Thrombotic Thrombocytopenic Purpura Complicated with Hypereosinophilic Syndrome

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Abstract

An 80-year-old woman was referred to our hospital because of eosinophilia and thrombocytopenia. She presented with persistent pruritus and cough. Laboratory examinations showed persistent eosinophilia, and there was no underlying cause, consistent with hypereosinophilic syndrome (HES). After admission, she developed a neurological deficit, and microangiopathic hemolytic anemia. She was diagnosed with thrombotic thrombocytopenic purpura (TTP) and successfully treated with corticosteroids and plasmapheresis. Although TTP has been described in association with pregnancy, cancer, collagen diseases, infection, and drug intake, hypereosinophilia is not a well-documented cause of this disorder. To our knowledge, this is only the second case of TTP with HES, proved to be caused by ADAMTS13 inhibitor.

Key words: thrombotic thrombocytopenic purpura, hypereosinophilic syndrome, thrombotic microangiopathy, eosinophilia


Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, renal involvement, neurologic symptoms, and fever (1). It develops mainly in patients who have underlying conditions such as pregnancy, cancer, collagen diseases, infections including HIV, and drug intake such as immunosuppressive agents, chemotherapeutic agents, and ticlopidine (2). Recent studies have indicated that the deficiency of A Disintegrin-like and Metalloprotease with Thrombospondin Type 1 Motif, 13 (ADAMTS13) is a cause of TTP (1, 2).

Hypereosinophilic syndrome (HES) is a rare disorder defined as persistent eosinophilia, for which no underlying cause can be found despite extensive diagnostic evaluation, and which is associated with organ dysfunction (3). It commonly involves the heart, lungs, central nervous system, skin and gastrointestinal tract. Tissue infiltration and the local release of cytokines and humoral factors by the eosinophils lead to tissue damage although the exact mechanism has not been elucidated. Considerable heterogeneity exists among patients with HES, and various subtypes of the disorder have been recently recognized. To date, 3 cases of thrombotic microangiopathy (TMA) associated with HES have been reported (4, 5). Among them, there was only one case of TTP caused by the inhibitor against ADAMTS13; that was suspected to be a drug-induced case (5). Here, we present a patient with HES who developed TTP by the inhibitor against ADAMTS13 and was successfully treated with corticosteroids and plasma exchange.

Case Report

An 80-year-old woman was referred to our hospital for evaluation and therapy of eosinophilia and thrombocytopenia. She had had a history of right nephrectomy due to renal tumor 22 years previously, and resection of mediastinal tumor 10 years earlier. She was receiving no permanent medication. Three months earlier, she developed persistent pruritus and cough. Her white blood cell count at that time was 6.4×10⁹/L with 15% eosinophils. Hemoglobin was 11.4 g/dL, platelet count 302×10⁹/L, lactate dehydrogenase...
(LDH) 208 U/L (normal range <211 U/L), and total bilirubin 0.5 mg/dL. Her primary care physician treated her with antihistamines and steroids for external application, but her symptoms were not resolved. One month prior to admission, she presented with anorexia, nausea, and vomiting. At presentation, her physical examination was remarkable for petechiae, ecchymoses, and bilateral wheezing, but showed no evidence of neurological symptoms. Her white blood cell count was 12.3×10^9/L with 69% eosinophils (absolute eosinophil count was 8.5×10^9/L). Hemoglobin was 7.7 g/dL, platelet count 6×10^9/L, LDH 1,131 U/L (normal range <229 U/L), total bilirubin 1.83 mg/dL, blood urea nitrogen 43.1 mg/dL, and creatinine 1.5 mg/dL. Reticulocyte count was not increased. Prothrombin time and partial thromboplastin time were normal. Serum IgE and vitamin B12 levels were significantly elevated. Stool examination was negative for ova and parasites. An antinuclear antibody, antineutrophil cytoplasmic antibody, and antidouble-stranded DNA antibody were all negative. Complement levels were normal. A chest radiograph and a computed tomographic scan were normal. A bone marrow aspirate showed marked hypereosinophilia in a background of normocellular bone marrow (Fig. 1). The eosinophil count was 25.8%, and the myeloblast count was less than 5%. Chromosomal karyotype analysis of bone marrow cells showed the 46, XX pattern in all 20 cells analyzed. FIP1L1-PDGFRα rearrangement was not detected by FISH analysis of bone marrow cells. The patient showed persistent eosinophilia in blood, increased numbers of bone marrow eosinophilia, and myeloblasts < 20% in blood or marrow. Moreover, there was no demonstrable disease that could cause the eosinophilia, and no evidence of a clonal myeloid disorder. So she was diagnosed with HES according to the criteria of World Health Organization Classification of Tumours (6).

