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CASE REPORT

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Successful treatment of reactive hemophagocytic syndrome by plasmapheresis and high-dose γ-globulin in a patient with systemic lupus erythematosus

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Abstract A 31-year-old woman who had been administered corticosteroid and immunosuppressive agents for systemic lupus erythematosus (SLE) without flare-up was diagnosed as having reactive hemophagocytic syndrome (HPS) with severe disseminated intravascular coagulation. The causative underlying disease was uncertain, but it was not the SLE itself. Her fulminant HPS with increased serum ferritin and inflammatory cytokines (sIL-2R, TNF-α, IL-6, and IFN-γ) was successfully treated with plasmapheresis and high-dose γ-globulin therapy.

Key words Hemophagocytic syndrome · Virus-associated hemophagocytic syndrome · Plasmapheresis · High-dose γ-globulin · Systemic lupus erythematosus

Introduction

Reactive hemophagocytic syndrome (HPS) is a benign histiocytic disorder characterized by hemophagocytosis due to stimulated histiocytes in the bone marrow and reticuloendothelial systems, resulting in pancytopenia, hepatosplenomegaly, and disseminated intravascular coagulation (DIC).[1–3] Although the underlying disease is not always clear, the known causative disorders include infection, particularly virus-associated HPS (VAHS), lymphoma-associated HPS (LAHS), or autoimmune-associated HPS (AAHS), specifically acute lupus HPS (ALHS).[4] There is a high incidence of HPS accompanied by systemic lupus erythematosus (SLE). Based on SLE, HPS is thought to be induced by viral or bacterial infection, as well as some drugs such as nonsteroidal anti-inflammatory drugs, and the flare-up of SLE is not necessarily associated with HPS. We report on a patient whose SLE was complicated with fulminant HPS, and who was successfully treated with plasmapheresis and intravenous high-dose gammaglobulin (γ-glob) therapy. The combined therapeutic effects were suspected to be related to hypercytokinemia in this patient.

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Case report

A 31-year-old Japanese woman was admitted to our hospital on August 21, 1997, with spiking high fever and general fatigue. In 1979, she was diagnosed as having SLE based on facial erythema, photosensitivity, proteinuria, positive antinuclear antibody (ANA), and anti-DNA antibody. She was treated with methylprednisolone (PSL) pulses, followed by PSL at 60 mg/day for lupus nephritis. Before the present hospitalization, she had been successfully treated with tapered doses of PSL at approximately 15 mg/day for the past 18 years. Various immunosuppressive agents were combined with PSL one after another as follows: azathioprine (50 mg/day, 5 years), cyclophosphamide (50 mg/day, 2 years), or mizoribine (150 mg/day, 5 years). Before admission, she was treated with PSL at 12.5 mg/day and with mizoribine at 150 mg/day. Physical examination on admission revealed a body temperature of 38.2°C. Small tender cervical lymph nodes were palpable, but skin erythema was not observed. She had not complained of sicca signs or Raynaud's phenomenon. The peripheral blood counts revealed white blood cells at 6600/μl (metamyelocytes 2%, stab 30%, segment 47%, monocytes 6%, lymphocytes 10%, atypical lymphocytes 5%), red blood cells at 3.86×10^6/μl, hemoglobin at 10.5 g/dl, reticulocytes at 25‰, and platelet count at 59×10^3/μl. Lactate dehydrogenase (LDH) was high at 401 U/l (normal 96–220). C-reactive protein (CRP) was elevated at 4.5 mg/dl, and the erythrocyte sedimentation rate was increased at 57 mm/h. Urinalyses showed a one plus positive

protein, negative occult blood, and urinary excretion of protein accounted for 0.2 g/day. ANA was positive with a speckled pattern. Rheumatoid factor was less than 10 U/ml. Serum IgG was slightly elevated at 2040 mg/dl without showing a monoclonal pattern. She was positive for anti-Sm antibody, anti-RNP antibody, and anti-SS-A. Anti-DNA antibody (RIA) was 11 U/ml (normal <6) and complement activity (CH50) was 29.4 U/ml (normal 29–48), and these data did not change in the several months before admission. The serological activity of SLE was not thought to have increased. Coagulation studies showed disseminated intravascular coagulation (DIC), D–D dimer of 18.7 μg/ml (normal <0.5), FDP-E of 681 ng/ml (normal <100), thrombin antithrombin complex of 51.9 ng/ml (normal <3.0), and plasmin α_2PI complex of 2.3 μg/ml (normal <1.0).

