Idiopathic Hypereosinophilic Syndrome Presenting Acute Abdomen

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Abstract

We describe a 27-year-old man with hypereosinophilic syndrome (HES) presenting acute abdomen due to acute thrombosis of the mesenteric artery, who had a past history of eosinophilic pneumonia followed by multiple arterial thromboses of the extremities. At the recurrence of eosinophilia, he was treated with high-dose corticosteroids. Immediately after the reduction of peripheral blood eosinophils, he suddenly developed perforation of the intestine due to acute thromboses of mesenteric arteries despite sustained anticoagulation therapy. Molecular analysis demonstrated that the *FIP1L1-PDGFR* fusion gene was negative. Histopathology showed thrombi and eosinophilic inflammation of arteries. It is important to recognize that HES could be a cause of acute abdomen.

Key words: eosinophilic pneumonia, *FIP1L1-PDGFR* fusion gene, mesenteric artery, multiple thromboses

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Introduction

The hypereosinophilic syndrome (HES) comprises heterogeneous hematologic disorders characterized by unexplained sustained eosinophilia ($>1,500$ eosinophils/ μ l for more than 6 months), which is associated with signs and symptoms of organ involvement (1, 2).

Quite recently, approximately 50% of the cases of HES were reported to be caused by a cryptic deletion on chromosome 4q12, resulting in the generation of *FIP1L1-PDGFR* fusion gene (3-6). *FIP1L1-PDGFR* is a constitutively activated tyrosine kinase that provides proliferative and survival signals, and that can be inhibited by the small molecule kinase inhibitor imatinib (3, 6). *FIP1L1-PDGFR* positive patients show a dramatic response to imatinib therapy, and most of them achieve complete hematological and molecular remission. Several studies have indicated that at least two subgroups of HES patients can be distinguished: those with the lymphocytic variant of HES and those with the myeloproliferative variant of HES (3, 5, 7-9). The remaining HES patients that cannot be classified into these two subgroups are considered as idiopathic HES.

Here, we report a patient with idiopathic HES manifesting

acute abdomen due to acute thrombosis of mesenteric arteries.

Case Report

A 27-year-old man was readmitted with the past history of eosinophilic pneumonia due to the recurrence of hypereosinophilia. Previously, in April 2001, he visited another hospital, presenting high fever and increasing cough. Chest CT showed air-space consolidations on both lungs (Fig. 1A). His blood count showed leukocytosis (21,000/ μ l) with 54% eosinophils. Bone marrow aspiration showed marked eosinophilia but no karyotypic changes in chromosomal analysis. Pulse therapy with methylprednisolone was immediately started and resulted in clinical and radiological improvement. Then, corticosteroid was tapered on outpatient basis. In July 2003, blood circulation to right upper extremity and both thighs had progressively worsened. An angiogram demonstrated ultimate complete occlusion of bilateral brachial (Fig. 1B) and popliteal arteries (not shown). A right brachial-to-brachial artery bypass was performed. Because of the progression of thrombotic gangrene, amputations below bilateral elbows and knees were inevitably conducted in the orthopedic surgery department of our hospital. Postop-

Figure 1. (A) Chest CT scan of the patient demonstrates the air-space consolidation of bilateral lower lobes in April 2002. (B) Angiogram shows complete obstruction of bilateral brachial arteries of the same patient in July 2003.

eratively, he had been undergoing a physical rehabilitation program, while taking daily 10 mg of prednisolone as maintenance dose for the suppression of eosinophilia.

At the recurrence of eosinophilia, he was readmitted to our hospital in January 2005. Chest CT scan demonstrated minimal residual interstitial changes. Laboratory examination showed WBC count was 19,800/ μ l with 18% eosinophils. Serum immunoglobulin E was 1,830 IU/ml. Serum IL-5 level was elevated up to 201 pg/ml. Both lupus anticoagulant and anti-cardiolipin antibody were negative. Anti-neutrophil cytoplasmic antibody (p-ANCA and c-ANCA) was also negative. His international normalized ratio was maintained in the range above 3.0. *FIP1L1-PDGFR* fusion gene was negative by RT-PCR analysis, and T-cell receptor gamma gene rearrangement suggesting T cell clonality was negative (10, 11). Then, the diagnosis of idiopathic HES was made. He began to be treated with high-dose corticosteroids (50 mg daily of prednisolone). Although the remarkable reduction of peripheral blood eosinophils was promptly achieved, he suddenly developed severe abdominal pain and underwent an emergency laparotomy including the resection of the ileum and colon and colostomy. The perforation of ileum and colon due to acute thrombosis of the mesenteric artery was found despite sustained anticoagulant therapy consisting of warfarin and BayaspirinTM (Fig. 2A and B). Pathology of the resected specimen demonstrated numerous inflammatory cells including neutrophils

and eosinophils infiltrated into the Tunica intima of the arteries with thrombosis without granuloma formation (Fig. 2C). After surgery, he has been quite well on a maintenance dose of prednisolone.

