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CASE REPORT

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Two cases of reactive hemophagocytic syndrome: a patient with adult-onset Still's disease and a patient with herpes zoster and autoimmune abnormalities

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Abstract We report two cases of bone marrow hemophagocytosis. One patient had adult-onset Still's disease, and the other had herpes zoster associated with potential autoimmune abnormalities. Our findings suggested a possible role of cytokines and/or antibodies in the induction of hemophagocytosis in patients with connective tissue diseases and/or immune abnormalities.

Key words Adult-onset Still's disease (AOSD) · Reactive hemophagocytic syndrome (HPS) · Virus-associated hemophagocytic syndrome (VAHS)

Introduction

Reactive hemophagocytic syndrome (HPS) is the widely used unifying term for various hemophagocytic diseases resulting from the systemic proliferation of benign histiocytes. It has been reported to be associated with viral infection (virus-associated hemophagocytic syndrome; VAHS) or bacterial infection, as well as malignancy (lymphoma and carcinoma), myelodysplastic syndrome, and autoimmune rheumatic diseases.[1] Among the rheumatic diseases, HPS is observed in the course of systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), progressive systemic sclerosis, rheumatoid arthritis, and adult-onset Still's disease (AOSD).[2–10] Autoimmune-associated hemophagocytic syndrome (AAHS) has been proposed as a collective clinical entity that encompasses such diseases.[6,7] Here we report the cases of two patients with HPS whose clinical and laboratory manifestations may contribute to clarifying the mechanism of AAHS.

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Case reports

Case 1

The patient was a 24-year-old woman who was admitted to our hospital with spiking fever, polyarthralgia, and a transient salmon-colored rash on her neck and chest wall. Blood tests showed a white blood cell (WBC) count of $7.1 \times 10^3/mm^3$, a red blood cell (RBC) count of $347 \times 10^4/mm^3$, a hemoglobin (Hb) of 7.4 g/dl, and a platelet count of $9.1 \times 10^4/mm^3$. Her WBC occasionally exceeded $15 \times 10^3/mm^3$ during the course of her dsisease. Her erythrocyte sedimentation rate (ESR) was 128 mm/h (normal range [n] <20) and her C-reactive protein (CRP) titer was 2.2 mg/dl (n < 0.3). Her levels of GOT, GPT, and lactate dehydrogenase (LDH) were elevated to 167 IU/l (n = 10–40), 413 IU/l (n = 5–40), and 1219 IU/l (n = 200–450), respectively. Her serum level of interleukin (IL)-6 was elevated to 128 pg/ml (n < 5.0), and her serum ferritin level was 7900 ng/ml (n = 3.4–320). Splenomegaly was detected by abdominal ultrasonography (US). A bone marrow examination revealed mature histiocytes that showed marked phagocytosis of hematopoietic cells (Fig. 1a). Immunohistochemical studies showed that there was no immunoglobulin in the cytoplasm of these bone marrow histiocytes (Fig. 1b).

The patient was negative for several autoantibodies, including antinuclear antibody (ANA), anti-DNA antibody, and antiphospholipid antibody (aPL). Tests for viral infection using viral antibody assays (cytomegalovirus, Epstein–Barr virus, herpes simplex, and parvovirus B19), bacterial infection, and malignancy were all negative. The patient's clinical and laboratory findings were compatible with AOSD.[11] She was diagnosed as having HPS associated with