She was treated with antibiotics, antifungal drugs, and gabexate mesilate (FOY), but her high fever (more than 39°C) continued. Her pancytopenia was progressive, with white blood cells at 2900/μl, hemoglobin at 9.8 g/dl, and platelet count at 39×10^3/μl on the 10th day of hospitalization. Repeated blood and urine cultures were negative for bacteria and fungus. Her general condition had worsened due to a tendency to bleed and persistent high fever. Serum levels of ferritin and soluble IL-2R (sIL-2R) were markedly high at 7560 ng/ml (normal 6.6–59.6) and 2019 IU/ml (normal 220–530), respectively. Moreover, serum inflammatory cytokines were markedly increased, with IL-6 at 51.0 pg/ml, TNF-α at 45 pg/ml, and IFN-γ at 39.4 IU/ml. Serum IL-6 was measured by chemiluminescent EIA (Fijirebio, Tokyo, Japan). TNF-α (Otsuka, Tokushima, Japan) and IFN-γ (Biosource Europe, Belgium) were tested using an ELISA kit. The serum 2′,5′-oligoadenylate synthetase levels were high. Serum antibody tests for EBV (VCA-IgG, ×640; VCA-IgM, less than ×10; EA-IgG, not decided; EBNA, ×40) revealed a post-infection pattern. EBV DNA was detected by polymerase chain reaction with peripheral mononuclear cells. Both IgG and IgM antibodies for human parvovirus B19 were negative by ELISA. Tests for cytomegalovirus, herpes simplex virus, and varicera-zoster virus antibodies using ELISA were positive for IgG and negative for IgM, and suggested no evidence of recent infection. Marked hepatosplenomegaly was shown by abdominal computed tomography, but ultrasound cardiography did not detect pericardial effusion. A bone marrow smear revealed stimulated histiocytes, which showed hemophagocytosis of erythroblasts, granulocytes, and platelets (Fig. 1).

Based on these findings, the patient was diagnosed as having fulminant reactive HPS complicated by severe DIC and hypercytokinemia. The causative disorder of the reactive HPS was uncertain, but it was not thought to be ALHS.

On day 14, she began methyl-PSL pulse therapy, but the high fever persisted and the DIC state progressed with increased ferritin and sIL-2R. Simultaneously, serum LDH and AST levels were high at 816 U/ml (normal 96–220) and 105 U/ml (normal 0–28), respectively. With the administration of high-dose γ-glob (20 g/day for 5 days) her fever was reduced, with an improvement in the thrombocytopenia and leucocytopenia. However, the effect of high-dose γ-glob was only transient. On day 28, 10 days after high-dose γ-glob therapy was begun, cyclosporin A was orally administered at a dose of 2.5 mg/kg/day. Thereafter, her fever slightly decreased, but after about 10 days of cyclosporin A treatment, she became febrile again (temperature over 38°C) with a trough level of 50–60 ng/ml. Her general condition was deteriorating. Her DIC state was progressive, with an increased D–D dimer at 109.8 μg/ml and a decreased platelet count at 58×10^3/μl. She was therefore treated with plasmapheresis, followed by high-dose γ-glob therapy. Plasmapheresis was carried out for three consecutive days with a membrane-type plasma separator (Plasmaflo op-05w, Asahi Emers, Tokyo, Japan), and 3–4 l treated plasma was exchanged for fresh frozen plasma (30 units/day). As a result, her fever gradually diminished and her general condition improved (Fig. 2). Clinical laboratory abnormalities such as DIC markers, CRP, LDH, thrombocytopenia, and leukocytopenia were all reduced. Serum ferritin, sIL-2R, and other inflammatory cytokines decreased after the combination of plasmapheresis and high-dose γ-glob therapy (Fig. 3). Her condition was followed for 30 months after treatment, during which time there was no flare-up of reactive HPS.

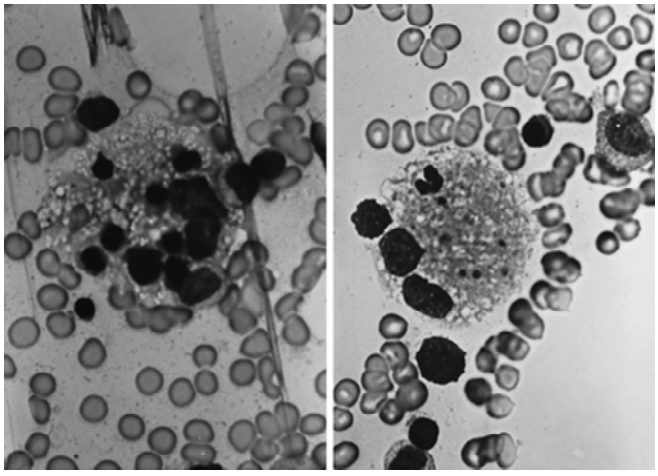

Fig. 1. Bone marrow aspirate showing stimulated histiocytes with phagocytosis of hematopoietic cells, including platelets, neutrophils, and erythroblasts (May–Giemsa stain)

