CASE STUDY

Limb-Threatening Arterial Thrombosis in a Patient with Eosinophilic Granulomatosis with Polyangiitis

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Abstract Eosinophilic granulomatosis (EGPA), or Churg-Strauss syndrome, is a rare and necrotizing systemic vasculitis, which affects small-to-medium-sized vessels and often manifests with severe asthma and eosinophilia. We report a case of a 72 year-old male with a two-year lung-biopsy proven history of EGPA who presented with retiform purpura and patchy necrosis on his bilateral shins, which progressed to sharply demarcated, stellate ulcerations with surrounding erythema within two weeks. Laboratory work up revealed elevated anti-Cardiolipin IgM, rheumatoid factor, erythrocyte sedimentation rate, and C-reactive protein, although P-neutrophil cytoplasmic antibody (P-ANCA) and C-neutrophil cytoplasmic antibody (C-ANCA) were negative. Vascular studies revealed long anterior tibial and dorsalis pedis artery occlusion and severe small vessel disease in plantar digital arteries. Despite treatment with intravenous cyclophosphamide, pulse-dose methylprednisolone, and pentoxifylline, the patient experienced disease progression and limb threatening arterial thrombosis. This case highlights the importance of vascular and neuropathic sequelae that may result from untreated or undertreated EGPA in P-ANCA-negative patients without active pulmonary symptoms.

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Case

A 72 year-old male with a history of eosinophilic granulomatosis with polyangiitis (EGPA), hypothyroidism, and corticosteroid-induced diabetes mellitus presented with worsening lower extremity skin lesions. Fifteen months

prior to presentation, he developed refractory asthma with associated weight loss and fevers. A diagnosis of EGPA was made via lung biopsy. Treatment was initiated with 80 mg methylprednisolone daily and three 1500 mg boluses of cyclophosphamide over two months. The steroid dose was tapered and he was subsequently maintained on 10 mg of prednisone daily. Although his pulmonary symptoms improved, he developed progressive loss of sensation and intermittent purpuric eruptions and erosions in his bilateral lower extremities while on maintenance low dose prednisone therapy. Three months prior to presentation, he underwent a right partial second toe amputation in the setting of dry gangrene for occluded right anterior tibial artery.

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Initial physical examination revealed purpuric dermal plaques bilaterally on the patient's distal lower extremities. His shins and calves demonstrated retiform purpura and patchy necrosis, livedo racemosa, and hemorrhagic vesicles bilaterally. Over the course of two weeks, these progressed to sharply demarcated, stellate ulcerations with surrounding erythema (Fig. 1).

Laboratory findings revealed elevated erythrocyte sedimentation rate (97 mm/h) and C-reactive protein (100 mg/mL) with an absolute eosinophil count within normal limits. Anti-cardiolipin IgM antibody was elevated at 26. Thrombotic and vasculopathy work up revealed negative lupus anticoagulant and anti-cardiolipin IgG antibody, ruling out the presence of antiphospholipid syndrome. Immunology work up including P-neutrophil cytoplasmic antibody (P-ANCA) and C-neutrophil cytoplasmic antibody (C-ANCA) was negative except for low Complement-4 (C4), borderline ANA (1:160 titer), and elevated rheumatoid factor (>600 IU/mL). Vascular studies (lower extremities arterial pressures and pulsed volume recording doppler) revealed long anterior tibial and dorsalis pedis artery occlusion and severe small vessel disease in plantar digital arteries. Punch biopsy of the edge of a retiform plaque on his left ankle revealed necrotic epithelium and eccrine coils, consistent with infarcted skin.

Treatment included a 1500 mg bolus of intravenous cyclophosphamide, 250 mg pulse-dose intravenous methylprednisolone every 6 hours for 72 hours, and 400 mg oral pentoxifylline three times daily. A maintenance dose of 30 mg of prednisone twice daily was later initiated. His initial lesions quickly progressed to dry gangrene over his right third and fourth toes, as well as his left first through fourth toes over the course of two weeks (Fig. 1).

Discussion

The differential diagnosis for dermal vascular compromise and accompanying cutaneous necrosis includes vasculitis, vasculopathy, non-uremic calciphylaxis, and angioinvasive

infections.¹ Our extensive work up revealed that inadequate treatment with only low dose prednisone in our patient with biopsy-proven EGPA led to disease progression and limb-threatening arterial thrombosis.

The proposed mechanism of thrombosis in EGPA involves increased eosinophils, which produce both cationic proteins and tissue factor (TF).² Cationic proteins including major basic protein, eosinophil cationic protein, and eosinophil peroxidase inhibit natural anticoagulant factors in the clotting cascade, while TF directly initiates the clotting cascade.² In Ames et al's 2010 review, a total of 12 arterial and 12 venous thrombosis cases were reported. Every patient noted to have a thrombotic event either had an unreported or negative P-ANCA.² Recent studies reveal that P-ANCA negative patients tend to have a much higher tissue infiltration by eosinophils.³ During their tissue migration, eosinophils may be maximally thrombogenic.⁴ Thus, P-ANCA negative EGPA patients may demonstrate a higher risk for thrombosis.

At the same time, EGPA only results in vascular occlusion and arterial thrombi in rare cases.² Typically, the disease presents with asthma, allergic rhinitis, and sinusitis. Patients subsequently develop eosinophilia, and later vasculitis.⁵ Patients with uncomplicated EGPA initially receive low dose prednisone at 0.5–1.5 mg/kg/day.^{6,7} Those refractory to steroids or with major organ involvement are treated with corticosteroids in combination with an immunosuppressant such as cyclophosphamide.^{6,7} Neurologic symptoms, which affect 60–70% of patients,⁸ may indicate disease progression resulting from the effect of the disease on the microcirculation.² P-ANCA negative EGPA patients may benefit from thromboprophylaxis as they experience a higher risk of thrombosis.

Although the association between P-ANCA and EGPA exists, a recent study revealed that only half of EGPA patients test positive for P-ANCA. P-ANCA positivity is less commonly linked to cutaneous lesions and cardiovascular involvement of EGPA.⁹ Our review highlights the importance of vascular and neuropathic sequelae that can occur with untreated or undertreated EGPA in the absence

Figure 1 (a): Lower extremities of patient upon initial presentation to dermatology. Retiform purpura, patchy necrosis, livedo racemosa, palpable purpura, and hemorrhagic vesicles bilaterally. (b): Lower extremities of patient two weeks later. Sharply demarcated, stellate ulcerations with mild surrounding erythema.

of P-ANCA-positivity and lack of active pulmonary symptoms.

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