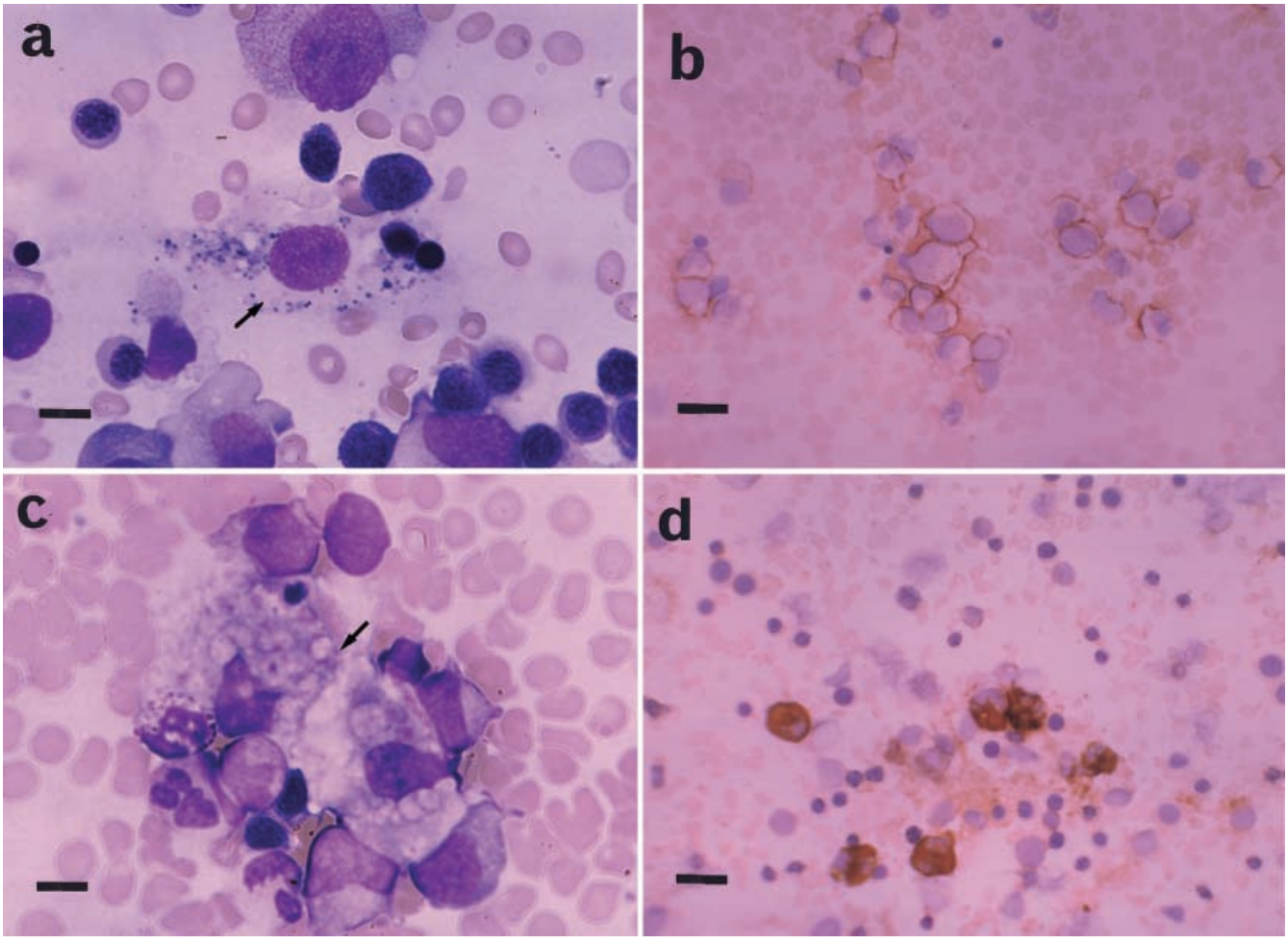

Fig. 1. Hemophagocytosis in the bone marrow of **a** patient 1 and **c** patient 2 (**a**, **c**; May–Giemsa stain, $\times 10^3$). In both patients, there is histiocyte-mediated phagocytosis of megakaryocytes, erythroblasts, and neutrophils. *Arrows* indicate hemophagocytic macrophages. Immunohistochemical staining of the bone marrow in **b** case 1 and **d** case 2 (anti-IgG antibody stain, $\times 400$). *Bars*: **a**, **c** 10 μm; **b**, **d** 25 μm

AOSD, and was treated with steroids, including methylprednisolone pulse therapy. Although she did not fully respond to this treatment, low-dose methotrexate (5–7.5 mg/week) was effective (Fig. 2a). Bone marrow hemophagocytosis was nearly absent when a second bone marrow aspiration was performed 8 weeks after the start of treatment.

