Reactive Hemophagocytosis in Systemic Lupus Erythematosus

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A patient with systemic lupus erythematosus (SLE) developed reactive hemophagocytosis. This case did not show any underlying diseases such as infection or malignancy other than SLE itself. The mechanisms inducing hemophagocytosis in SLE seem to be heterogeneous and remain to be elucidated. Although an immune complex-mediated mechanism in cases with acute lupus hemophagocytic syndrome has been proposed, we suggest the possible involvement of IL-1β as the pathogenesis of our case.

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Introduction

Reactive hemophagocytosis is characterized by the activation of histiocytes with prominent hemophagocytosis in the bone marrow and reticuloendothelial systems, and its occurrence is usually associated with underlying disorders such as viral infection and lymphoma. Recently, Wong KF et al reported patients with reactive hemophagocytosis which occurred in association with underlying active systemic lupus erythematosus (SLE) itself, and proposed the disease entity of acute lupus hemophagocytic syndrome (ALHS) (1). The occurrence of ALHS was closely related with the presence of high titers of antinuclear antibodies (ANA) and hypocomplementemia, indicating that the immune complex-mediated mechanisms might be responsible for the pathogenesis of ALHS. We report here a case of SLE-associated reactive hemophagocytosis which suggested the possible involvement of cytokine-mediated activation of histiocytes rather than the immune complex-mediated mechanism.

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Case Report

A 29-year-old man was introduced to our hospital in 1994 because of fever of unknown origin which occurred after sun burn. He was diagnosed as having SLE based on the following symptoms and laboratory data: facial rash, photosensitivity, oral ulcer and positive ANA and anti-DNA antibody. The level of anti-DNA antibody was elevated up to 37.6 U/ml but hypocomplementemia was not observed. He was well treated with low-dose corticosteroids and non-steroidal anti-inflammatory drugs. However, in October 1996 he was admitted to our hospital because of lasting fever and pancytopenia. Pancytopenia was initially noticed 5 months before admission and had gradually worsened. No symptoms suggestive of active SLE were observed other than fever. The blood cell count showed white blood cell (WBC) 2.1×10⁹/l (7% neutrophils, 13% monocytes, 80% lymphocytes), red blood cell (RBC) 3.17×10¹²/l, hemoglobin 9.3 g/dl, reticulocytes 0.3%, platelet count 72×10⁹/l. Glutamic oxaloacetic transaminase (GOT) was 37 IU/l, glutamic pyruvic transaminase (GPT) 19 IU/l, lactate dehydrogenase (LDH) 790 IU/l. Erythrocyte sedimentation rate (ESR) was elevated (82 mm/h) and C-reactive protein (CRP) was positive (1.3 mg/dl). ANA was weakly positive (diffuse type, ×20), and the level of anti-DNA antibody was rather increased (28.5 IU/ml) as compared with the previous data (<10 IU/ml). Platelet-associated immunoglobulin G (IgG) (PA IgG) was positive (100.4 ng/10⁷ cells), although other autoantibodies, including anti-neutrophil antibody, direct Coomb’s test, anti-extractable nuclear antigen (ENA) antibodies and rheumatoid factor (RF) were negative. Hypocomplementemia was not observed (C3 89 mg/dl, C4 38.5 mg/dl, plasma level of complement (CH50) 42.6 U/ml). Circulating immune complexes were not detected. Serum ferritin was increased up to 1,745 μg/l. Coagulation studies did not show any signs of disseminated intravascular coagulation (DIC). Serum levels of cytokines: IL-1β, IL-2, IL-6, interferon (IFN)-γ, TNF-α were investigated and an increased level of IL-1β was found (0.889 pg/ml; normal ≤0.567). Bone marrow study revealed hypoplastic marrow with characteristic feature of the reactive hemophagocytosis (Fig.)
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Figure 1. Hemophagocytosis in bone marrow. The stimulated histiocytes showed phagocytosis of various hematopoietic cells including granulocytes, erythroblasts, erythrocytes and platelets. Histiocytic phagocytosis of mature neutrophil is noted (May-Giemsa stain, ×1,000).