Discussion

The clinical course of HPS varies from mild to severe fulminant.[1,5] The mortality rate among immunocompromised patients with VAHS is reported to be high, at about 40%.[6] This differs from cases of ALHS in which the underlying disease is SLE, since this can frequently be treated effectively with methyl-PSL pulse therapy only.[7] Over the age of 30, the presence of DIC, increased serum ferritin, and jaundice are the major factors indicating a poor prognosis.[8] The hypercytokinemia that results from acti-

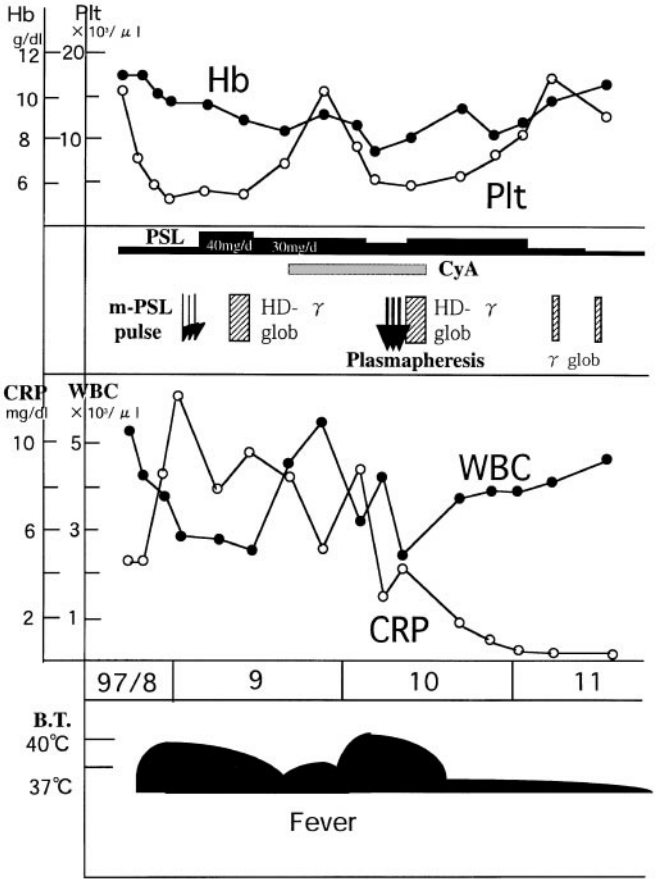

Fig. 2. Clinical course. *m-PSL*, methylprednisolone; *HD-γ glob*, high-dose γ-globulin; *CyA*, cyclosporine A

