Hypereosinophilic syndrome complicated by severe vascular damage and gangrene

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ABSTRACT

Hypereosinophilic syndrome (HES) is a complex multisystem disease characterized by sustained overproduction of eosinophils. A 40-year-old woman presented with digital ischemia and gangrene on her distal fingers and toes. We diagnosed HES on the basis of marked eosinophilia, accumulation of eosinophils in organs, and cutaneous eosinophilic vasculitis after having excluded all differential diagnoses. On digital subtraction angiography, occlusion of several arteries of both lower legs was noted. HES may be associated with severe vascular damage including gangrene. The occurrence of digital gangrene is a differential diagnostic challenge that should also include investigations of blood parameters, such as eosinophils. (J Vasc Surg Cases and Innovative Techniques 2019;5:384-7.)

Hypereosinophilic syndrome (HES) is a complex multisystem disease characterized by sustained overproduction of eosinophils. Diagnostic criteria for HES include the following: peripheral blood eosinophilia with eosinophil counts >1500/μL for at least 6 months; no evidence of parasitic, allergic, or other known causes of eosinophilia; presumptive signs; and symptoms of multiple organ involvement. The most common cutaneous features of HES are erythematous pruritic papules and nodules, angioedema, and urticarial plaques.[1-3] We here describe a patient with HES presenting with cutaneous eosinophilic vasculitis and severe vascular damage resulting in digital gangrene. The patient's consent was obtained for publication.

CASE REPORT

In 2017, a 40-year-old Taiwanese woman who lives in Dubai presented with a 6-year history of digital ischemia and gangrene on her distal fingers and toes (Fig 1, *a* and *b*). Moreover, she complained of itchy skin lesions on her lower legs (Fig 2, *c*). She had no history of relapsing infections, smoking, hypercholesterolemia, hypertension, asthma, allergic rhinoconjunctivitis, or Raynaud phenomenon including the tricolor phenomenon. A marked elevation of peripheral eosinophil count 2 years before her presentation was noted in her medical history (2015, 5.121/μL; 2016, 12.188/μL). Nevertheless, she was initially diagnosed with thromboangiitis obliterans and later with systemic sclerosis by her previous physicians. On admission, her medication included sildenafil (25 mg/d) and bosentan (125 mg twice daily).

On physical examination, red-brown eczematous papules and lichenified plaques were noted on her lower legs. Two 5-mm punch biopsies from the left leg revealed marked infiltration of neutrophils as well as eosinophils throughout the lower dermis and subcutis. Eosinophilic vasculitis of dermal vessels was observed as well (Fig 2). Laboratory investigations revealed an increased white blood cell count (32.280/μL) with severe eosinophilia (60.010/μL) and an elevation in serum eosinophil cationic protein (>34.1 μg/mL). Moreover, she had mild anemia of 10.5 g/dL. Stool parasite examination and serologic test results for serum antineutrophil cytoplasmic antibodies, immunoglobulin (Ig) M, IgA, vitamin B_{12}, serum tryptase, thrombocytes, human immunodeficiency virus/human T-lymphotropic virus, and hepatitis were negative or within the normal range. Serum IgG and IgE were elevated at 2059 mg/dL and 123.388 mg/dL, respectively. Antinuclear antibodies were elevated at 1:1280. Cryoglobulins were present, including a cold antibody titer of 1:2. Chest computed tomography and abdominal ultrasound did not reveal pathologic findings. Flow cytometry of her blood revealed a slightly elevated CD4/8 ratio of 4.6 and increased T_H2/T_H1 ratio of 3.7. $CD3^-CD4^+$, $CD3^+CD4^-CD8^-$, and $CD3^+CD4^+CD7^-$ cells were not found. There was no monoclonal T-cell receptor rearrangement in her blood. Digital subtraction angiography showed occlusion of the arteria tibialis anterior and proximal arteria fibularis on both legs. Moreover, occlusions of arteria tibialis posterior were demonstrated on both legs (Fig 3). Lung function investigations revealed chronic obstructive lung disease, decreased forced expiratory volume in 1 second, and decreased vital capacity. Bronchoscopy including lavage showed abundant eosinophils. Even though she was asymptomatic with regard to gut symptoms, coloscopy revealed mild mucosal eosinophilia. Peripheral blood smear showed increased number of eosinophils without signs of dysplasia. Bone marrow aspiration revealed an increased number of eosinophils (about 6%) without evidence for a malignant process, such as eosinophilic leukemia or myelodysplastic syndrome.

