Eosinophilia with Granulomatosis and Polyangiitis in a 57-Year-Old Man with Worsening Muscle Pain

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About the Author

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Abstract

Eosinophilia with granulomatosis and polyangiitis (EGPA, previously called Churg-Strauss syndrome or allergic granulomatosis and angiitis) is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis affecting small-sized vessels, which typically occurs in patients with a history of allergic rhinitis or asthma. The most serious cases arise from the involvement of other organ systems, notably the cardiovascular system. Importantly, patients may first exhibit non-specific manifestations such as malaise, fever, anorexia, and weight loss. This variable presentation and the potential for multi-organ involvement can lengthen time to diagnosis and delay treatment.

We describe a patient who presented with progressive myalgias on the background of recently diagnosed rhinosinusitis who was ultimately diagnosed with EGPA. This case is meant to alert general internists to the diagnostic challenges of EGPA.

Résumé

La granulomatose éosinophilique avec polyangéite (anciennement, le syndrome de Churg et Strauss ou angéite allergique granulomateuse) est une vasculite liée à des anticorps anticytoplasme des polynucléaires neutrophiles (ANCA) qui touche les petits vaisseaux sanguins, apparaissant chez des personnes ayant des antécédents de rhinite allergique ou d'asthme. Les cas les plus graves surviennent quand la vascularite s'étend à d'autres systèmes organiques, plus particulièrement au système cardiovasculaire. Il est important de noter que les premières manifestations peuvent être d'ordre général, comme un malaise, de la fièvre, de l'anorexie et une perte de poids. En raison de ce tableau clinique variable et de la possibilité de l'atteinte multiorganique, le diagnostic peut être long à établir, ce qui risque de retarder le traitement.

Case

A 57-year-old man presented to the emergency department with worsening muscle pain of the lower extremities, bilaterally. The patient had been well until approximately two weeks prior to presentation, when he noticed a deep ache in his thighs with activity and a precipitous decline in performance as goalie in his recreational hockey league ("I was letting in too many goals"). The pain became more severe, affecting his daily physical functioning; soon the discomfort prevented him from standing for more than 15 minutes at a time. He subsequently developed migratory swelling and pain, first affecting the right heel, then moving to the right wrist, the plantar aspect of his left foot, and the left knee. He began experiencing intermittent drenching night sweats and endorsed a recent weight loss of about 6 kg. Finally, he developed bilateral shoulder and jaw pain that prompted him to seek medical attention by presenting to hospital.

His medical history included chronic rhinosinusitis with polyposis, diagnosed endoscopically 10 months earlier, for which he was taking inhaled budesonide and formoterol twice daily and mometasone furoate monohydrate intranasally as required. He did not have a history of asthma. He took no other medications.

The physical exam revealed vital signs, including temperature, that were within normal limits. Examination of his lower and upper limbs revealed no objective weakness and the neurological exam was normal. His gait was antalgic bilaterally and he was unable to hold his arms above his head secondary to pain. Respiratory exam was normal, musculoskeletal examination demonstrated no active joints, and there was no rash. He was admitted to hospital for further workup and management.

Initial blood work was significant for an elevated white blood cell count at $20.44 \times 10^9/L$, with a differential revealing an eosinophil level of $9.61 \times 10^9/L$. Electrolytes and creatinine were within normal limits. Testing of inflammatory markers revealed an erythrocyte sedimentation rate of 25 mm/hr and a C-reactive protein of 82.9 mg/L. Creatine phosphokinase (CPK) was mildly elevated at 371 IU/L. Urinalysis showed 2+ blood. Chest radiograph was normal. Serology for parasitic infection and an autoimmune panel were pending.

His muscle pain was treated with naproxen 500 mg orally twice daily. His symptoms improved and he was discharged the following day, with an outpatient rheumatology follow-up appointment in one week. Three days later, he returned to the emergency department with new-onset left foot numbness and interval development of a rash over his legs and scalp. His

muscle pain returned and was significantly worse, affecting nearly his entire upper and lower limbs, with attenuation in the symptomatic relief provided by naproxen. On examination, he had decreased sensation to light touch affecting the left lower limb and evidence of new purpuric lesions on his palms, lower limbs, and dorsum of the feet. He also had blanchable papular lesions on his forehead. Musculoskeletal examination revealed tenosynovitis at the left second to fourth metatarsophalangeal joints. Testing for muscle power was limited secondary to pain. Repeat blood work demonstrated a rising CPK at 1,040. Testing for perinuclear (p)-anti-neutrophil cytoplasmic antibody (ANCA) was positive. Magnetic resonance imaging (MRI) of the lower limbs demonstrated diffuse edema of the musculature bilaterally consistent with myopathy. Nerve conduction and electromyography studies did not show a deficit. Echocardiogram and pulmonary function tests were normal. Chest computed tomography (CT) was subsequently performed and did not suggest active lung involvement. He was initiated on prednisone 60 mg daily with rapid improvement of his myalgias. He was discharged from hospital with plans for close follow-up with a rheumatologist specialized in vasculitis.

