Idiopathic hypereosinophilic syndrome with cutaneous necrosis and multiorgan embolism

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INTRODUCTION

Hypereosinophilic syndrome (HES) is characterized by an absolute eosinophil count of 1.5×10^9/L or greater for at least 6 months or on 2 examinations (interval $\geq$ 1 month). HES can cause multiple-organ dysfunction, including the skin (37%), lung (25%), gastrointestinal tract (14%), heart (5%), and nervous system (3%),[1] but multiple organ thromboses with cutaneous necrosis are rare. We report an idiopathic hypereosinophilic syndrome (HES_I) with cutaneous necrosis, deep venous thrombosis of the lower extremities, pulmonary embolism (PE), and liver infarction successfully treated with pulmonary thrombolysis, left lower extremity venous mesh implantation, anticoagulation, and glucocorticosteroids (GCs).

Abbreviations used:

CT:	computed tomography
GCs:	glucocorticosteroids
HES:	hypereosinophilic syndrome
HES_I:	idiopathic hypereosinophilic syndrome
PE:	pulmonary embolism

CASE REPORT

In May 2013, a 41-year-old man was admitted to our department with a 20- × 18-cm cutaneous necrosis on his left thigh (Fig 1, *A*). It began as a 4- × 5-cm nodule without redness, itch, or pain in April and rapidly progressed to necrosis in the following 2 weeks. Laboratory examinations found leukocytosis (12.77×10^9/L) and hypereosinophilia (8.8%).There was no history of medication, trauma, or fever or family history suggestive of inherited thrombophilia.

On admission, he had slight right chest pain, cough with bloody sputum and no fever or short of breath. Laboratory examinations found leukocytosis (36.59×10^9/L) with hypereosinophilia (21.15×10^9), thrombocytopenia (19×10^9/L), elevated liver enzymes (alanine aminotransferase, 178 IU/L; aspartate aminotransferase, 68 IU/L; gamma-glutamyl transferase, 329 IU/L), and slightly increased procalcitonin (0.51 ng/mL).The coagulative function test found elevated fibrinogen (4.15 g/L) and D-dimer (82.20 mg/LFEU).The workup for allergic, parasitic, rheumatologic, and immunologic diseases was unremarkable. Chest computed tomography (CT) found bilateral patchy clouding opacity and a small pleural effusion. Abdominal ultrasound scan was normal. Histopathology from the necrotic lesion found hyperkeratosis of the epidermis, mild hypertrophy of the stratum spinosum, localized massive necrosis and hemorrhage in the dermis with infiltration of marked lymphocytes, histiocytes, and eosinophils (Fig 1, *B*).

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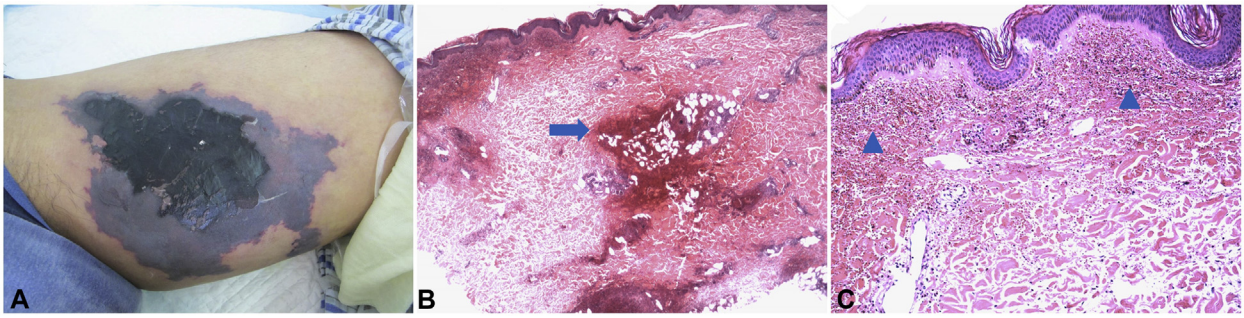

Fig 1. Cutaneous and pathologic findings of HES_I. **A**, Cutaneous necrosis on the left thigh. Histopathology. **B**, Necrosis and hemorrhage in dermal (*arrows*). **C**, Perivascular inflammation with marked lymphocytes, histiocytes, and eosinophils (*arrowheads*).

