CLINICAL VIGNETTE

EGPA Onset After COVID-19 Infection

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Case

A 66-year-old male without significant past medical history presented to the Emergency Department with shortness of breath, arthralgias, left upper extremity numbness and bilateral lower extremity rash. One month prior, the patient contracted COVID-19 with only mild symptoms of cough. He started Paxlovid therapy on the day of diagnosis and completed a five-day course with complete resolution of symptoms. One week after, he noted onset of dyspnea on exertion and arthralgias in bilateral knees, hips, and elbows. Two weeks later, he developed bilateral lower extremity edema and new non-pruritic, non-tender rash on the shins, ankles and feet, sparing the soles. On the day of admission, the patient reported a "pinched nerve" on his left shoulder blade which radiated down his arm, with associated left-hand weakness.

Prior to his COVID-19 infection, he was very active, playing tennis multiple days a week. Extended review of systems was negative, including no weight loss, fevers, night sweats, chest pain, palpitations, syncope, or gastrointestinal symptoms. He denied intake of raw or undercooked food and had no unusual environmental exposures. His only recent travel was to New Mexico where he stayed in the city with no exposure to animals. He had no asthma or atopy and denied drug or environmental allergies. Family history was unremarkable for malignancies or autoimmune conditions. Patient previously drank one to two glasses of wine daily but consumed no alcohol since contracting COVID-19. He did not smoke or use recreational drugs. The patient was sexually active with one partner. He completed a five-day course of Paxlovid, had taken Ibuprofen 200mg every four hours since the onset of arthralgias. There were no other medications or supplements.

On admission, the patient appeared well and was hemodynamically stable. Vital signs were normal: temperature 36.6°C (97.9°F), blood pressure 154/97 mmHg, heart rate 96 bpm, respiratory rate 18 bpm, and oxygen saturation 98% on room air. Physical exam was notable for 1+ peripheral edema and non-blanching, palpable, purpuric rash on bilateral lower extremities (Figure 1). There was decreased sensation in his left hand and weakness in the median nerve distribution. He was unable to abduct or flex the first through third digits of his left hand. Otherwise, motor strength was 5/5 throughout and sensation was grossly intact. Cardiopulmonary and abdominal exams were unremarkable and there were no joint effusions.

Admission laboratory testing included white blood cell count of 27,270/uL with an absolute eosinophil count of 16,250/uL, hemoglobin 14.4 g/dL, and platelets 252,000/uL. Comprehensive metabolic panel was within normal limits. The patient underwent imaging with high resolution computed tomography (HRCT) of the chest which demonstrated bronchial wall thickening consistent with large and small airway disease, as well as consolidative densities consistent with eosinophilic pneumonia (Figure 2). CT sinus with contrast showed extensive mucosal thickening and bony thinning or dehiscence. Given his dyspnea, cardiac evaluation included transthoracic echocardiogram which demonstrated normal biventricular systolic function, no significant valve abnormalities, IVC with greater than 50% in respiratory change, and estimated RVSP at 28mmHg. Serial high-sensitivity troponin was unremarkable, and BNP was normal at 69. Evaluation of reported jaw claudication included normal bilateral temporal artery ultrasound, with no evidence of giant cell arteritis.

Multiple services consulted including: Rheumatology, Allergy and Immunology, Hematology/Oncology, Dermatology, Infectious Disease (ID), Neurology, Endocrinology, and Head and Neck Surgery (ENT). The admission differential diagnosis included autoimmune vasculitis, infection, malignancy, hypereosinophilia syndrome, asthma, allergy, adrenal insufficiency, and eosinophilic pneumonia.

Additional testing revealed erythrocyte sedimentation rate 38 mm/hr, c-reactive protein 2.5 mg/dL, rheumatoid factor 97, IgE 1011 klU/L, IgG4 subclass 373, kappa quantitative free light chains 49.22 mg/L, lambda quantitative free light chains 28.65 mg/L, ANCA MPO positive 634.9 CU, c-ANCA 1:20 titer, p-ANCA 1:320 titer, proteinase-3-Ab <20.0 CU, creatine kinase 2190 U/L. Other autoimmune studies including ANA, CCP, C3/C4 were negative or within normal limits. Infectious testing was unremarkable, with negative HIV, hepatitis, tuberculosis, Giardia, Cryptosporidium, Entamoeba, Plasmodium, Schistosoma, Strongyloides, Cocci, and Aspergillus. Sputum culture and bacterial blood cultures were negative. Although respiratory fungal culture grew some candida albicans, ID thought this was colonization and recommended against treatment. A left leg skin punch biopsy revealed acute vasculitis with associated inflammatory infiltrate containing eosinophils and neutrophils in the superficial/deep vessels, consistent with small vessel/leukocytoclastic vasculitis and a pattern that can be seen in

eosinophilic granulomatosis with polyangiitis (EGPA) (Figure 3).

