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A Case of Therapy-resistant Idiopathic Hypereosinophilic Syndrome with Severe Disseminated Intravascular Coagulation

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Abstract Disseminated intravascular coagulation (DIC) is a rare complication of idiopathic hypereosinophilic syndrome (HES). We report a case of therapy-resistant HES complicated with DIC, in which the sequential profile of vascular endothelial adhesion molecule, eosinophil granule proteins, and several cytokines during clinical course were observed. Serum proteins derived from eosinophil granules and serum soluble vascular cell adhesion molecule 1 had elevated and fluctuated along with the eosinophilia and DIC. The level of serum tumor necrosis factor-α, which stimulates eosinophil attachment to endothelium, was also high in overt DIC. These findings suggest that there may be strong interactions between eosinophils and vascular endothelium and that adherence of eosinophils to endothelium and production of eosinophil granule proteins may contribute to the development of DIC in HES.

Key words: hypereosinophilic syndrome, disseminated intravascular coagulation, eosinophil granule proteins, cytokines

Introduction

Idiopathic hypereosinophilic syndrome(HES) is a rare disorder, characterized by persistent unexplained eosinophilia with organ involvement. Eosinophils infiltrate various organs, such as bone marrow, heart, lung, liver, and nerves, resulting in multiple organ damage.[1] Coagulation disorder is an uncommon complication in HES and only a few cases that complicated with disseminated intravascular coagulation syndrome (DIC) were previously reported.[2)3)] The pathophysiological relation between eosinophilia and coagulopathy is not understood well.

We report herein a case of therapy-resistant HES complicated with DIC, with sequential refer to the profile of vascular endothelial adhesion molecules, eosinophil granule proteins, and several cytokines during the clinical course.

Materials and Methods

Serum interleukin 5 (IL-5, reference range: < 10 pg/ml), IL-10 (reference range: < 7.05 pg/ml), soluble IL-2 receptor (sIL-2R, reference range: 145 - 519 U/ml), and soluble vascular cell adhesion molecule 1 (sVCAM-1, reference range: 358 - 1,020 ng/ml) were measured by enzyme-linked immunosorbent assay. Serum interferon γ (IFN-γ, reference range: < 20.6 pg/ml) was measured by enzyme immunoassay. Serum IL-6 (reference range: < 4.0 pg/ml) and serum tumor necrosis factor-α (TNF-α, reference range: < 6 pg/ml) were measured by chemiluminescent enzyme immunoassay. Eosinophil cationic protein

(ECP, reference range: < 15.7 μg/l) and eosinophil protein X (EPX, reference range: < 0 μg/ml) were measured by radioimmunoassay. Sera were stored at -20° C until use.

Case report

A 54-year-old Japanese male had been well until one month earlier before admission when high fever and general fatigue developed. Physical examination on admission showed mild anemia and hepatomegaly, which was palpable up to 7 cm below the right costal margin, but no splenomegaly or lymphadenopathy. Heart sounds were normal and there were no eruptions. Neurological examinations revealed no abnormalities. Peripheral blood count revealed anemia (Hb 9.2 g/dl) and thrombocytopenia (platelets 8.9 x 10^4/μl). WBC was 9,500/μl with 74% eosinophils, which exhibited no morphological abnormalities. No atypical lymphocytes were observed. Bone marrow findings revealed hypercellular marrow and 26% eosinophils with various stages of maturation. Chromosome analysis showed a normal karyotype. The score of neutrophil alkaline phosphatase was normal. Serum vitamin B_{12} level was 1,296 pg/ml. Biochemical studies revealed total bilirubin 0.6 mg/dl, AST97IU/l, ALT45IU/l, LDH1629IU/l with type 3 isozyme dominant, and C-reactive protein 2.7 mg/dl. A coagulation study was almost normal except for a slight increase in the fibrinogen/fibrin degradation products (FDP) and D-dimer. Both anti-nuclear antibody and rheumatoid factor were negative. The serum level of IgE was normal. Repeated performed blood cultures were all negative, and there was no evidence of parasite infection. Chest X-ray was normal and abdominal ultrasonography and computed tomography showed only hepatomegaly. Percu-taneous liver biopsy revealed only mild proliferation of bile ducts in Glisson's sheath. No findings of hepatitis or atypical cell infiltration were observed. Upper and lower gastrointestinal endoscopy revealed no inflammatory or malignant lesion. Electrocardiogram and cardiac ultrasonography were unremarkable.

Clinical course

Although extensive examinations for eosinophilia were performed, no apparent etiology for eosinophilia was identified. Thus the diagnosis of HES was made.