Discussion

HES is a condition of sustained hypereosinophilia $>1,500/\mu$ l for more than six months with organ involvement. Tissue eosinophilic infiltration frequently involves the heart, lung, skin, and nervous system. Thus, HES is well known as a heterogeneous disorder with clinically variable manifestations. Until recently, the diagnosis could only be made after the exclusion of other causes of eosinophilia such as infections, inflammation and neoplastic diseases (1, 2).

Recent reports (3, 5) document the efficacy of imatinib mesylate (low dose such as 100 mg/day) in a majority of HES patients (65%). The discovery of the novel *FIP1L1-PDGFR* fusion gene, which is a gain-of-function gene on chromosome 4q12, elucidated the theoretical background of the effectiveness of imatinib mesylate in HES patients (3, 6, 9). Consequently, the detection of *FIP1L1-PDGFR* fusion gene is useful for distinguishing patients with myeloproliferative variant of HES from those with idiopathic HES.

The present patient is categorized as idiopathic HES, because neither *FIP1L1-PDGFR* fusion gene nor T-cell receptor gamma gene rearrangement was detected. The occur-

Figure 2. (A) Emergency laparotomy of the patient demonstrated broad area of perforation of the small intestine. (B) By direct vision, thrombi clogged the branches of mesenteric artery as indicated by arrows. (C) High magnification view of the inner table of the mesenteric artery (Hematoxylin-Eosin stain, $\times 200$ original magnification). The thrombus is present in the upper left side of the picture. There are infiltrations of the eosinophils (as indicated by arrows) in Tunica intima, some of which are breaking through Elastica interna into Tunica media (*). However, the rest of Tunica media is almost free of inflammation (not shown).

rence of acute vascular thrombosis of mesenteric artery could not be prevented despite anti-coagulant therapy (12). There have been two reports on arterial disease similar to this patient. One is a report of the development of thromboangitis obliterans requiring amputation of the legs in a 47-year-old man with HES (13), and the other is a report of the development of brachial artery occlusion requiring brachial-to-brachial bypass surgery in a 28-year-old woman with HES (14). However, vascular thrombosis of the mesenteric artery has never been reported among patients with HES in the literature (15). Published gastrointestinal manifestations of HES include ascites, diarrhea, gastritis, colitis, pancreatitis, cholangitis and hepatitis, but not intestinal perforation (2). The possibility of Churg-Strauss syndrome could be fi-

nally excluded by the lack of a history of asthma, the absence of the extravascular granuloma formation in histopathology, and the negative result of p-ANCA (9, 16).

Light microscope study of a resected specimen of the ileum showed marked infiltration of neutrophils and eosinophils involving almost exclusively the Tunica intima of small mesenteric arteries. However, neither Charcot-Leiden's crystals nor extravascular granulomas were observed in histopathology. Theoretically, eosinophil cationic protein (ECP) by its binding to thrombomodulin is implicated as the cause of the inactivation of the anticoagulation (17).

The eosinophil releases several granule proteins which are known to be cytotoxic, to incite thrombosis, or to cause endothelial damage. The release of eosinophil major basic pro-

tein and eosinophil cationic protein after infiltration of tissues and thrombosis leads to eosinophilic end-organ damage in concert (18). The cause for the thrombosis is multifactorial. Vascular adhesion molecule (VCAM-1) and platelet-activating factor may also play a part. Based on our experience, in order to prevent thrombosis, long-term warfarin treatment is necessary and the international normalized ratio of the patient should be kept in a range higher than 3.0, together with the immediate suppression of blood eosinophilia.

Treatment modalities other than corticosteroid, cytotoxic agents and interferon-alpha that might be offered to *FIP1L1-PDGFRα* gene-negative patients include monoclonal anti-IL5 antibody therapy and non-myeloablative bone marrow transplantation (BMT). First, preliminary studies with anti-IL5 antibodies have demonstrated a dramatic and prolonged

decrease of peripheral eosinophil counts in the majority of patients with HES in response to even a single dose of antibody regardless of the underlying cause (19, 20). But, monoclonal anti-IL5 antibody is currently unavailable except in clinical trials being conducted in Europe and America. Secondly, non-myeloablative BMT has been used successfully in several patients with HES (21). However, this treatment modality should be reserved for patients who became resistant to imatinib and *FIP1L1-PDGFRα* fusion gene-negative patients with progressive organ damage despite standard treatment because of BMT-associated morbidity and mortality (22).

In conclusion, it is important to recognize the possibility of acute thrombosis of the mesenteric artery as the cause of acute abdomen seen among patients with hypereosinophilia.

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