The patient was diagnosed with EGPA, as the best explanation for his constellation of symptoms. He was not started on prednisone 65mg (1mh/kg). Within 24 hours, his WBC count dropped from 24,300/uL to 9,510/uL, and absolute eosinophil count dropped from 14,540/uL to 360/uL. He noted improved left-hand mobility and was able to form a ring with his fingers within two days. He was discharged four days after admission, on prednisone 65mg daily, sulfamethoxazole/trimethoprim double strength three times a week, pantoprazole 40mg daily, ergocalciferol 1250mcg weekly, and saline and Fluticasone nasal sprays as needed for symptoms. He was scheduled outpatient follow up in primary care, rheumatology, dermatology, ENT, neurology, and allergy.

Discussion

EGPA, formerly known as Churg-Strauss Syndrome, is a rare, multi-system, inflammatory disease characterized by late-onset asthma, blood and tissue eosinophilia, and vasculitis affecting small-to-medium vessels.[1] It is the least common of the anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV). To date, no validated diagnostic biomarkers exist to dependably differentiate EGPA from other diseases. There is not consistently established set of criteria for diagnosis.[2] The few published investigations in Europe, US, and Australia suggest that EGPA prevalence ranges between 10 and 22 per million people.[3] The mean age at diagnosis of EGPA is 50 years with no gender predominance.[4,5] Typical EGPA consists of three phases 1) a prodromic 'allergic' phase characterized by asthma and chronic rhinosinusitis, 2) an eosinophilic phase with pronounced eosinophilia (usually exceeding ≥1500 cells/uL or 10%) and 3) a vasculitic phase, characterized by manifestations of small-vessel vasculitis such as glomerulonephritis, purpuric rashes, and mononeuritis multiplex, as in our patient. These phases can overlap, arise in any order, or not develop at all.[2,6,7] Our patient demonstrated many of the classic epidemiologic, clinical, radiographic, and histologic findings of EGPA.

The precise pathogenesis of EGPA remains unclear but is likely multi-factorial. Genetic predisposition, inhalation of environmental antigens such as industrial solvents or dust, exposure to certain asthma medications, as well as fungal and viral infections have been speculated to be inciting events, without definitive evidence to date.[8] Our patient had none of risk factors for EGPA. His COVID-19 infection one month prior was a plausible trigger SARS-CoV-2 has been associated with the development of other vasculitides, including leukocytoclastic (LCV), immunoglobulin A (IgA), Kawasaki, and cutaneous small vessel vasculitis.[9-11] There is one prior case report of a new EGPA diagnosis after COVID-19 recovery in a 42-year-old male with no past medical history.[12]

Current understanding of ANCA-associated vasculitis pathogenesis consists of an initial insult that generates an aberrant autoimmune response.[13] SARS–CoV-2, in addition to its primary respiratory involvement, can bind and directly invade vascular endothelial cells of several systems throughout the body. These include cerebral, cardio-pulmonary, and renal microvasculature.[14] Autopsies have demonstrated SARS-CoV-2 induced multisystem vascular damage, increased permeability, and endotheliitis.[15] There is also evidence of cytokine release syndrome, with specific involvement of interleukin-6 and tumor necrosis factor-alpha in the COVID-19 inflammatory response.[16] Karampoor et al. posit that SARS-CoV-2 antigens may trigger antigen-antibody complex deposition inside vascular walls that lead to vasculitis.[12] The idea of initial insult followed by immunologic dysfunction, includes the possible association of COVID-19 infection with subsequent development of autoimmune vasculitis. The correlation between COVID-19 infection and EGPA warrants further investigation and may lead to better understanding of COVID-19 induced immune dysregulation and other complications.

The temporal association between this patient's COVID-19 infection, recovery, and new onset EGPA suggests possible COVID-19 induced EGPA. As EGPA remains challenging to diagnose due to its rarity and variable clinical presentation, a high index of suspicion is needed for prompt diagnosis and appropriate treatment. This patient's rapid recovery of neurological function and correction of marked eosinophilia with the initiation of prednisone treatment may have prevented permanent damage and morbidity and ultimately, may have improved outcome.

