeloperoxidase antibody (MPO) of 457.9 CU (positive >=20.0 CU). Proteinase-3 antibody was negative. A kidney

biopsy showed necrotizing vasculitis with giant cells, consistent with granulomatosis with polyangiitis (GPA) (Figures 2, 3).

Diagnosis

Common things being common, her stroke presentation was consistent with an ischemic stroke in a patient with traditional risk factors. Her worsening respiratory status was attributed to pneumonia given her fevers, leukocytosis, and pulmonary consolidations. Lastly, her kidney failure was ascribed to acute tubular necrosis in the setting of severe sepsis. However, after a negative infectious work-up and a lack of clinical improvement with antibiotics, other diagnoses had to be considered. The preceding episodes of sinusitis with subsequent respiratory and kidney failure, together with the supportive laboratory and pathology findings, led to the diagnosis of granulomatosis with polyangiitis.

In retrospect, her initial presentation of dyspnea on exertion and refractory sinusitis were indeed the first manifestations of GPA. Annually, 1 in 7 US adults is diagnosed with acute sinusitis while the prevalence of GPA is only 3 per 100,000.[1,2] According to the 2012 IDSA Clinical Practice Guidelines, patients who fail both first and second line antimicrobial therapies for bacterial sinusitis should have imaging and be further evaluated for non-infectious etiologies.[3] GPA is defined by the 2012 revised Chapel Hill criteria as a necrotizing granulomatous small-to-medium vessel vasculitis involving the upper and lower respiratory tracts.[4] Anti-neutrophil cytoplasmic antibodies (ANCA) are highly associated with GPA, specifically cytoplasmic-staining ANCA (c-ANCA). These antibodies may develop after programmed cell death during the early inflammatory response or possibly by molecular mimicry related to staphylococcus aureus. After antibodies develop, they bind to vascular cell walls causing inflammation and necrosis.[5]

Although c-ANCA is classically associated with GPA, we present a case of p-ANCA associated GPA, which can be seen in up to 10 percent of patients.[6] GPA vasculitis commonly affects the ear, lung, and kidneys (ELK triad), but may manifest in any organ system.[7] Central nervous system (CNS) involvement occurs in about 6 to 13 percent of patients. In hindsight, this patient's stroke was most likely a CNS manifestation of small vessel vasculitis.[1]

Management

The patient was treated with steroids, plasmapheresis, and rituximab. Her hospital course was complicated by an acute gastrointestinal bleed and multiple aspiration pneumonias. Unfortunately, she suffered a cardiac arrest due to an aspiration event and was ultimately transitioned to comfort care. She passed away 17 months after her symptoms of dyspnea began.

GPA is almost always fatal without treatment. However, with treatment (typically steroids plus rituximab or cyclophosphamide, and plasmapheresis for pulmonary hemorrhage or renal failure), about 90 percent of patients attain remission and 80 percent survive at 10 years. However, despite treatment, GPA can result in death in 5 to 12 percent of patients during the first year. Thus, prompt diagnosis and treatment is essential.

Upon reflection, this patient's disease manifestations were each individually explained when taken in isolation: severe sinusitis in a susceptible host, acute hearing loss due to sinusitis, dyspnea from uncontrolled COPD, leukocytosis due to infection, hypoxia due to diastolic dysfunction and sleep apnea, stroke due to cardiovascular risk factors, pyuria due to a urinary tract infection, and acute kidney injury due to sepsis. However in hindsight, a unifying diagnosis was present.

While rare, a diagnosis of GPA should be considered in patients with non-resolving sinusitis, especially if there is evidence of lung or kidney disease. Though common things are indeed common, taking a step back to examine the whole picture, especially for complex patients with fragmented episodes of care, might help to arrive at a unifying diagnosis and even sometimes, a zebra.

Figures

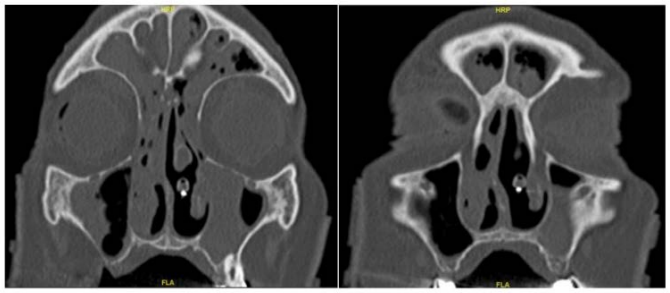

Figure 1. Mucosal thickening of the paranasal sinuses with air-fluid level and aerated secretions in the left sphenoid sinus. New bilateral mastoid and middle ear effusions.

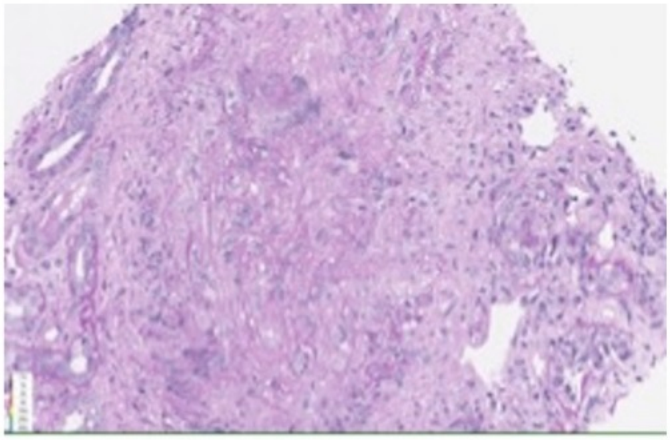

Figure 2. Kidney biopsy section demonstrating fibrinoid necrosis and a giant cell.

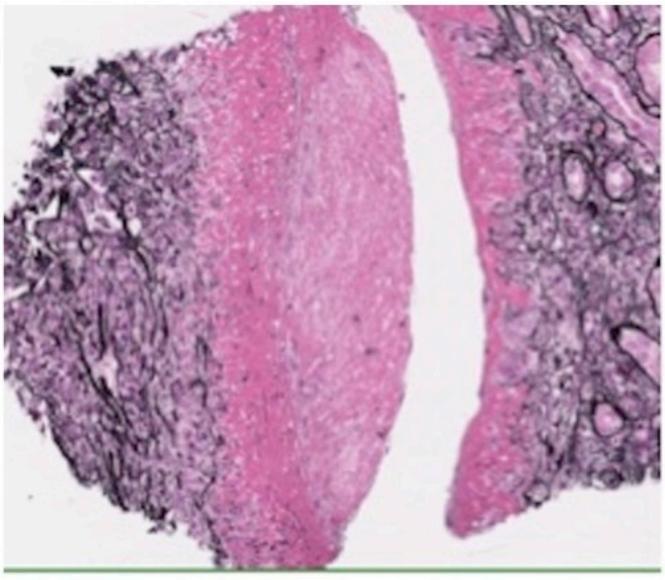

Figure 3. Kidney biopsy section with Jones stain demonstrating fibrinoid necrosis of an intralobuluar artery.

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