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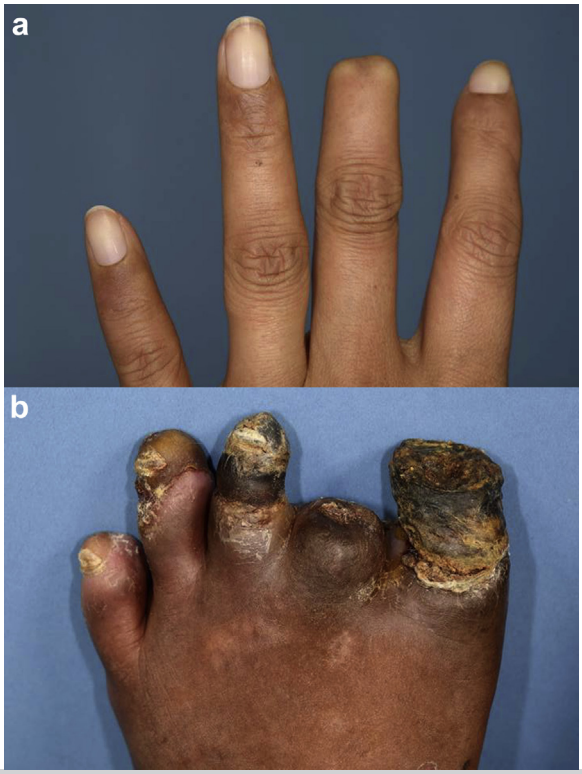

Fig 1. In a patient with hypereosinophilic syndrome (HES), the amputated distal phalanx of the third digit of the left hand **(a)** and more or less severe gangrene of all toes of the left foot **(b)**.

Mast cells were scanty. *FIP1L1/PDGFRA* gene fusion was not detected. In part, necroses of the toes were surgically removed. The patient showed a dramatic improvement after high-dose intravenous prednisolone (starting dose, 250 mg/d; maintenance dose, 10 mg/d for 4 weeks, thereafter 5 mg/d for 4 weeks) in a tapered dose regimen, including prompt normalization of blood eosinophil levels. At follow-up 3 months later, the patient reported that gangrene did not recur, and the surgery sites completely healed. Moreover, the itchy skin lesions on the lower legs had improved.

DISCUSSION

HES is a rare heterogeneous condition with different subtypes, including myeloproliferative, lymphocytic, overlap, familial, and undefined types. However, myeloproliferative HES (M-HES) and lymphocytic HES (L-HES) represent the most common subtypes.[1,2] In general, the most common systems involved in HES are the hematologic, cutaneous, cardiovascular, pulmonary, and neurologic, among others. The majority of patients with M-HES show a fusion of genes encoding Fip1-like 1 (*FIP1L1*) and platelet-derived growth factor receptor α (*PDGFRA*).[1,2] Compared with patients with L-HES, M-HES patients more frequently show dysplastic eosinophils on peripheral smear, serum vitamin B_{12} level >1000 pg/mL, serum tryptase >12 ng/mL, anemia or thrombocytopenia, hepatosplenomegaly, bone marrow cellularity >80%, myelofibrosis, or spindle-shaped mast cells in the bone marrow.[1,2]

In L-HES, eosinophilia is generated by increased production of eosinophil hematopoietins, such as interleukin 5 that is produced by activated T lymphocytes. These abnormal T-cell populations show atypical patterns of surface markers and can be characterized from peripheral blood using flow cytometry or T-cell receptor rearrangement studies.[1,2] Markedly elevated serum IgE levels and the occurrence of cutaneous lesions are other factors indicative of L-HES. As also documented in this case, skin abnormalities are commonly the presenting feature of HES. There is a particularly high prevalence (up to 94%) of skin involvement in $CD3^{-}CD4^{+}$ L-HES patients.[1-6] Unlike the male predominance in the M-HES population, L-HES cases are evenly divided between male and female patients. Although the disease course of L-HES is generally more protracted, there must be specific concern for progression to lymphoma, in particular in $CD3^{-}CD4^{+}$ patients.[1,2] All in all, our clinical findings favored a diagnosis of L-HES, despite the fact that we could not detect common L-HES T-lymphocytic phenotypes (eg, $CD3^{-}CD4^{+}$) on flow cytometry. We also excluded other causes of eosinophilia, such as infections, medication, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), eosinophilia-myalgia syndrome, and IgG4-related disease.[1,2,7] Elevation of IgG is observed in about 20% of L-HES patients, but it is a hallmark of IgG4-related disease, which is an important differential diagnosis of HES. However, organ involvement clearly differs from that of L-HES.[7] The observation of elevated antinuclear antibodies and cryoglobulinemia is an unusual feature in HES and might rather be an unspecific epiphenomenon in this case. Nozawa et al,[8] however, reported a case of HES with synchronous malignant B-cell lymphoma and gastric tubular adenocarcinoma complicated by paraneoplastic cutaneous vasculitis with mixed cryoglobulinemia. They interpreted these complications as an important sign of paraneoplastic syndrome. In this case, however, we did not find evidence for any malignant neoplasms.

