Hypereosinophilic Syndrome Accompanied by Buerger’s Disease-like Femoral Arterial Occlusions

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Abstract

A case of hypereosinophilic syndrome (HES) with a rare complication of Buerger’s disease-like large arterial occlusion (AO) was successfully treated with emergent percutaneous transluminal angioplasty and anticoagulants plus corticosteroid. By reviewing 15 reported cases of HES with AO including the present case, we found man predominance but no other consistent characteristics in HES with AO, such as age, smoking history, eosinophil counts or previous treatments, thus, predicting AO in HES patients appears to be difficult. Vessel intervention should be considered as a treatment option, since treatment delay in some patients has resulted in the amputation of extremities.

Key words: arterial occlusion, corticosteroid, hypereosinophilia, vessel intervention

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Introduction

Hypereosinophilic syndrome (HES) is a relatively rare hematologic disorder characterized by persistent increased numbers of peripheral eosinophils not caused by other factors, such as hematologic malignancies, allergy, parasitic infection, autoimmune disorders, or concomitant cancerous disease (1-8). HES affects patients with diverse backgrounds, has varied clinical manifestations and different treatment courses. HES has been classified into three subtypes, namely, the myeloproliferative (MP) type, lymphocytic (LC) type and idiopathic type, according to molecular pathophysiology and clinical behavior, and is recently categorized as a chronic myeloproliferative disorder in the latest WHO classification (1). The MP type, often associated with the FIP1L1-PDGFRA fusion kinase, tends to have a more aggressive clinical course in terms of organ damage and the progression to leukemia, and mostly overlaps the definition of chronic eosinophilic leukemia (CEL) in the latest WHO classification. The LC type is characterized by overproduction of Th2-type cytokines, such as interleukin (IL)-5, frequently represents an underlying T-cell disorder and sometimes develops T cell lymphoma later, however, the latest WHO classification excludes this subtype with apparent T cell immune disorders or malignancies from HES. Idiopathic HES does not meet the criteria of MP or LC type HES, and most importantly, it lacks the evidence for clonal eosinophil proliferation (1, 7-9). HES requires drug therapies, such as corticosteroids (CS), interferon-\alpha, or imatinib mesylate, to repress eosinophil counts for preventing both organ damages caused by excess inflammation due to tissue infiltration of hyperactive eosinophils, and the transformation to hematologic malignancies (4, 5).

Vessel occlusion caused by hypercoagulopathy due to excess eosinophil activation is one of the most severe complications of HES. Vessel occlusion is often a life-threatening event, e.g., acute myocardial infarction, and requires treatments in addition to the treatment administered to control peripheral eosinophil counts and activities (3, 10). Here, we report a case of HES complicated by the sudden onset of a relatively large, Buerger’s disease-like arterial occlusion (AO) in the lower extremities that was successfully treated with emergent percutaneous transluminal angioplasty (PTA).
plus drug therapies including CS and anticoagulant drugs. Following a review of the previously reported 14 cases of HES with peripheral AO and our case, we discuss the risks and histories associated with the development of AO, and suggest treatment for HES with AO (11-23).

Case Report

A 19-year-old man was initially brought to our hospital with persistent high pyrexia and pneumonitis. He was given acetaminophen to relieve pyrexia. The patient had no past history of allergic diseases. Blood examination revealed leukocytosis (12.2×10^9/l) with hypereosinophilia (4.0×10^9/l), thrombocytopenia (45.0×10^9/l), liver dysfunction and the elevation of C-reactive protein (5.8 mg/dl). Prolonged prothrombin time (16.5 sec) and increased fibrinogen derived product (24.4 μg/ml) and D-dimer (15.3 μg/ml) were also identified. According to the diagnostic definition (24), he was diagnosed with disseminated intravascular coagulation (DIC). Serum levels of IgE, IL-5 and soluble IL-2 receptor (sIL-2 R) were also elevated: 1350 IU/ml (normal range: <27.5-138.3 IU/ml), 25 pg/ml (0-8 pg/ml), and 3450 U/ml (<420 U/ml), respectively, however, there was no evidence for abnormal T cell population. Serum granulocyte-macrophage colony-stimulating factor (GM-CSF) was within the normal range. FIP1L1-PDGFRα fusion gene was absent in his blood cells. Autoantibodies, such as anti-nuclear antibody, P-ANCA, C-ANCA, or anti-cardiolipin antibody, were negative. Bone marrow study showed no abnormality in cell number, blast cell ratio, morphology, or karyotype. Based on these findings, he was diagnosed as having HES (1-9). CS therapy, including methylprednisolone pulse therapy, normalized his eosinophil counts and resolved all of his symptoms.