Figures

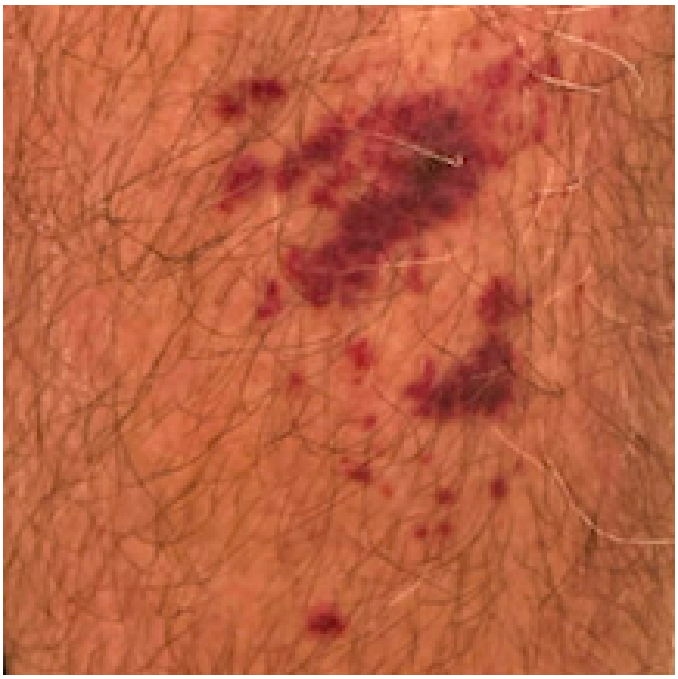

Figure 1. Non-blanching, palpable, purpuric rash on the anterior shin of the patient's left lower extremity.

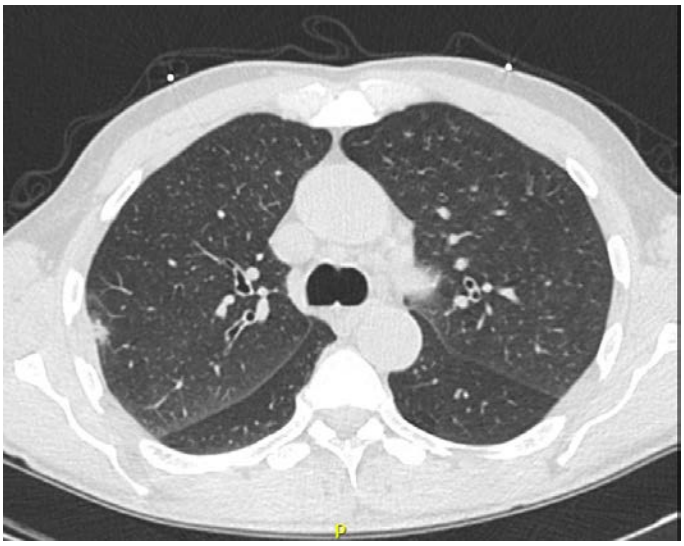

Figure 2. HRCT chest showing diffuse bronchial wall thickening with lower lung predominant scattered foci of mucostasis and diffuse air trapping consistent with large and small airway disease as well as prominent subcentimeter short axis intrathoracic lymph nodes.

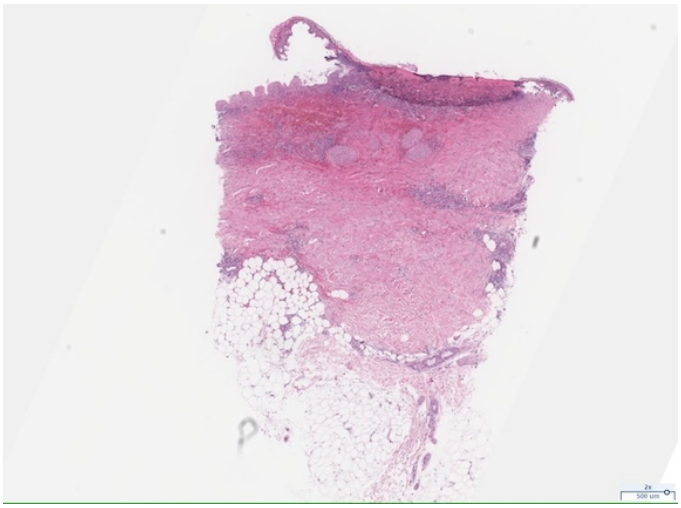

Figure 3A. Skin punch biopsy (low-power, 2x, H&E stain) showing epidermal ulceration and underlying superficial and deep dermal vessels with perivascular inflammation and extravasated erythrocytes.

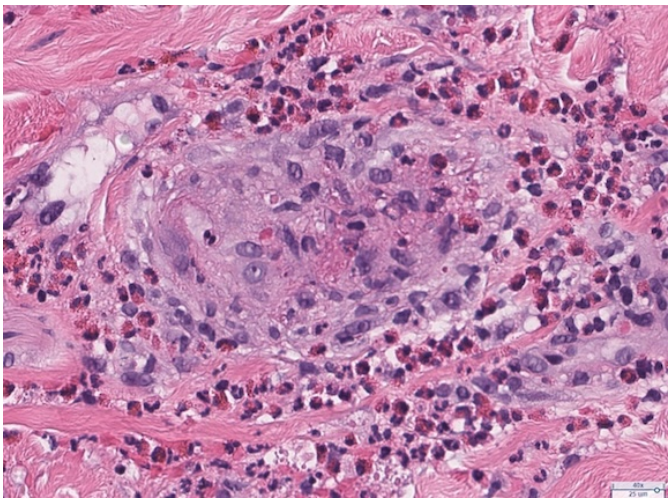

Figure 3B. Superficial dermal small vessel involved by eosinophil-rich vasculitis (high-power, 40x, H&E stain).

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