Case 2

A 21-year-old man was admitted to our hospital complaining of malaise, spiking fever (39–40°C), and chest pain. He had occasionally experienced fever of unknown origin (FUO) during the previous year, which had shown spontaneous remission, and had become positive for ANA, anti-RNP antibody, and anti-SS-A antibody before hospitalization. On admission, physical examination revealed cervical lymphadenopathy and herpes zoster on his chest wall. Laboratory tests gave the following results: WBC, $3.3 \times 10^3/mm^3$; RBC, $400 \times 10^4/mm^3$; Hb, 11.9 g/dl; platelet count, $5.8 \times 10^4/mm^3$; GOT, 445 IU/l; GPT, 424 IU/l; LDH, 2411 IU/l; ESR, 17 mm/h; and CRP, 3.3 mg/dl.

The serum levels of several cytokines were also elevated: IL-6 was 1840 pg/ml, IL-10 was 31 pg/ml ($n < 5$), tumor necrosis factor (TNF)-α was 22 pg/ml ($n < 5$), and macrophage-colony-stimulating factor (M-CSF) was 19 pg/ml ($n < 8$). The patient's serum ferritin level was 2893 ng/ml. Several autoantibodies were positive, including ANA (1:1280, $n < 1:40$), anti-RNP antibody (4932 U/ml, $n < 7.0$), and anti-SS-A antibody (14.8 U/ml, $n < 7.0$), although several other autoantibodies were negative (anti-DNA antibody, anti-Sm antibody, and aPL) and hypocomplementemia was not observed (CH_{50} was 41.0 U/ml, $n = 30–40$).

Clinical and laboratory findings allowed us to exclude malignancy, as well as viral infections other than herpes zoster. This patient also did not fulfill the diagnostic criteria for autoimmune rheumatic diseases such as MCTD or Sjögren's syndrome.[12,13] His bone marrow showed the characteristic features of reactive hemophagocytosis (see Fig. 1c), and immunohistochemical studies revealed that the cytoplasm of the bone marrow histiocytes was stained for immunoglobulins (see Fig. 1d). This indicated that antibodies had been taken up by the histiocytes in his marrow.

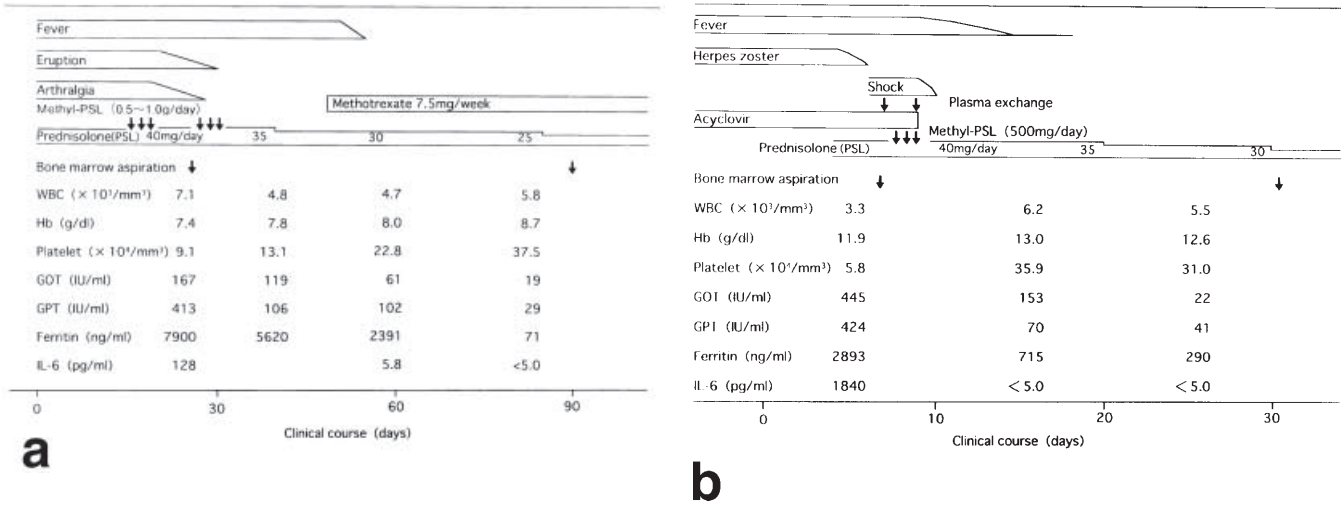

Fig. 2a and b. Clinical course of the patients. **a** Case 1. **b** Case 2. *PSL*, prednisolone; Hb, hemoglobin; Il, interleukin

