

Skin-limited idiopathic hypereosinophilic syndrome presenting with retiform purpura



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INTRODUCTION

Idiopathic hypereosinophilic syndrome (IHES) is a rare disorder defined by (1) eosinophilia (eosinophil count $> 1.5 \times 10^9/L$) on 2 examinations 1 month apart, (2) organ damage and/or dysfunction attributable to tissue hypereosinophilia, and (3) lack of clear alternate cause.¹ Eosinophil-related organ damage consists of eosinophilic infiltrates associated with fibrosis, thrombosis, and cutaneous erythema or ulceration. It occurs predominantly in men ages 20 to 50 years.² Systemic manifestations include cardiomyopathy, neuropathy, hepatosplenomegaly, and thromboembolism, with skin lesions as the dominant symptom in most patients.² We report a case of skin-limited IHES presenting as retiform purpura and highlight the importance of early diagnosis and intervention in this heterogeneous condition.

CASE REPORT

A 51-year-old Taiwanese male smoker with dyslipidemia presented with 2 weeks of painful ulcers and cyanosis of the distal lower extremities associated with 7 months of pruritic papulosquamous eruptions of the trunk and extremities refractory to doxycycline, terbinafine, topical and intralesional triamcinolone, ivermectin, and low-dose prednisone. One month before presentation, he experienced hand and foot numbness and progression of rash on the lower extremities with hyperkeratosis, scale, and erythema. Home medications were atorvastatin and as-needed oxycodone and acetaminophen, with no recent changes; past medical history and review of systems were otherwise unremarkable.

Physical examination was notable for retiform purpura and edema of the bilateral lower

Abbreviation used:

IHES: idiopathic hypereosinophilic syndrome

extremities, with ulcerations on a background of livedo and cyanosis. The trunk and extremities had firm, erythematous, hyperpigmented, dome-shaped, excoriated papules and nodules (Fig 1). Right dorsalis pedis pulse was undetectable on Doppler studies. The patient was admitted for ambulation-limiting pain, Doppler studies suggesting complete vascular occlusion, and prominent eosinophilia.

Differential diagnosis for the underlying cause of vascular occlusion and hypereosinophilia included primary systemic versus drug-induced vasculitis, antiphospholipid antibody syndrome, rheumatologic disease, infection, cutaneous and hematologic malignancy, cardioembolic phenomena, and paraproteinemia. Admission laboratory test results were notable for white blood cell count of 17.7 K/uL (30.3% eosinophils [absolute eosinophils, $5.36 \times 10^3/\mu L$]), hemoglobin level of 13.7 g/dL, C-reactive protein level of 87.4 mg/L, and normal antinuclear antibody panel and rheumatoid factor test results. Absolute eosinophils were 4.35×10^3 and $0.67 \times 10^3/\mu L$ in 2012 and 2006, respectively. Computed tomography–angiography showed opacification of bilateral peroneal arteries. The ankle-brachial index was 0.48 and 0.72 in the right and left lower extremities, respectively. Serum studies showed elevated immunoglobulin E (970 kU/L), with unremarkable results for erythrocyte sedimentation rate, tryptase, antineutrophil cytoplasmic antibody, complement, cardiolipin, β -2-glycoprotein, and cryoglobulins. Platelet count was 209 K/uL,

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Fig 1. Retiform purpura, ulcerations, and hyperpigmented erythematous papules and cyanosis of the bilateral lower and upper extremities on presentation.

international normalized ratio was 1.1, and partial thromboplastin time was 31.1 seconds. Flow cytometry, T-cell receptor, toxicology screenings, and urinalysis were unremarkable other than a positive result for urine oxycodone, a home medication. Results of infectious workup, including tests for HIV, rapid plasma reagin, QuantiFERON-TB Gold In-Tube test (QFT-GIT, Qiagen, Germantown, MD), *Strongyloides* species, *Trichinella* species, *Toxocara* species, human T-cell lymphotropic virus, filariasis, stool ova and parasites, urine histology, and *Streptococcus* species, were negative. Bone marrow biopsy showed marked eosinophilia without evidence of myeloproliferative neoplasm. Cytogenetics showed normal male karyotype and no rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1* on fluorescence in situ hybridization. Results for peripheral *BCR/ABL* mutation and elevated c-Kit level were negative, although the result for the Janus kinase (JAK) 2 V617F mutation was positive, with low allele burden of 0.06% (unclear clinical significance given negative bone marrow biopsy result).^{3,4} Head, abdomen, and pelvis computed tomography scans, abdomen ultrasonography, and transthoracic echocardiography were unremarkable. Lack of asthma history and negative results of sinus computed tomography suggested against eosinophilic granulomatosis with polyangiitis.⁵ Notably, left lower-extremity biopsy, taken below the knee at an area of inflammation at the edge of retiform purpura, showed diffuse dense dermal perivascular and interstitial eosinophilic infiltrate with small and

medium-sized vessel thrombosis and epidermal necrosis. Evidence to suggest a primary vasculitis (including vessel wall infiltration by inflammatory cells and fibrinoid necrosis) was not seen. There were no microorganisms on periodic acid–Schiff or Brown-Brenn stain (Fig 2).

