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CASE REPORT

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# Reactive hemophagocytic syndrome in a case of systemic lupus erythematosus that was diagnosed by detection of hemophagocytosing macrophages in peripheral blood smears

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**Abstract** A 38-year-old woman with pancytopenia and liver dysfunction was diagnosed with active systemic lupus erythematosus (SLE). On days 9 and 10 of admission, peripheral blood smears showed macrophages phagocytosing platelets, and reactive hemophagocytic syndrome (HPS) was diagnosed. Hemophagocytic syndrome was successfully treated with high-dose prednisolone therapy and one course of methylprednisolone pulse therapy. Detection of hemophagocytosing macrophages in peripheral blood smears would be a useful and noninvasive method of diagnosing SLE-associated HPS.

**Key words** Cytokine · Hemophagocytic syndrome (HPS) · Hemophagocytosis · Peripheral blood smear · Systemic lupus erythematosus (SLE)

## Introduction

Reactive hemophagocytic syndrome (HPS) is a potentially fatal condition associated with various infections, neoplasms, and autoimmune diseases.[1–4] Hemophagocytic syndrome is characterized by the excessive activation of macrophages, which results in hemophagocytosis, cytopenia, fever, elevated serum ferritin level, abnormal liver function, and coagulopathy. Although the mechanism of the development of reactive HPS in autoimmune diseases remains unclear, several cytokines and autoantibodies have been implicated in its pathogenesis.[1,2,4,5] Here we describe a patient with reactive HPS associated with active systemic lupus erythematosus (SLE) and with increased serum levels of macrophage colony-stimulating factor (M-CSF), tumor necrosis factor (TNF)-α, and soluble interleukin-2 receptor (sIL-2R). In this patient, reactive HPS could be diagnosed early by detection of hemophagocytosing macrophages in peripheral blood smears.

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## Case report

A 38-year-old woman was referred to our hospital in July 2002 with a 2-week history of high fever. She had been administered a nonsteroidal anti-inflammatory drug and antimicrobial agent (cefcapene pivoxil) for 2 weeks, but these medications had no effect on the fever. Four days prior to presentation at our hospital, she had visited a different hospital where pancytopenia and liver dysfunction were found. She was then referred to our hospital and admitted.

On physical examination, the patient was alert but had persecutory delusion and marked illogical thinking. Her body temperature was 38.9°C. Muscle strength was 4/5 in her arms and she had difficulty standing from a squatting position. There were no skin lesions, oral ulcers, or arthritis. Her white blood cell count was 1500/μl (normal range, 3700–8000/μl), stab neutrophils 34.0%, segmented neutrophils 49.0%, lymphocytes 15.0%, monocytes 2.0%, hemoglobin 9.6 g/dl (11.5–15.0 g/dl), and platelet count $10.7 \times 10^4$/μL ($13.0–40.0 \times 10^4$/μl). Her direct Coombs test was positive. Urinalysis showed a protein level of 0.8 g/day, hematuria and granular casts, indicating that she had glomerulonephritis. She was diagnosed with SLE based on the findings of psychosis, glomerulonephritis, pancytopenia, elevated serum levels of anti-double-strand DNA antibody [>400 IU/ml (normal range, <10 IU/ml)] and anticardiolipin dependent on β2-glycoprotein 1 antibody [10.4 U/ml (0–3.4 U/ml)], and positivity for anti-Sm antibody, and antinuclear antibody (×1280, speckled pattern) in the serum. Her IgG index was 0.55 (0.33–0.55). The activity of SLE was considered to be high because of the markedly elevated

serum level of anti-double-strand DNA antibody and low serum levels of complements: Her $CH_{50}$ level was 1 U/ml (33–48 U/ml), C3 level 37 mg/dl (44–102 mg/dl), and C4 level 1 mg/dl (14–49 mg/dl). Moreover, reactive HPS was suspected due to elevated serum levels of transaminases and ferritin; she had an aspartate aminotransferase level of 218 IU/l (10–40 IU/l), alanine aminotransferase level of 92 IU/l (5–40 IU/l), and ferritin of 1878 ng/ml (10–90 ng/ml). Although there was little evidence of hemophagocytosis in repeated bone marrow studies, peripheral blood smears obtained on days 9 and 10 of the hospitalization showed several mature macrophages phagocytosing platelets, confirming the diagnosis of HPS (Fig. 1). She had elevated serum levels of M-CSF [2420 pg/ml (normal, <600 pg/ml)], TNF-α [14 pg/ml (<6.0 pg/ml)], and sIL-2R [1890 U/ml (<520 U/ml)]. The serum interferon (IFN)-γ level was below the detection limit. Additional tests did not reveal any malignancies or infectious diseases including Epstein–Barr virus and cytomegalovirus (CMV) infections. Therefore, reactive HPS was considered to be associated with active SLE. The patient was periodically monitored for CMV antigenemia.