A year after termination of CS therapy, he was readmitted for claudication due to blood flow deficiencies in both legs. He did not smoke regularly during this period. The leukocyte count was 9.8×10^9/l with 2.6×10^9/l of eosinophils, and the platelet count was decreased to 11.4×10^9/l. Serum IgE was elevated to 610 IU/ml, while sIL-2R and coagulation tests were within the normal range. Autoantibodies remained negative. Angiography revealed complete obstruction at the lower part of the left superficial femoral artery for a 10 centimeter length with thrombus, collateral formation (Fig. 1A), perfusion delay and the vermicular-shaped structure at all three branches below the popliteal artery (Fig. 1B). To relieve the complete obstruction, emergent plain old balloon angioplasty (POBA) and antithrombus therapy with urokinase were performed. He was also given CS and antiplatelet, anticoagulant, and vasodilative drugs. These combination therapies successfully resolved his arterial occlusion resulting from a large thrombus and hypereosinophilia.

Discussion

The present case was diagnosed as HES, according to both the classical Chusid’s criteria and the latest WHO classification (1, 3, 7-9). Despite the high serum levels of sIL-2 R and IL-5 at the onset, the patient did not have accompanying T-cell disorder or malignancy. At his first presentation, he was treated with acetaminophen, and he later showed a positive reaction in the drug-lymphocyte stimulation test. It is possible that the abnormal activation of the lymphoid system driven by the acetaminophen treatment might accelerate cytokine production at the initial presentation in this case. However, drug-induced hypereosinophilia was diagnostically excluded, because hypereosinophilia relapsed even after cessation of acetaminophen administration at the onset of AO. The diagnosis of CEL was excluded, because our case did not show the evidence for clonal eosinophil proliferation, such as the FIP1L1-PDGFRα fusion gene, the accumulation of dysplastic mast cells, or high serum levels of vitamin B12 or GM-CSF (8, 9).

During remission after the termination of CS treatment,
the present case was affected by severe arterial occlusions in his legs that required emergent PTA. Buerger’s disease is an obstructive thromboangiitis that normally affects mid- to small-sized arteries distal to the popliteal arteries and often appears in young men. Thus, differentiating this case of Buerger’s disease-like peripheral arterial complication of HES from Buerger’s disease was difficult, but we based the diagnosis on the concomitant relapse of hypereosinophilia and the lack of smoking history. The other disease which should be differentially diagnosed in this case was Churg-Strauss Syndrome (CSS). The diagnosis of CSS requires fulfilling 4 of 6 criteria established by the American College of Rheumatology, namely, asthma, eosinophilia, mononeuropathy, transient pulmonary infiltrates on chest X-rays, paranasal sinus abnormalities, and biopsy containing a blood vessel with extravascular eosinophils (25). The present case fulfilled only two of these criteria.

We reviewed the backgrounds and clinical features of previously reported cases of HES with peripheral AO (Table 1) (11-23). We found from the 15 cases available for review that HES with AO occurs predominantly in men, while characteristics related to age, eosinophil counts, serum IgE level, or smoking habits were not correlated with the condition. Most reports did not identify the subtype of HES, i.e., CEL or idiopathic HES. The sites affected also varied among the cases, and most patients had pathologic arterial obstructions at multiple sites. POBA and the antithrombus therapy with urokinase effectively recanalized the complete obstruction of the left lower femoral artery, and CS therapy effectively resolved the incomplete obstructive lesions. According to the literature, CS therapy for peripheral arterial occlusions is not efficacious in all cases, and some patients required amputation despite CS treatment (Table 1) (11, 12, 23). Although eosinophils may be directly cytotoxic through the local release of toxic substances including cationic proteins, enzymes, reactive oxygen species, pro-inflammatory cytokines, and arachidonic acid-derived factors (5, 7, 8, 14, 26), the exact mechanism of eosinophil-related tissue damage is unknown. Therefore, the prediction and prevention of HES-related AO remain difficult. Further study is expected to clarify the pathogenesis of arterial complications of HES, which will assist in the identification of patients at high risk for vessel complications and in the establishment of better treatments.

In conclusion, AO accompanied by HES in our patient was successfully treated with emergent PTA in addition to anticoagulant and CS drug therapy. Our literature review suggests that emergent focal therapeutic interventions, such as interventional radiology, are effective for the sudden onset of AO in HES, as severe sequelae developed in some patients treated only with CS. Our study also revealed the difficulty of predicting the complication of peripheral arterial occlusions in HES based on patient clinical characteristics. Therefore, this type of relatively rare and emergent complication should be considered in patients suffering from HES, due to the lack of reliable markers for AO.

References


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