Given the eosinophilia and skin involvement without identifiable underlying etiology, a diagnosis of IHES was made under consensus guidelines.¹ Starting on hospital day 5, the patient was treated with oral prednisone 80 mg daily for 5 days before transitioning to intravenous methylprednisolone 1000 mg daily for 5 days, followed by a 3-week taper to 80 mg daily. Treatment also included heparin and high-potency topical steroids. Steroid treatment rapidly reduced circulating eosinophils, stabilized existing skin lesions, and prevented new lesions.

Lower-extremity arterial insufficiency was treated with nifedipine 20 mg and sildenafil 40 mg 3 times daily, doxazosin 2 mg daily, warfarin, and aspirin. However, pre-existing areas of ischemia and ulceration remained unimproved. Steroid tapering was continued on an outpatient basis, with hydroxyurea 500 mg daily added for steroid-sparing antieosinopoietic effect (used effectively in *PDGFR* mutation–negative IHES requiring prednisone).⁶

Follow-up showed no new lesions, although acral gangrene progressed with worsening pain, decreased sensation, and necrotic demarcation (Fig 3). Intrinsic small-vessel disease, likely sequelae of prior thrombosis, left no options for

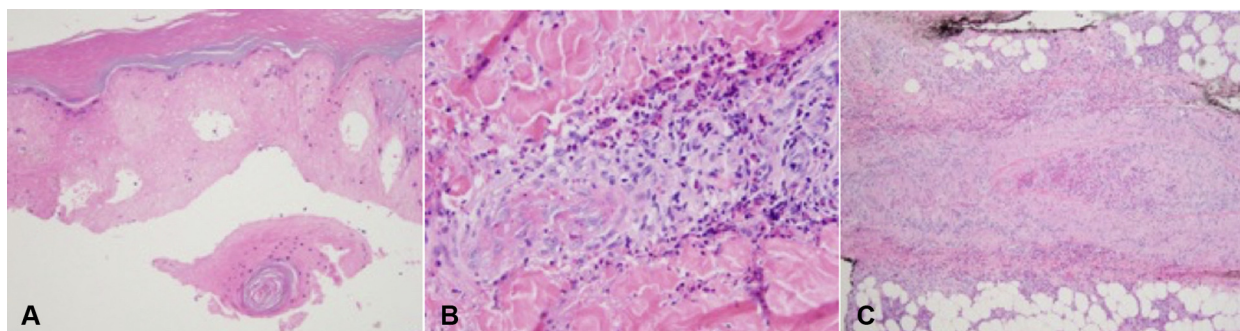


Fig 2. **A**, Left lower extremity biopsy with epidermal necrosis. **B**, Diffuse dense dermal perivascular and interstitial eosinophil-rich inflammatory infiltrate. **C**, Small and medium-sized vessel thrombosis.



Fig 3. Progression of gangrene and necrotic tissue of the lower extremities.

revascularization. The patient had right below-knee amputation and left transmetatarsal amputation 3 months after discharge.

DISCUSSION

Peripheral eosinophilia can be seen in helminthic infection, allergic disease, hematologic/myeloproliferative disorders, Wells syndrome, eosinophilic granulomatosis with polyangiitis, recurrent cutaneous necrotizing eosinophilic vasculitis, and

hypereosinophilic syndrome.^{7,8} Cutaneous manifestations of hypereosinophilia include angioedematous and urticarial lesions, erythematous and pruritic papules/nodules, vesiculobullous eruptions, ulcerations with dermal arteriolar microthrombi, and generalized erythroderma, presenting a unique diagnostic challenge.²

This case shows retiform purpura with peripheral eosinophilia and vascular occlusion rapidly progressing to tissue necrosis and gangrene. Given the

lack of definitive vessel wall pathology with negative results for antineutrophil cytoplasmic antibody, cryoglobulin, antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, and C3/C4 tests, vasculopathy from hypereosinophilia and prothrombotic activity was favored over primary eosinophilic vasculitis, the latter of which generally occurs in middle-aged Asian men and is associated with retiform purpura from arteriovenous thrombosis.⁸

Thrombosis in IHES may be related to significant longstanding eosinophil activation leading to degranulation of tissue factor-containing granules.^{1,2,8} Suggested mediators include eosinophilic cationic protein, which enhances factor XII activity and binds endogenous heparinoids, and major basic protein, which causes direct endothelial damage and collagen exposure.⁸ Although high-dose steroids resolved inflammation, vasodilation and anticoagulation were unsuccessful in halting thrombosis.⁸ Given the ulcerated retiform purpura and severe arterial insufficiency, our patient likely presented too late to avoid infarct and gangrene.

Predicting disease extent and outcome in patients with IHES and concurrent thrombosis remains challenging. Although more than 50% of IHES patients have cardiovascular and neurologic complications, our patient experienced primarily cutaneous involvement with severe local tissue infarction.⁵ This is consistent with the updated IHES definition, which decreases the required duration of hypereosinophilia

and expands systemic organ involvement to include cutaneous manifestations.¹ Physicians should have a low threshold of suspicion for IHES and its prothrombotic state in patients with pruritic papulosquamous eruptions or erythematous papules/nodules and engage in prompt workup and treatment to avoid long-term sequelae.

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