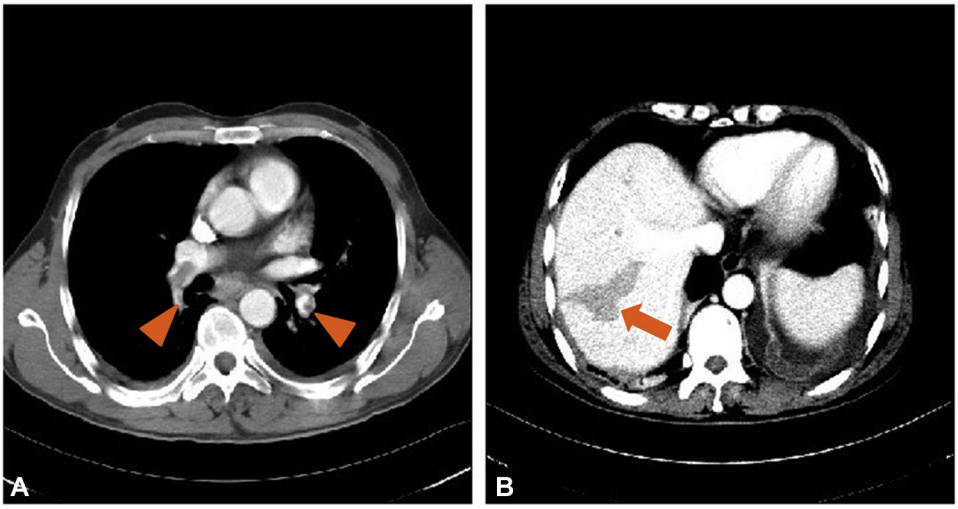

Fig 2. CT scan of chest and abdomen. **A**, Pulmonary embolism (*arrowheads*) and **B**, liver embolism (*arrows*).

The bone marrow aspiration showed a high ratio of eosinophils to leukocytes (27.5%).

Under the suspect diagnosis of HES_I, the patient was treated with methylprednisolone, 40 mg/d for 5 days, with decreased eosinophils. Because of aggravation of the right chest pain, especially with inhalation, and fever (38.6°C), enhanced chest CT confirmed PE and liver infarction (Fig 2, *A* and *B*). An ultrasound scan of the lower extremity showed thrombosis of the left great saphenous vein, superficial femoral vein, popliteal vein, and posterior tibial vein. Ultrasonography of the heart, abdomen, and vascular neck was normal. Because of multiorgan thrombosis, the patient was treated with pulmonary thrombolysis, left lower extremity venous mesh implantation, low-molecular-weight heparin followed by rivaroxaban (20 mg/d) and aspirin (100 mg/d), and methylprednisolone (40 mg/d) for hypereosinophilia. Three days later, chest pain and cough with bloody sputum resolved without fever and shortness of breath. CT pulmonary angiography found the dissolution of pulmonary thrombi after therapy. One week later, the eosinophil and platelet levels returned to normal (eosinophils, 5.0%, 0.55×10^9/L; platelet, 109×10^9/L). Aspirin was discontinued after 1 week. The skin necrosis on the left thigh healed with skin grafting in late July. The doses of methylprednisolone were tapered to stop, but rivaroxaban continued. The patient was asymptomatic with normal eosinophil count and no new formation of embolism during the subsequent 5-year follow-up. The laboratory information, complications, and the treatment modalities during the course of the disease are displayed in Table I.

DISCUSSION

In 2011, the International Cooperative Working Group on Eosinophil Disorders modified the old

Table I. Patient characteristics during the course of the disease

	Before admission (04/2013)	On admission (24/5/2013)	At the first week of corticosteroid treatment (30/5/2013)	At the beginning of CDT and anticoagulant treatment (03/06/2013)	At 10 d of anticoagulant treatment (11/06/2013)
Leukocyte count	12.77 × 10^9/L	36.59 × 10^9/L	23.08 × 10^9/L	12.36 × 10^9/L	10.93 × 10^9/L
EO%	8.80%	57.80%	36.50%	34.50%	5.00%
Eosinophil count	Absence	21.15 × 10^9/L	8.42 × 10^9/L	4.27 × 10^9/L	0.55 × 10^9/L
Platelet count	Absence	19 × 10^9/L	35 × 10^9/L	94 × 10^9/L	109 × 10^9/L
Coagulative function	Normal	APTT 34.60 sec	APTT 34.80 sec	APTT32.60 sec	Normal
		Fibrinogen (4.15 g/L)	Fibrinogen (4.06 g/L)	Fibrinogen (4.15 g/L)	Normal
		D-dimer (82.20 mg/L FEU)	D-dimer (Not detectable)	D-dimer (2.34 mg/L FEU)	D-dimer (19.79 mg/L FEU)
New thrombus and/or embolism		No	Pulmonary embolism and liver infarction	No	No
			Left lower extremity venous thrombosis		
Skin lesion	Nodule	Necrosis 20 cm × 18 cm	Without expanding	Without expanding	Without expanding
Antiplatelet therapy				Aspirin (100 mg/d)	Aspirin (100 mg/d)
Anticoagulant therapy				LMWH	Rivaroxaban (20 mg/d)
				Rivaroxaban (20 mg/d)	