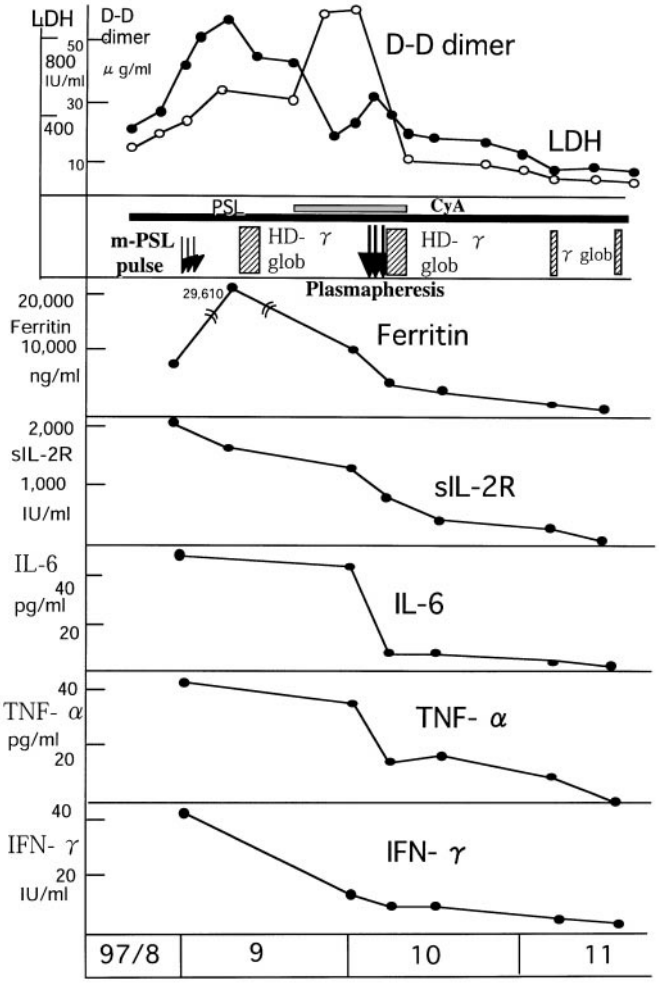

Fig. 3. Changes of D–D dimer, serum ferritin, and inflammatory cytokines. *sIL-2R*, soluble interleukin-2 receptor; *IL-6*, interleukin-6; *TNF-α*, tumor necrosis factor-α; *INF-γ*, interferon-γ

vated macrophages or T cells is thought to be important in HPS. Lay et al.[9] reported that infection of T cells by Epstein–Barr virus (EBV) selectively upregulates the TNF-α expression which, in combination with IFN-γ and probably other cytokines, has been observed to activate macrophages in vivo. Various cytokines such as IFN-γ, TNF-α, and IL-6 play major roles in the pathogenesis of HPS.[2,3] On admission, the general condition of this patient was poor. She had a high fever and a tendency to bleed due to severe DIC. Her serum sIL-2R, ferritin, TNF-α, IL-6, and IFN-γ were markedly elevated before plasmapheresis and high-dose γ-glob therapy. Following this combined therapy, the serum ferritin and cytokine levels were reduced in association with improvements in her clinical condition. Her laboratory data for pancytopenia, high serum LDH, and D–D dimers were improved in correlation with the decreasing cytokine levels. Serum ferritin and inflammatory cytokine levels reflected the activity of reactive HPS.

There was no evidence of a flare-up of SLE at any time during her clinical course; thus, the underlying disorder causing the reactive HPS remained unclear. However, the most likely cause was thought to be VAHS.

A variety of treatment modalities for reactive HPS have been used. The effectiveness of methyl-PSL pulse therapy,[7] cyclosporin A,[10,11] and etoposide[12] have been reported. Accumulating reports[2,10,11] have suggested the usefulness of cyclosporin A in the treatment of HPS, and it was found to be very effective for the severe progressive form of adult onset Still's disease, which is similar to HPS in that it is pathogenetically characterized by hypercytokinemia.[2] Cyclosporin A is known to suppress the cytokine production of helper T cells and inhibit the mitochondrial permeability transition by TNF-α, which destroys mitochondria and induces cell death in apoptosis.[2,13] In this patient, despite treatment with cyclosporin A, DIC was progressive and a high fever recurred. It was difficult to evaluate the effect of cyclosporin A, because the dose administered was insufficient. However, cyclosporin A can itself produce an immunodeficient state and make patients more susceptible to viral infection, especially SLE patients who have previously been treated with immunosuppressive agents over a long period. Immunosuppressive agents such as cyclosporin A may cause a weakened immune state, thus increasing the possibility that the virus will not be eliminated. It is important that the treatment of immunocompromised patients dose not further weaken their immune function.

Long-term administration of cyclosporin A should be avoided whenever possible.

This patient underwent high-dose γ-glob therapy twice. The first time, the high-dose γ-glob therapy was useful, but HPS activity could not be sufficiently suppressed by only one such course. The next high-dose γ-glob therapy was very effective because it was combined with plasmapheresis, which ameliorated the course of the disease, suggesting the immediate elimination of hypercytokinemia without a lapse into multiple organ failure. We thought that combined high-dose γ-glob and plasmapheresis could halt the fatal clinical course of reactive HPS in the present patient. Such therapy is very useful in immunocompromised hosts. Successful treatment with high-dose γ-glob for reactive HPS has been reported in a few other cases.[14,15] Although the mechanisms of action of high-dose γ-glob are complex, they are thought to include a direct neutralizing action on viruses, blocking of Fc receptors, anti-idiotype effects, and possibly down-regulation of helper T cell activation, immunoglobulin synthesis, and immune stimulation.[2] This patient's fulminant clinical status was improved by plasmapheresis and high-dose γ-glob. Further studies are required to confirm the usefulness of this therapy in immunocompromised patients, such as those with connective tissue disease, who have previously been treated with immunosuppressive agents over long periods of time.

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