After admission, thrombocytopenia had developed to 5.4 x 10^4/μl with rapid and marked increase of D-dimer, 127 μg/ml. The levels of thrombin-antithrombin complex and plasmin-plasmin inhibitor complex were also high, 80 μg/l, and 14 mg/l, respectively. These findings indicated the development of DIC. Prednisolone (55 mg/day) and gabexate mesilate (2,000 mg/day) were instituted for HES and for DIC, respectively. The steroid therapy resulted in the marked reduction of eosinophils in peripheral blood (Fig. 1). Pyrexia and DIC had improved with the resolution of eosinophilia, but his liver showed only a little reduction in size. Along with the taper of prednisolone, high fever developed again and eosinophilia and DIC became apparent. One course of combination chemotherapy (CHOP; cyclophosphamide, doxorubicin, vincristine, prednisolone) was performed with transient reduction in the number of eosinophils. Eosinophilia and other accompanied symptoms reappeared and rapid progression of anemia and thrombocytopenia were observed after the recovery from CHOP therapy. Bone marrow examination revealed hypercellular marrow with numerous smudges of cells and eosin-stained necrotic tissue, suggesting the presence of bone marrow necrosis. Methylprednisolone pulse therapy (1,000 mg for 3 days and tapered) was performed without effectiveness. Although vincristine (2 mg /body) and prednisolone (50 mg/day) were administered subsequently, pancytopenia occurred and DIC became exacerbated. Bone marrow aspiration showed many hemophagocytes in the smudge. Pancytopenia had not improved and severe bleeding from gingiva, subcutaneous tissue, gastrointestinal tract, and lung developed, and the patient expired on the 184th hospital day.

At autopsy gross examination showed hepatomegaly, bone marrow necrosis, and massive bleeding from the lung and gastrointestinal tract. On microscopic examination, there were no significant histopathological

findings in the liver. Cardiac muscles were not damaged. Inclusion bodies were seen in the liver, lung, pancreas, adrenal gland, and bone marrow, indicating systemic cytomegalovirus infection.

Serum ECP, EPX, and sVCAM-1 were elevated on admission and fluctuated during the clinical course (Fig. 1).

Discussion

Most cases of eosinophilia is caused by a reactive proliferation of eosinophils accompanied with some diseases. In the present case, however, there were no relevant causes of eosinophilia, such as allergic disease, skin disease, collagen disease, malignant tumor, or infection of parasites. Systemic cytomegalovirus infection, revealed at autopsy, was not considered to be the primary cause of HES. It might occur secondary to immunosuppression in the end stage of clinical course. Although it is reported that several specific cytogenetic abnormalities in chronic eosinophilic leukemia and HES were noted,[4)5)] morphological findings of eosinophils were normal and clonal proliferation of eosinophils could not be confirmed at least by chromosome analysis in this case. Due to the extremely high levels of serum sIL-2R and ferritin, the presence of lymphoid malignancies was also suspected, but no immature blastic cells were detected in peripheral blood, bone marrow, or liver. We diagnosed this case as an acute progressive type of HES, though taking account for the well-known criteria of HES that requires persistant eosino-philia for at least six months.[1)]

HES rarely accompanies DIC. In a few reported cases of HES with DIC, the coagulopathy was successfully treated by prednisolone and/or cyclosporin.[2)3)] The association

