

Extensive Digital Gangrene Without Evidence of Large-vessel Occlusion in Hypereosinophilic Syndrome

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Hypereosinophilic syndrome (HES) comprises a group of rare disorders characterized by persistence of blood hypereosinophilia ($>1500 \text{ mm}^{-3}$) for >6 months; and definite signs of organ involvement without the secondary causes of eosinophilia (1). Cutaneous findings are present in up to 50% of patients with HES, e.g. pruritic papules, eczema-like patches, urticarial plaques, and angioedema (1). In HES patients, occlusions of intermediate- to large-sized arteries frequently cause peripheral ischaemia and even digital gangrene (2–6). Digital necrosis without evidence for vascular occlusion has rarely been described in patients with HES (7). We report here a case of HES complicated by severe digital gangrene without angiographic evidence of occlusion of peripheral arteries, but with histopathological evidence of occlusion of cutaneous small vessels by micro-thrombi.

CASE REPORT

A 41-year-old Korean man presented with a 3-month history of painless digital gangrene and bony exposures on the distal fingers (Fig. 1a). The patient had a smoking history of 15 pack-years (1 pack/day for 15 years) and had had Raynaud's phenomenon for the past 9 months. An elevation of peripheral eosinophil count one year before his presentation was noted in his medical history. On physical examination, brownish eczema-like patches and lichenified changes were noted on all extremities (Fig. 1b). A 3-mm punch biopsy from the arm revealed marked infiltration of eosinophils throughout the lower dermis

and subcutaneous fat layer (Fig. 2a). In addition, necrotizing eosinophilic vasculitis of a dermal vessel and prominent luminal micro-thrombus were observed (Fig. 2b). Initial laboratory investigation revealed an increase in white blood cell count ($19,270 \text{ mm}^{-3}$) with severe hypereosinophilia ($9,980 \text{ mm}^{-3}$, 49% of total leukocytes) and an elevation in serum eosinophil cationic protein (ECP) ($>200 \mu\text{g/l}$). Stool parasite examination, serum anti-neutrophil cytoplasmic antibodies, and anti-nuclear antibodies were all negative. Ground-glass opacities on both lower lung fields were noted via chest computed tomography (CT), corresponding to a decrease in diffusion lung capacity by 82%. CT-angiographic study of the upper extremities revealed no evidence for occlusion of any of digital arteries or large vessels. We initially decided to treat the patient with systemic corticosteroid; however, he refused all treatments and bone marrow biopsy for further evaluation.

DISCUSSION

HES encompasses a spectrum of diseases, which can be classified into several variants (8).

Digital necrosis is a rare complication in HES. In a previous case series, Kawata et al. (9) suggested that such gangrene could result from a thromboangiitis obliterans (TAO)-like artery occlusion with male preponderance; but no higher rate of occurrence in smokers than non-smokers (9). In our patient, the angiographic study revealed no evidence of large-vessel occlusion, suggesting an involvement of smaller vessels instead.

In line with this, we found a prominent micro-thrombus packing the vasculature of the lower dermis. The underlying mechanism for vascular thrombus formation in HES is currently poorly understood. Previously, it was shown that cytotoxic ECP could play a role in the inhibition of a specific anticoagulant, thrombomodulin. The inhibited activity of thrombomodulin was related to the thromboembolism found in eosinophilic endocarditis (10). In addition, ECP seemed to participate in eosinophil-induced vascular injury (11), and smoking history was associated with an elevated serum ECP level, which might in turn accelerate vascular damage (12). Together, an increase in serum ECP level in our case might influence further microvascular injury, leading to severe digital gangrene.



Fig. 1. (a) Digital necrosis with bony exposures on the finger-tips. (b) Brownish eczema-like patches and lichenified changes were noted on the left leg and other extremities.

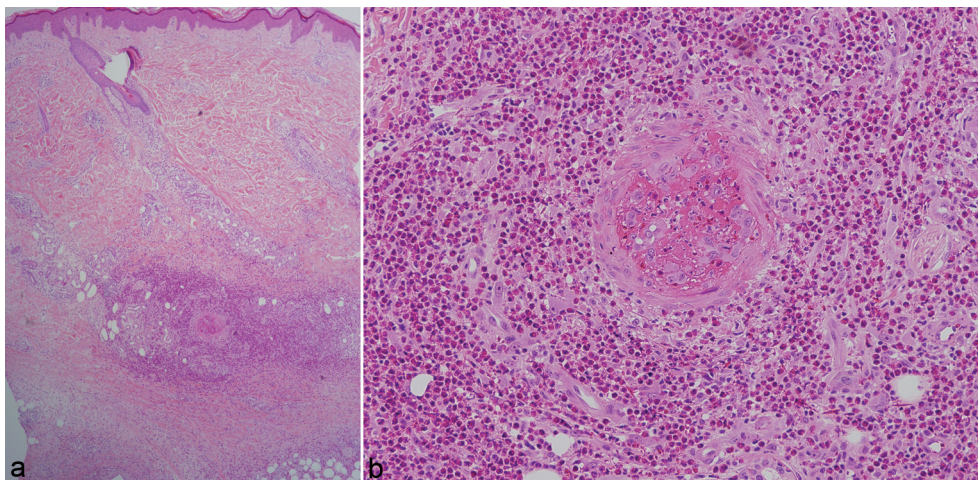


Fig. 2. (a) Marked infiltrate of eosinophils throughout the lower dermis and subcutaneous fat layer (haematoxylin-eosin (H&E) stain; original magnification: $\times 40$). (b) Fibrinoid change in the vessel wall and prominent luminal micro-thrombus with surrounding eosinophils were noted. (H&E; original magnification: $\times 200$).

True TAO, characterized by painful ulcers on the acral areas should be differentiated. Vascular abnormalities revealed on the imaging studies may not be a useful clue in differentiating TAO from TAO-like occlusion in HES (3, 5, 9). Typical pain occurring in patients with TAO may be a differential point, as necrosis in HES can be painless, as in our patient. Furthermore, histopathological findings of marked infiltration of eosinophils in HES can easily distinguish it from true TAO, where mixed-cellular infiltration is characteristic (13). Necrotizing eosinophilic vasculitis found in HES can also serve as differentiating clue (2, 14, 15).

Systemic corticosteroid is the treatment of choice for HES with the exception of *FIP1L1-PDGFR*A-positive myeloproliferative HES and chronic eosinophilic leukaemia, where imatinib mesylate is the first-line option (1, 8). However, digital gangrene in HES has been reported to be poorly responsive to corticosteroid therapy (5, 7). Vascular angioplasty combined with the use of anticoagulants and systemic corticosteroid showed a successful treatment outcome in a patient with arterial occlusion-associated digital necrosis in HES (9). However, vascular intervention cannot be employed without evidence of definite arterial occlusion. Discontinuation of tobacco use may be the definitive therapy, as in the case of TAO (13).

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