On admission, the patient received red cell and platelet transfusions because of hemorrhagic tendency. Two days later, she developed a sudden neurological deficit with coma, and microangiopathic hemolytic anemia. Laboratory results included the following: hemoglobin 7.2 g/dL; platelet count 14×10^9/L; LDH 2,317 U/L; total bilirubin 5.03 mg/dL with 1.94 conjugated; blood urea nitrogen 53.8 mg/dL; creatinine 0.9 mg/dL; and haptoglobin not detectable. Peripheral blood smears revealed the presence of schistocytes and reticulocytosis. Results of direct and indirect antiglobulin tests were negative. Serum fibrinogen and coagulation profile were normal. The activity of ADAMTS13 was found to be below 0.5%, and an inhibitor against the protease was found to be 5.1 Bethesda U/mL. On the basis of these findings the diagnosis of TTP was made. The patient immediately received plasma exchange at a dose of 40 mg daily concurrent with exchange plasmapheresis with fresh frozen plasma. She underwent 6 consecutive daily exchange sessions. After plasma exchange procedures, she had an immediate hematological response with gradual improvement in neurological status. An attempt of tapering plasmapheresis in combination with plasma infusion was successful. The patient’s eosinophilia was also resolved. After 3 weeks of treatment, the plasma infusion was stopped, and tapering of prednisolone was started. Five weeks after the initiation of treatment, the ADAMTS13 activity was found to be 40%, and an ADAMTS13 inhibitor was not detectable. The clinical course and treatment are shown in Fig. 2. She was discharged 6 weeks after admission. The patient remains in complete remission for more than 6 months.

Discussion

Thromboembolism is one of the most serious complications in HES. It has been suggested that about one-quarter of HES patients develop thromboembolic complications and that 5-10% die as a result of these complications (7). The mechanisms underlying the thrombotic diathesis in HES are not fully understood, but the four main granule proteins released by eosinophils; major basic protein (MBP), eosinophil derived neurotoxin (EDN), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO). These have been thought to cause hypercoagulation. ECP has been reported to promote coagulation through a factor XII-dependent mechanism (8). MBP and EPO have been shown to be platelet agonists (9). MBP can inhibit the anticoagulant activities of endothelial membrane by binding to thrombomodulin (10, 11). Moreover, hypothiocyanous acid (HOSCN), the predominant oxidant of EPO, has been shown to stimulate tissue factor expression in endothelial cells, raising the possibility that EPO, via the generation of HOSC, functions to promote thrombosis (12). In patients with HES, the most described thromboembolic events are intracardiac and pulmonary thrombosis, and cases such as cutaneous thrombosis, hepatic vein thrombosis, disseminated intravascular coagulation, aortic thrombosis, and cerebral sinus thrombosis, have also been reported (7, 13-17). But there have been only 2 reports of TMA associated with HES (4, 5). Liapis et al reported 2 cases of HES who developed acute renal failure, showed clinical and laboratory findings of hemolytic uremic syndrome and TTP, and had findings of TMA with evidence of degranulated eosinophils in the renal biopsy (4). They suggested that cytopathic effectors released by degranulated
eosinophils led to endothelial injury and TMA, however, the activity of ADAMTS13 and the existence of the inhibitor against it were not examined in these 2 cases. On the other hand, Al Aly et al reported a HES case with TTP caused by the inhibitor against ADAMTS13 (5). The patient was treated with imatinib mesylate and subsequently developed TTP, suspected to be a drug-induced case, although TTP has not previously been reported in association with imatinib mesylate (5). In the present case, there was no history of medication and underlying disease without HES, therefore, the inhibitor against ADAMTS13 might have been induced by increased eosinophils, however, the association between HES and TTP remains unclear.

Recently, imatinib mesylate has been reported to be effective for HES with the FIP1L1-PDGFRα fusion gene (18). Therefore, we investigated whether our patient had the FIP1L1-PDGFRα rearrangement or not. But this fusion gene was not detected by FISH analysis although RT-PCR was not performed. After the initiation of prednisolone therapy, the eosinophil level in our patient was rapidly decreased (Fig. 2) and her symptoms, such as pruritus and cough, were also resolved. A remission of HES is sustained with maintenance therapy in which the prednisolone dose is below 10 mg per day, and there is also no sign of recurrence of TTP.

In summary, we describe a case of HES developing TTP and successfully treated with corticosteroids and plasmapheresis. Our report suggests that hypereosinophilia might lead to TTP although the mechanism remains to be elucidated. The complication of TTP should be considered as one of the differential diagnoses if a patient with HES develops thrombocytopenia.

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