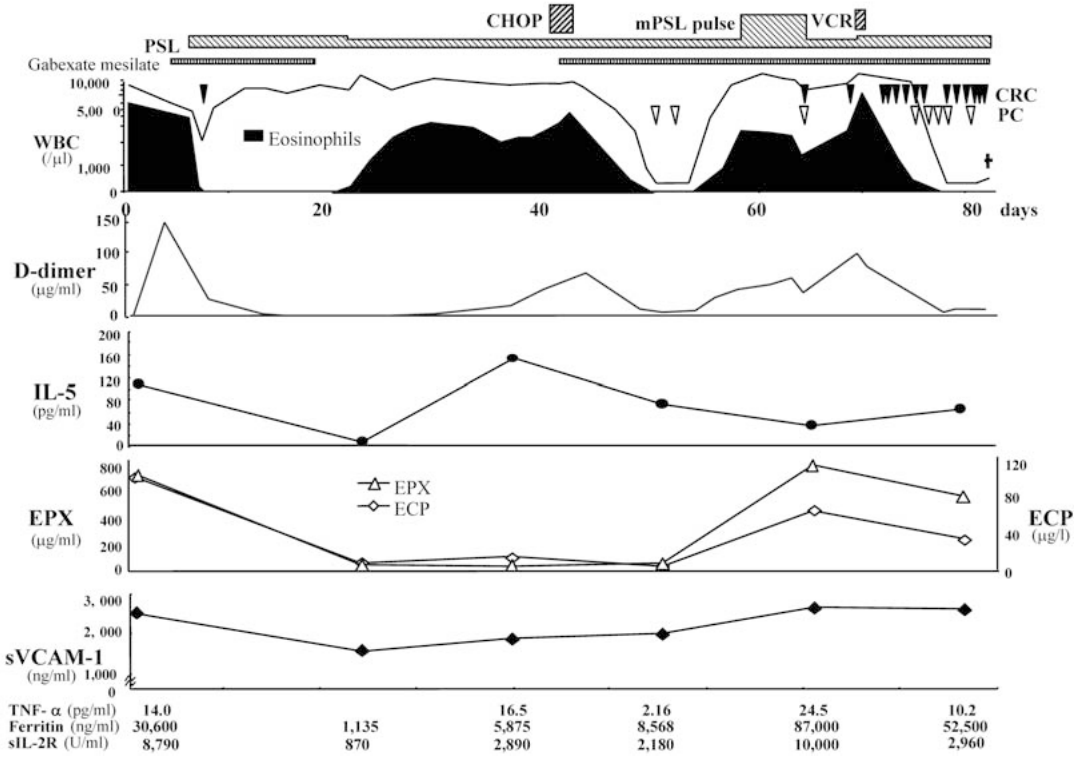

Fig. 1 The clinical course. PSL indicates prednisolone; mPSL, methylpredni-solone; VCR, vincristine; CHOP, cyclophosphamide, hydroxydoxorubicin, vincristine and prednisolone; WBC, white blood cell counts; IL-5, interleukin-5; EPX, eosinophil protein X; ECP, eosinophil cationic protein; sVCAM-1, soluble vascular cell adhesion molecule 1; TNF-α, tumor necrosis factor-α; sIL2-R, soluble interleukin-2 receptor; CRC, concentrated red cells; PC, platelet concentrate.

between DIC and eosinophilia has not been clear. Yamada et al. suggested the possibility that the eosinophil granule proteins, such as ECP, EPX, eosinophilic peroxidase (EPO), and major basic protein (MBP) induce DIC in HES.[2] It was also reported that EPO and MBP induce an activation of platelets in vitro.[6]

Our case is the first report that the eosinophil granule proteins are measured sequentially in the HES with DIC. In this case, both serum ECP and EPX were markedly elevated and fluctuated along with the eosinophilia and DIC. Serum soluble VCAM-1 also elevated and changed similar to the ECP, EPX, and eosinophil counts (Fig. 1). These findings suggest that there may be strong interactions between eosinophils and vascular endothelium. It was also reported that eosinophils express very late antigen 4 (VLA-4, integrin α4β1), through which eosinophils adhere to VCAM-1 expressed on the vascular endothelium and this adherence is stimulated by TNF-α.[7][8] In this case, the level of serum TNF-α was high, and such event might be expected.

The pathophysiology of eosinophilia with DIC is not well known. Adherence of eosinophils to vascular endothelium was promoted by TNF-α and production of eosinophil granule proteins might contribute to development of DIC in this case.

IL-5 is known as a key cytokine in the process of eosinophil differentiation and activation. IL-5 is secreted not only by T lymphocytes, especially Th2 cells, but also by eosinophils in an autocrine manner. In this case, the serum level of IL-5 was extremely high on admission and changed quite parallel to eosinophil counts. IL-5 was able to become as a good marker of HES in this case. However, it was not clear whether elevation of IL-5 was a primary cause of eosinophilia or reflected the secondary secretion by increased number of eosinophils.

We also examined the serum level of other Th1 and Th2 cytokines. The serum levels of IL-6 and IL-10, known as Th2 cytokines, were high on admission. The serum level of IFN-γ, one of Th1 cytokines, and sIL-2R were also elevated on admission (Table 1). Although it is not clear how this state of hypercytokinemia was associated with HES and DIC, these cytokines might play some important roles in the pathogenesis of HES, especially in aggressive cases complicated with DIC.

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Table 1 Cytokine examination on admission.

IL-5	161 pg/ml	(< 10 pg/ml)
IL-6	76 pg/ml	(< 4 pg/ml)
IL-10	220 pg/ml	(< 7.05 pg/ml)
IFN-γ	310 U/ml	(< 20.6 pg/ml)
sIL-2R	8790 U/ml	(145 - 519 U/ml)

( ): normal range.

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