CLINICAL VIGNETTE

Eosinophilic Granulomatosis with Polyangiitis (EGPA) without History of Asthma

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Case

A 65-year-old female with a history of (SARSCOV-2) COVID-19 infection and a COVID-19 vaccine administered two months thereafter presented to an urgent care nine months later with a history of week-long drenching night sweats, bilateral leg pain, and a dry cough. Her chest x-ray in urgent care showed opacity tracking along the anterior aspect of her left second rib, possibly indicative of an osteoblastic lesion. The patient was advised to go to the closest emergency department (ED) and follow up with a computed tomography (CT) Chest. In the ED our patient's emergent lab work noted WBC 11.56 10^3/uL with elevated eosinophils, count >500/uL on differential normal range (4.5-11.0 10^3/uL). ESR MM/HR was notably elevated at 102 (N<30) with CRP of 61.30 MG/L (N=0.3-1.0 MG/L). A repeat Chest X-Ray in the ED read by the radiologist noted likely pneumonia reporting a linear appearing confluent airspace opacity in the left upper lobe with suggestion of air bronchograms. The patient also had a slightly elevated d-dimer of 0.60 UG/ML FEUs so a Computed Tomographic Angiogram (CTA) Chest was completed while still in ED. The study was read by radiology and noted no evidence of pulmonary embolism or pneumonia but bilateral lung masses with mediastinal, bilateral hilar, and mediastinal lymphadenopathy likely representing malignancy, with a primary lung cancer high on the differential. The patient was discharged from the hospital without antibiotics and advised to schedule an outpatient consultation with an oncologist.

In the oncology office, the patient completed a positron emission tomography (PET)-CT scan which noted fluorodeoxygluclose (FDG) avid left upper lobe nodular consolidations with surrounding ground-glass, right lower lobe masslike consolidation, and mediastinal lymphadenopathy, as described. The differential diagnosis included malignancy versus infection. Patient reported her appetite as good and she has no weight loss over the last 6 months. She had generalized fatigue and weakness at baseline, though she was active (plays tennis). The oncologist felt it was not clear if the lung masses in the left upper (LUL) and right lower lobes (RLL) represented separate malignancies, metastases, infections, or a combination of these. There were hypermetabolic lymph nodes seen in the mediastinum, but were considered to be reactive. The patient was scheduled to see infectious disease for possible evaluation of infectious sources along with a Cardiothoracic surgeon and Interventional Pulmologist to determine how to best sample the two lung masses and lymph nodes.

Infectious disease specialist noted that the patient was born in New York and traveled to Southern California and Southern Florida in the last nine months. The patient has never lived overseas nor had recent travel. No pets at home, no farm or animal exposures. No history of unpasteurized milk consumption. She never lived in an aggregate setting. She denied a history of smoking or intravenous (IV) drug abuse. Infectious disease (ID) noted both tuberculosis and non-tuberculosis mycobacteria can present in this manner with fatigue, myalgias and pulmonary lesions with mediastinal lymphadenopathy. ID also noted other possibilities to include but not limited to Cryptococcus, Nocardia, and Burkholderia (Melioidosis). ID recommended diagnostic bronchoscopy as having the highest yield for both infectious and non-infectious processes and to send for bacteria, MTB, NTM, fungal pathogens including endemic fungi, and other atypical bacterial pathogens (including nocardia, Burkholderia, anaerobes).

On bronchoscopy the left upper lobe lung biopsy confirmed Eosinophil-rich granulomatous inflammation with necrosis. Our patient was subsequently advised to return to the hospital to expedite rheumatologist consultation. Her anti-neutrophil chemotactic antibody (ANCA) test was noted to be equivocal with a Serine protease 3 Antibody IgG level of 23 AU/mL (normal <19 AU/mL). Given the pathology and elevated eosinophil count on differential, the rheumatologist felt the clinical presentation was consistent with an evolving ANCA-associated vasculitis with pulmonary eosinophilic granulomatosis with polyangiitis (EGPA) involvement. The patient did not have evidence of renal, neurologic, myocardial, ocular or cutaneous involvement. PET scan was not suggestive of below the diaphragm involvement.

The rheumatologist prescribed glucocorticoid systemic therapy, but without a pulse dose given the lack of severe manifestations. Patient was discharged with 50 mg of prednisone daily (1mg/kg), a weekly bisphosphonate, GI prophylaxis, Vitamin D / Calcium supplementation, and PJP prophylaxis with bactrim. She was advised to get further COVID-19 vaccination prior to discharge but declined.

Discussion

Eosinophilic Granulomatosis with Polyangiitis is an inflammatory vasculitis which infiltrates the small and medium sized arteries with a mean age of diagnosis of 50 years.[1] The vasculitis impacts major organ systems most commonly the lungs but also cardiovascular, peripheral nervous system, gastrointestinal, and kidneys. Most common presentation symptoms are bronchospasm, nasal and sinus symptoms and peripheral neuropathy. At presentation of EGPA symptoms may include weight loss, fever, myalgia, arthralgia, pulmonary opacities, cardiomyopathy, kidney disease and gastrointestinal disease. EGPA can present as either ANCA positive or negative.