Discussion

Eosinophilia with granulomatosis and polyangiitis (EGPA) is a vasculitis of the small-sized blood vessels associated with hyperes eosinophilia and necrotizing granulomatous inflammation.¹ It is a multisystem disorder typically occurring in patients with a history of allergic rhinitis or asthma. It has an incidence of 0.6–6.8 per million per year.² The mean age of diagnosis is 40 years, with no known gender predominance.³ Both vessel inflammation and eosinophilic proliferation are thought to play a role in organ damage, although the exact pathogenesis is not completely understood.⁴

Among the three ANCA-associated vasculidities (EGPA, granulomatosis with polyangiitis, and microscopic polyangiitis), EGPA is the least common.⁵ The most commonly involved organ is the lung, followed by ear, nose, and/or throat (ENT) involvement and skin; other frequently affected systems include the cardiovascular, gastrointestinal, renal, and central nervous systems. Nearly 40% of patients with EGPA have circulating ANCAs, predominantly directed against myeloperoxidase, with a perinuclear staining pattern (p-ANCA).⁶ Different subtypes of disease may exist with clinical characteristics that differ according to ANCA status⁷: patients with ANCA positivity have been found to be more affected with renal disease, mononeuritis, purpura, and alveolar haemorrhage; cardiac involvement, lung infiltration, and systemic manifestations are more frequently seen in patients who are ANCA negative.^{6,8}

The American College of Rheumatology has developed six criteria for the classification of EGPA: presence of asthma; eosinophilia >10%; mononeuropathy or polyneuropathy; pulmonary infiltrate; non-fixed paranasal sinus abnormality; and extravascular eosinophils on biopsy of a blood vessel. The presence of any four or more of the six criteria produces a sensitivity of 85% and a specificity of 99.7% for diagnosis.⁹ Importantly, these criteria were devised as a classification system to distinguish EGPA from other vasculitides, rather than a formal checklist for the diagnosis of EGPA.

The presentation of EGPA is far from uniform. The initial phase can last years and generally involves allergic rhinitis, nasal polyposis and sinusitis, and/or asthma.² This is followed by the occurrence of vasculitic manifestations, such as skin involvement and/or mononeuritis multiplex. Constitutional symptoms are also often present at diagnosis (40–75%), including fever, weight loss, myalgias, and arthralgias.² At diagnosis, 40–75% of patients have skin involvement, most frequently palpable purpura, but other lesions such as cutaneous nodules or papules with an urticarial appearance can be seen.² Other organ systems are also frequently involved. Between 38–77% of patients can have parenchymal lung involvement. Gastrointestinal manifestations, which occur in 20–50% of patients, may include abdominal pain, vomiting, or diarrhea.¹⁰ Cardiac involvement, present in 27–47% of patients, includes cardiomyopathy and eosinophilic pericardial effusion and is of paramount importance to discern due to its heightened association with disease-related morbidity.^{4,11} Up to 27% of patients may have renal involvement, mainly in the form of focal segmental or pauci-immune glomerulonephritis.¹²

The initial and cornerstone of treatment for EGPA is corticosteroids. For patients with evidence of systemic vasculitis, treatment is initiated with prednisone (or equivalent) at a dose of 1 mg/kg per day. Additional immunosuppressive agents are typically added in cases of refractory or severe disease, such as impending respiratory failure, cardiac involvement, glomerulonephritis, and/or severe motor neuropathy. Most patients with EGPA improve with glucocorticoid therapy alone.¹³ Once symptomatic remission has been achieved, the dosage of steroid is gradually tapered over 12–18 months, as tolerated by the patient. However, a report of patients without poor prognosis factors (i.e., no cardiac, renal, or central nervous system involvement) indicated that almost 80% of those who achieved remission required long-term, low-dose glucocorticoid therapy because of lingering asthma or rhinitis.¹³

Conclusion

This was the case of a 57-year-old man with progressive myalgias affecting the upper and lower limbs, associated with weight loss and migratory tenosynovitis, and with a history of allergic rhinitis. Diagnosis only became apparent as the other manifestations of EGPA developed with eosinophilia, skin involvement, and neuropathy. This case highlights the challenges associated with diagnosing EGPA. Given the multi-system and heterogeneous nature of the disease, keeping the diagnosis on one's radar, recognizing its presenting features, and including it in the differential diagnosis is essential.

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