After admission, he went into shock mediated by the viral infection. Plasma exchange therapy was performed in addition to the administration of acyclovir and prednisolone, and these treatments were effective (see Fig. 2b). Repeat bone marrow aspiration 4 weeks after the start of treatment showed a marked decrease in hemophagocytosis.

The treatments administered improved the symptoms of both patients. In addition, their hyperferritinemia, hypercytokinemia, and hemophagocytosis also responded well (see Fig. 2).

Discussion

We have presented a case of hemophagocytosis with AOSD (case 1) and a case of viral infection (herpes zoster)-associated hemophagocytosis with possible autoimmune abnormalities (case 2). AOSD is a systemic inflammatory disorder of unknown origin characterized by several clinical and laboratory findings, including a spiking fever, rash, polyarthralgia, and hyperferritinemia.[11] It is also frequently associated with bone marrow hemophagocytosis.[3,8] Viral infections have been known to induce derangement of the immune system, causing several related symptoms (including HPS), especially in patients with underlying autoimmune abnormalities like those found in case 2.[14] This may be due to the overproduction of cytokines and/or antiviral antibodies resulting from hyperresponsiveness of the immune system to a virus.

Elevation of cytokines and ferritin was observed in both patients, and the cytokines seemed to contribute to the development of HPS in both. Serum levels of cytokines such as IL-1, IL-6, TNF-α, interferon (IFN)-γ, and M-CSF are elevated in HPS when it is associated with infection, malignancy, and certain types of AAHS, including AOSD.[8,15] Virus-infected cells or malignant cells such as lymphoma cells are known to produce these cytokines, which can promote the activation of macrophages and thus mediate hemophagocytosis,[16,17] although the mechanism of cytokine production in AOSD is still unclear. Several reports have indicated that cytokine-activated macrophages release intracellular ferritin during the process of phagocytosis.[18,19] Cytokines thus appear to play an important role in the induction of hemophagocytosis by activating macrophages, and this results in the production of ferritin.

In case 1, a cytokine (IL-6) was thought to be related to the development of hemophagocytosis and the subsequent elevation of the serum ferritin level. However, it seems that antibodies to hematopoietic cells did not contribute to the hemophagocytosis in this patient, because no immunoglobulin incorporation was observed in her histiocytes (see Fig. 1b). In contrast, antibodies may have played a significant role in the hemophagocytosis seen in case 2 (see Fig. 1d). The participation of antibodies or immune complexes has been suggested in the induction of hemophagocytic phenomena in SLE-related HPS (acute lupus hemophagocytic syndrome) and AAHS.[2,6,7] We recently reported two cases of aPL-positive patients with HPS who showed immunoglobulin incorporation by bone marrow histiocytes,[9] but did not show hyperferritinemia or hypercytokinemia.[9,10] These cases suggested a possibly important role of aPL in the promotion of certain cases of AAHS. It is possible that aPL can bind to phospholipids expressed by various hematopoietic cells in some aPL-positive patients, and that the aPL-bound cells are then phagocytosed by histiocytes after binding between the aPL-Fc portion and the phagocyte Fc receptor, as indicated previously by in vitro experiments.[20] In case 2, although his aPL antibodies were negative, the cross-reaction of antiviral antibodies with hematopoietic cell components induced by molecular mimicry may have contributed to the development of hemophagocytosis in cooperation with a marked elevation of cytokines. These patients, together with cases described previously,[9,10] suggest that HPS associated with connective tissue diseases or autoimmune diseases may be classified into antibody-dependent HPS (including possible immune complex

formation), cytokine-dependent HPS (case 1), and mixed HPS (case 2).

HPS may contribute to the development of cytopenia in autoimmune disorders more often than has previously been thought. However, further studies are needed to clarify the role and mechanism of hemophagocytosis in autoimmune-related cytopenia.

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