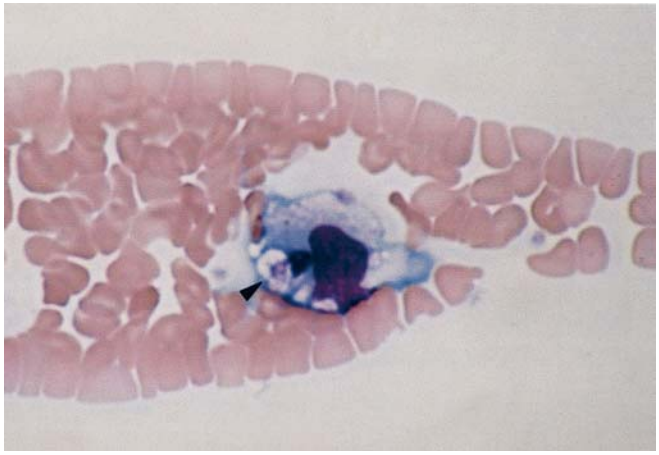

**Fig. 1.** Peripheral blood smear obtained on day 10 of admission showing a mature macrophage phagocytosing a platelet (*arrowhead*). The macrophage contains numerous small vesicles (May–Giemsa stain, ×400)

High-dose prednisolone therapy (60 mg/day) was started on day 10 of admission, but her liver dysfunction worsened with a further increase in the serum ferritin level to a maximal level of 2991 ng/ml. One course of methylprednisolone pulse therapy (1000 mg/day for 3 days) was administered from days 15 to 17 and high-dose prednisolone therapy was continued thereafter. Her muscle weakness, elevated serum ferritin level, and the activity of SLE including pancytopenia and low serum complement level, improved (Fig. 2). However, her psychosis remarkably worsened after the methylprednisolone pulse therapy. Moreover, her serum ferritin level started to increase again on day 30, and CMV-positive leukocytes (CMV-antigenemia) were detected in the peripheral blood on day 35 (Fig. 2).

Therefore, the dose of steroid was gradually reduced starting on day 39 and intravenous immunoglobulin (IVIG) was administered for 3 days on days 44 through 46. Thereafter, her psychosis, CMV-antigenemia, and elevated serum sIL-2R level gradually improved. On day 86, the serum levels of TNF-α, M-CSF, and sIL-2R became normal with a TNF-α level of <5.0 pg/ml, M-CSF level of 557 pg/ml, and sIL-2R level of 372 U/ml. The dose of prednisolone was reduced to 29 mg/day, and she was discharged on day 116. Two years after she was discharged, the dose of prednisolone was reduced to 7 mg/day in our outpatient department, and she has had no recurrence of HPS.

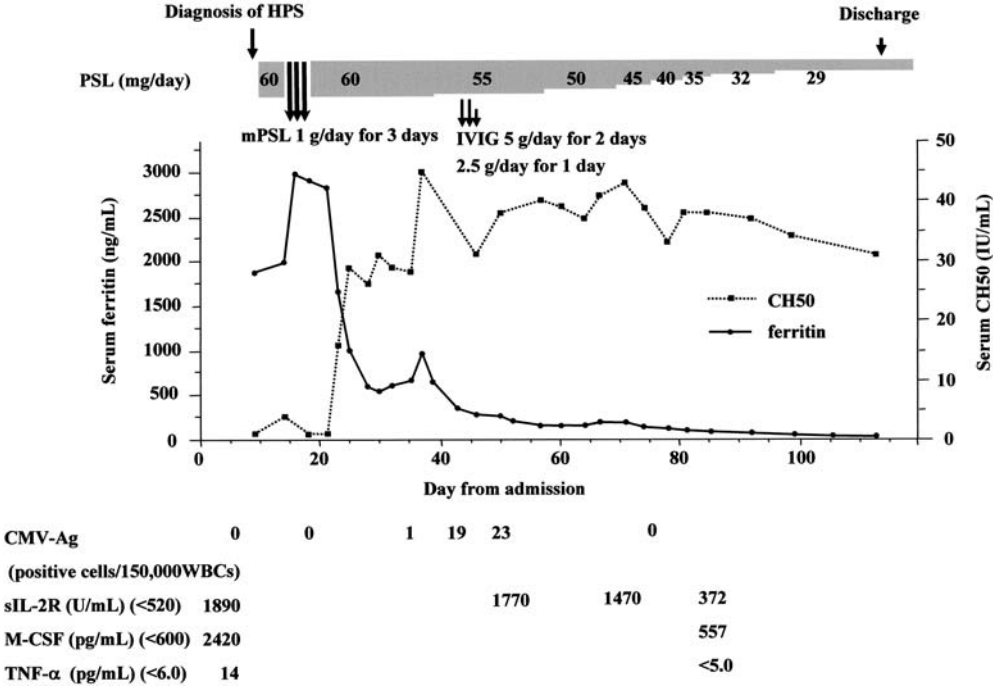


**Fig. 2.** Clinical course of the patient. *PSL*, prednisolone; *mPSL*, methylprednisolone; *IVIG*, intravenous immunoglobulin; *CMV-Ag*, cytomegalovirus antigenemia; *WBCs*, white blood cells; *sIL-2R*, soluble interleukin-2 receptor; *M-CSF*, macrophage colony-stimulating factor; *TNF-α*, tumor necrosis factor-α