CDT, Catheter-directed thrombolysis; *LMWH*, low-molecular-weight heparin.

criteria of HES combining blood HE or tissue HE associated with HE-related organ damage and proposed a new classification to delineate various forms of HES, including neoplastic HES, reactive HES, and HES_I. Our case fulfilled the criteria with bone marrow and tissue lesions, eosinophilic infiltration, organ damage, and peripheral blood hypereosinophilia (>1.5 × 10^9/L), except the duration. Although hypereosinophilia lasting not less than 6 months or present on 2 examinations (interval ≥1 month) is required for the diagnosis,[2] in the case of evolving life-threatening end-organ damage such as PE, the diagnosis of HES can be made immediately to avoid delay in therapy.[3] Because all the other examinations excluded parasitic infections, adverse drug reactions, and inflammatory or neoplastic diseases, and decrease of hypereosinophilia by GCs showed the current patient had HES_I, neoplastic HES or reactive HES can be excluded.

Cutaneous necrosis was the initial clue to the thromboembolic complications in our case.[4] Differential diagnosis may include eosinophilic granulomatosis with polyangiitis, purpura fulminans, and eosinophilic cellulitis. Arterial thrombosis (45%) was the most frequent thombotic complication in HES, whereas venous and mixed arteriovenous thromboses were 28% and 27%, respectively.[5] Mortality is attributed to cardiac dysfunction (33%), infection (20%), unrelated malignancy (20%), thromboembolic phenomena (13%), and vascular disease (13%).[6]

The pathogenesis of thrombosis in HES is elusive. Hypercoagulability may be associated with eosinophilic infiltration. Eosinophils contain granular proteins such as major basic protein, eosinophil cationic protein, eosinophil peroxidase, platelet-activating factor, and cytokines, especially interleukin (IL-5), which is crucial for eosinophil maturation and activation. All of these can again modify platelet function, stimulate activation of factor XII, activate platelets, and reduce the anticoagulating function of heparin and tryptase.[7,8] Although eosinophilia may be the primary cause of hypercoagulability and a thromboembolic event, other potential factors, including acquired or genetic causes, and enhanced tissue factor expression by blood eosinophils, may contribute to increase the thrombotic risk.[9]

GCs remain the first-line therapy for HES_I, which is effective in reducing eosinophils and slowing and preventing end-organ damage. The mechanism is to interfere with the transcription of proinflammatory genes necessary for eosinophil maturation, proliferation, migration, and chemoattraction. Although our patient's blood eosinophil counts decreased dramatically during the first week, the progression of

thromboembolism was not prevented. Additionally, hydroxyurea or interferon-α can be used as second-line agents for HES_I. Eosinophil-targeted biotherapeutics such as anti—IL-5 antibodies (mepolizumab and reslizumab), which are critical for eosinophil maturation and activation, appear promising in HES_I. Anti-Siglec-8-targeting antibody (AK002) and anti-IL-5Rα monoclonal antibody (Benralizumab) have been shown to lower eosinophil numbers, but more randomized trials are needed to confirm efficacy in HES.[10] Because pulmonary thrombosis is one of the major causes of death in HES, its prevention and treatment are urgent. Whether to use anticoagulation is still controversial, and anticoagulation should be considered for high-risk patients in the treatment of the potentially fatal complication.

Cutaneous necrosis in patients with HES warrants careful check for the possibility of thrombosis. Activation and aggregation of eosinophils, platelet activation, and coagulation possibly lead to tissue damage. The timely interventions with thrombolytic agents, the early use of corticosteroids, and anticoagulation therapy should be considered to prevent more widespread thromboembolism.

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