Thrombosis is a complication that can be seen in HES accompanied by eosinophilic vasculitis, which in combination with digital gangrene has sporadically been reported in patients with HES.[3-6] The underlying pathomechanism for vascular inflammation and thrombus formation or occlusion is obscure in HES. Previously, it was shown that cytotoxic eosinophil cationic protein 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.[9] In addition, eosinophil cationic protein seems to participate in eosinophil-induced vascular injury. Together, an excess of eosinophils with consecutive increase of serum levels of eosinophil cationic protein might influence

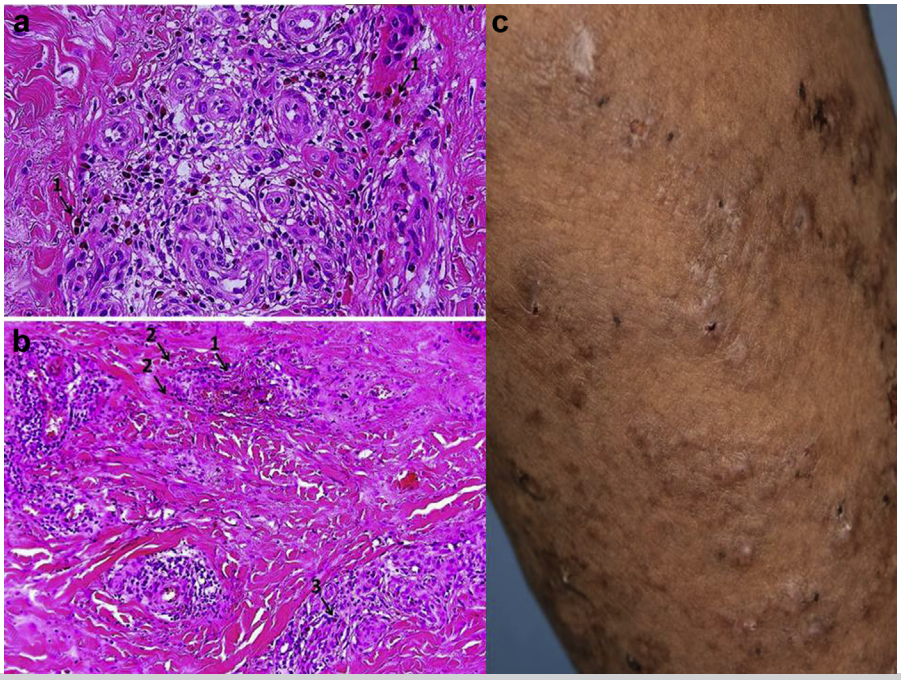

Fig 2. a, Histology of a biopsy specimen taken from the lower leg showed many eosinophils in the entire dermis, predominantly perivascular (*1*). **b,** Another biopsy specimen showed focal vessel destruction (*1*) with a few leukocytoclastic neutrophils and nuclear dust (*2*), with eosinophils located mainly around other (intact) vessels (*3*). **c,** The clinical picture showing red-brown, papulous plaques on the left lower leg of a patient with hypereosinophilic syndrome (HES).

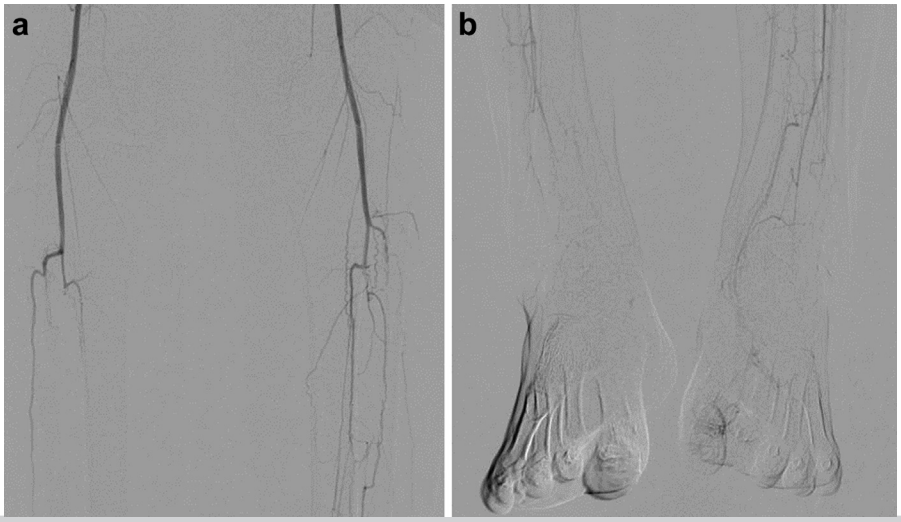

Fig 3. Digital subtraction angiography in a patient with hypereosinophilic syndrome (HES) revealed occlusion of the arteria tibialis anterior and proximal arteria fibularis on both legs **(a** and **b)**. Moreover, occlusions of arteria tibialis posterior are observed on both legs.

microvascular injury, leading to macrovascular damage and severe digital gangrene in this case.[10]

CONCLUSIONS

This case report demonstrates that HES may be associated with eosinophilic vasculitis and severe vascular damage leading to gangrene. The occurrence of digital gangrene is a differential diagnostic challenge that should also include investigations of blood parameters, such as eosinophils.

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