1. The hemophagocytic histiocytes ingested granulocytes, erythroblasts, erythrocytes and platelets. Repeated urine and blood cultures were negative. Sputum was negative for bacterial and fungal cultures. There was no serological evidence of recent infection with Epstein-Barr virus (by fluorescence antibody method; FA), cytomegalovirus (by enzyme-linked immunosorbent assay; ELISA). The serum tests for parovirus B19 (by enzyme immunoassay; EIA), hepatitis A, B and C (by ELISA), human T lymphotrophic virus type 1 (HTLV-1) and human immunodeficiency virus (HIV) (by particle-agglutination; PA) were also negative. Thus, no apparent signs of active infection or serological evidence of viral infection were detected. After an extensive study, no causative disorder for reactive hemophagocytosis could be detected other than underlying SLE. He was treated with high-dose corticosteroid therapy with intravenous administration of methylprednisolone, 1 g/day for 3 days followed by 1 mg/kg/day prednisolone p.o. in addition to granulocyte-colony stimulating factor (G-CSF) (5 μg/kg/day) for 3 days (Fig. 2). As the consequence of these treatments, rapid improvement of pancytopenia was obtained concomitantly with the suppression of hemophagocytic histiocytes and the decrease of serum ferritin levels. This improved state could be successfully maintained with low-dose corticosteroid until now and no recurrent infection was documented.

Discussion

We report here a case of SLE who developed reactive hemophagocytosis. Several authors have reported patients with SLE complicated by infection-associated hemophagocytic syndrome (IAHS) (2). However, the present case did not show any clinical or serological findings of active infection. The evidence of no recurrent infection during the immunosuppressive therapy and the successful result without any use of specific agents for infectious pathogen suggest the unlikeness that our case had underlying infection. In addition, in extensive studies no other known underlying diseases for reactive hemophagocytosis could be identified. Hemophagocytosis occurred concomitantly with the elevation of the titer of anti-DNA antibody. Therefore, we suggest that the reactive hemophagocytosis of the present case is associated with the progression of SLE.

Several mechanisms inducing reactive hemophagocytosis have been proposed in association with underlying diseases. Wong et al have proposed an immune complex-mediated bystander mechanism as the pathogenesis of ALHS, in which the deposition of circulating immune complex on the marrow hematopoietic cells results in histiocytic hemophagocytosis through the binding of the antibody in the complex or activated complements to the receptors on histiocytes (1). This mechanism does not seem to be involved in the present case, because neither high titers of circulating immune complexes nor low serum complement level were observed. On the other hand, an autoantibody-mediated mechanism may be one of the mechanisms of autoimmune-associated hemophagocytic syndrome, in which autoantibodies directed against hematopoietic cells sensitize these cells through their binding in the bone marrow, resulting in the stimulation of histiocytes with phagocytosis of these sensitized cells (3, 4). But, significant levels of autoantibodies directed against hematopoietic cells were not developed in the present case except for PA IgG, and thus this mechanism is also unlikely involved in our case. Considerable evidence suggests that cytokines play an important role in the mechanism inducing reactive hemophagocytic syndrome (5-10). In virus-associated hemophagocytic syndrome (VAHS) or lymphoma-associated hemophagocytic syndrome, it has been suggested that IL-2, IFN-γ and TNF-α secreted by virus-infected T lymphocytes or lymphoma cells activate histiocytes to induce hemophagocytosis (5, 6). Actually in the present case, an increased serum level of IL-1β was detected. The possible role of IL-1β has been reported in the pathogenesis of hemophagocytic syndrome (11, 12). Thus, this monokine might play an important role in the induction of reactive hemophagocytosis in our case. The successful result of immunosuppressive therapy may be through the reduction of the intensive response of this cytokine. The reason why IL-1β production was enhanced in the present case even in the absence of infection or other complications is not clear. The enhanced production of IL-1β might be associated with the progression of SLE activity, but the precise role of this cytokine in the pathophysiology of our case remains unclear and should be elucidated.

In conclusion, the mechanisms inducing hemophagocytosis in SLE seem to be heterogeneous, and in our case the induction of histiocytic hemophagocytosis might be via an aberrant production of inflammatory cytokine, IL-1β, which may result from the discordant immune response in SLE. Whatever the mechanism, it is important to recognize the possibility of SLE-associated hemophagocytosis, because prompt treatment using immunosuppressive agents should be considered in these cases.
Figure 2. Clinical course of the patient with reactive hemophagocytosis. mPSL pulse, high-dose corticosteroid therapy with intravenous administration of methylprednisolone (1 g/day for 3 days); PSL: prednisolone (p.o.), G-CSF: granulocyte-colony stimulating factor (5 μg/kg/day) for 3 days.

References

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