## Discussion

Reactive HPS associated with high activity of SLE was first reported by Wong et al. in 1991.[1] Since then, case reports of HPS in SLE patients have been accumulating.[1–4] Although the six patients reported by Wong et al. showed a good response to steroid therapy,[1] a recent review paper suggested that the prognosis of HPS in SLE patients is not necessarily favorable.[3] Therefore, early diagnosis and treatment of reactive HPS in SLE patients are essential for a good outcome. In our patient, the diagnosis of reactive HPS was confirmed by detection of hemophagocytosing macrophages in peripheral blood smears (hemophagocytosis in the peripheral blood). High serum M-CSF and TNF-α levels may reflect the presence of activated macrophages.

Hemophagocytosis in the peripheral blood has rarely been described in the literature: it was reported to occur in patients with natural killer lymphoma/leukemia,[6] bacterial infection,[7] and tuberculosis mycobacteremia,[8] and as a reactive condition after administration of granulocyte macrophage colony stimulation factor.[9] The frequency of hemophagocytosis in the peripheral blood among patients with reactive HPS is not known, but a recent report suggested that hemophagocytosing macrophages might appear in the peripheral blood from the early stage of bacterial infection-associated HPS.[7] Detection of hemophagocytosis in the bone marrow, spleen, or lymph nodes is usually required to make a definitive diagnosis.[4,10] However, hemophagocytosis is not always seen in bone marrow aspirates and biopsies from patients with HPS,[3] particularly in bone marrow specimens obtained at the time of onset of HPS.[11,12] Therefore, failure to demonstrate hemophagocytosis does not necessarily exclude the diagnosis of HPS.[12] In patients with HPS, hemophagocytosis is seen more frequently among liver biopsy and splenic biopsy specimens than among bone marrow biopsy specimens.[8] However, when performing these invasive biopsies, there is a risk of HPS-related thrombocytopenia and coagulopathy such as disseminated intravascular coagulation. In this context, detection of hemophagocytosing macrophages in a peripheral blood smear would be a useful and noninvasive method of diagnosing reactive HPS. Further studies are required to elucidate the frequency of hemophagocytosis in the peripheral blood among patients with reactive HPS associated with each condition.

The precise mechanisms of the development of reactive HPS in SLE patients remain unclear, but at least two mechanisms have been proposed: a cytokine-mediated mechanism[2,4,5] and an autoantibody (including immune complex)-mediated mechanism.[1,2,4] As for the cytokine-mediated mechanism, overproduction of macrophage-activating cytokines (e.g., IFN-γ, M-CSF, interleukin [IL]-18) by various cells may activate a large number of macrophages and lead to hemophagocytosis. Moreover, sustained activation of macrophages results in additional production of proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α), leading to the clinical syndrome of reactive HPS, which includes fever, liver dysfunction, and coagulopathy. Regarding the autoantibody-mediated mechanism, autoantibodies such as antiphospholipid antibodies may bind to various hematopoietic cells, and antibody-coated hematopoietic cells are then phagocytosed by macrophages via binding between the Fc portion of autoantibodies and the Fc receptor on macrophages.[2,4] In the present case, the serum contained several autoantibodies including anticardiolipin dependent on β2 glycoprotein 1 antibody, as well as elevated levels of M-CSF, TNF-α, and sIL-2R, suggesting that both an autoantibody-mediated mechanism and a cytokine-mediated mechanism were involved in the pathogenesis of HPS.

A treatment strategy for reactive HPS in SLE patients has not been established. Immunosuppressive therapy is indicated when HPS occurs during the course of active SLE.[3,4] However, if an opportunistic infection occurs while the patient is receiving immunosuppressive therapy, the dose of the immunosuppressive drugs needs to be reduced and antibiotic therapy should be instituted. Administration of IVIG may be indicated in both situations.[3,4] In our patient, a high dose of steroid and steroid pulse therapy were administered at the time of onset of HPS. When opportunistic infection by CMV was detected by careful monitoring of CMV-antigenemia, the dose of steroid was reduced and IVIG was administered.

In conclusion, the present case suggests that detection of hemophagocytosing macrophages in peripheral blood smears is a useful method of diagnosing HPS associated with SLE.

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