The clinical presentation of EGPA will often occur in phases: prodromal, eosinophilic, and vasculitic phase. The prodromal phase is often not recognized at time of diagnosis but recalled upon further phases. The prodromal phase can include wheezing, allergic rhinitis, adult atopic disease, and chronic rhinosinusitis. There could be peripheral blood eosinophilia during and before this phase. During the eosinophilic phase there will be eosinophilic infiltration of systemic organs such as the lungs or gastrointestinal tracts along with peripheral eosinophilia in the blood. There could be challenges in the diagnosis of patients in the eosinophilic phase if there are systemic glucocorticoids already prescribed for asthma. The vasculitis phase could be the most life-threatening impacting medium and small vessels and infiltrating major organs like the lungs, heart and kidneys. Vasculitic phase has nonspecific symptoms of fever, weight loss and malaise. The biopsies can present with extravascular granulomatosis or perivascular eosinophils.

There are multisystemic symptoms that can be present in EGPA most commonly respiratory but also kidney, neurologic, skin, sinus and cardiac. Our patient did exhibit vague symptoms of malaise but did not have asthma. Ninety percent of patients with EGPA have asthma.[2] EGPA is often diagnosed in patients with very difficult to control asthmatic respiratory symptoms in spite of a long course of systemic glucocorticoids, inhaled glucocorticoids and long-acting beta agonists.[2] Due to the repeated systemic glucocorticoids the peripheral blood eosinophilia is often masked by the steroids during attempts at diagnosis. Other presentations of EGPA will include allergic rhinitis, nasal polyposis, recurrent sinusitis, or otitis media. In addition of asthmatic respiratory symptoms patients will have a runny nose, sinus pressure and pain. There are also skin manifestations including nodules on extensor surface, petechiae, purpura or hives. Myalgia can impact 50 percent of patients with EGPA.[3] The cardiovascular manifestation of EGPA can often be the most concerning with patients presenting with pericarditis, pericardial effusion, heart failure, valvular abnormalities, and ECG changes. Similar to other vasculitis patients, EGPA increases risk for blood clots.[4] Some patients present with kidney manifestations including proteinuria, microhematuria, acute kidney injury or at its worst crescentic glomerulonephritis.[2]

There is no specific test to diagnose EGPA definitively, but a keynote characteristic of the disease is the eosinophilic infiltration of extravascular tissue, which can be demonstrated through laboratory tests, imaging, and biopsy. These labs often include peripheral eosinophilia, elevated serum immunoglobulin E levels, elevated inflammatory markers such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP), and a positive antineutrophil cytoplasmic antibodies (ANCA), which has been noted in 40-75 percent of patients with EGPA.[5] Radiographically, abnormalities that are predominantly seen include ground-glass opacities and consolidations, most commonly in the parenchymal airspaces,[6] which was noted on our patient's initial CT chest imaging. And lastly, a high percentage of tissue eosinophilia can be documented on a biopsy of the relevant organ system such as lungs, kidneys, endocardial tissue, or skin,[7] which in our patient was seen on bronchoscopy guided biopsy demonstrating eosinophil-rich inflammation of the left upper lung.

The American College of Rheumatology and European Alliance of Associations for Rheumatology (EULAR) updated the classification system in identifying EGPA among patients with small- or medium-sized vessel vasculitis in 2022.[8] The new system noted a score of 6 or more had a sensitivity of 85 percent and a specificity of 99 percent for EGPA.[8] The points are scored as follows: Blood eosinophil count ≥1000 cells/microL (+5 points), Asthma (a history of wheezing or the finding of diffuse high-pitched wheezes on expiration (+3 points), Nasal polyps (+3 points), Extravascular eosinophilic predominant inflammation on biopsy (+2 points), Multiple mononeuropathy (+1 point), Hematuria (minus 1 point), Elevated cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or anti-proteinase 3 antibody (minus 3 points). Our patient had a positive Extravascular eosinophilic predominant inflammation on biopsy providing 2 points but to negate the 2 with this new scoring indices lost 3 points with a positive anti-proteinase 3 antibody.[8] Based on our patient's biopsy, eosinophilia and clinical presentation, her diagnosis was made and she has responded to steroid therapy despite her low EULAR score.

In 2021 the American College of Rheumatology/Vasculitis Foundation (ACR/VF) guidelines adjusted treatment of EGPA based on if a patient had severe disease with life threatening end organ damage or non-severe disease. End organ damage includes active glomerulonephritis, pulmonary hemorrhage, cerebral vasculitis, progressive peripheral or cranial neuropathy, gastrointestinal bleeding due to vasculitis, pericarditis, or myocarditis.[9] The Five-Factor Score (FFS) and Birmingham Vasculitis Activity Score (BVAS) helps quantify disease activity. The FFS is also helpful for disease prognosis. The FFS score ranges from 0 to 2. A score of 0 when no risk factors present, one for one risk factor and any total greater than 2 receives a score of 2. The point is given if the patient is over 65, has Cardiac insufficiency, Gastrointestinal involvement, Renal insufficiency, or Absence of ear, nose, and throat (ENT) manifestations. Our patient only received one point for being 65. This further underscores the utility of scoring systems for atypical presentations and patients with milder disease.

Systemic glucocorticoids like prednisone remain the most common treatment for EGPA dosed at 0.5 to 1 mg/kg per day. For severe EGPA patients at risk for respiratory compromise, cardiac involvement, glomerulonephritis may need higher IV glucocorticoids prior to initiating oral steroids. In the case of severe EGPA and life-threatening disease cyclophosphamide or rituximab can be used to induce remission. There are also recommendations to use glucocorticoids plus mepolizumbab.[9] For non-severe EGPA treatment glucocorticoids can be combined with azathioprine, methotrexate, or mycophenolate to induce remission.

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