Preferential recovery by an intensive initial therapy from hemophagocytic syndrome complicated with adult onset Still's disease presenting as agranulocytosis and hypercytokinemia

Sirs,

A 39-year-old Japanese woman presented with sore throat, high fever (over 40°C), a salmon-pink rash over her entire body, polyarthralgia and myalgia, was admitted to our department in March, 2007. Laboratory data were as follows: red blood cells (RBC), 412 x10^4/mm^3; hemoglobin (Hb), 11.9 g/dl; white blood cells (WBC), 11,200/mm^3 (with 91% neutrophils); platelets (Plt), 27.0x10^4/mm^3; C-reactive protein (CRP), 8.7 mg/dl (normal; 0-0.17); serum ferritin, 9,375 ng/ml (normal; 5-100). Antinuclear antibody and rheumatoid factor were negative. Her blood, urine and throat cultures remained sterile. Diagnosis of adult onset Still's disease (AOSD) was made, and treatment with 1 mg/kg prednisolone daily was begun. Her symptoms, manifestations and acute phase parameters normalized within 2 weeks, and she was discharged, however, readmitted to our department, on 6 May, with similar manifestations at disease onset. In spite of the administration of 1g/day of methylprednisolone, on 12 May, remarkable neutropenia, thrombocytopenia, hyperferritinemia and elevation of transaminases developed; WBC, 200/mm^3 (with 0% neutrophils); Plt 1.7x10^4/mm^3; AST, 3,166 IU/l; ALT, 2126 IU/l; LDH, 10,586 IU/l; ferritin, 87,670 ng/ml. Serum levels of tumor necrosis factor alpha (TNF-α), soluble TNF receptor 1 (sTNFR1), sTNFR2, interleukin (IL)-1β, IL-6, IL-18 and macrophage colony-stimulating factor (M-CSF) were also significantly increased (Table I). Natural killer cell activity was not examined in this case. No infectious source could also be detected, including negative test results with serum anti-Epstein-Barr virus (EBV) viral capsid antigen IgM, polymerase chain reaction of EBV DNA, anti-cytomegalovirus IgM, pp65 antigen of cytomegalovirus and anti-human parvovirus B19 IgM, and the medication other than glucocorticoid dosage was not changed, suggesting this disease status is not induced by infectious pathogens or drugs. Disease entity of autoimmune-associated hemophagocytic syndrome (AAHS) is proposed (1-3), and AOSD is recognized as representative autoimmune disease which complicates with hemophagocytic syndrome (HPS) (3, 4). Bone marrow aspiration at that time revealed the many macrophages actively phagocytizing blood cells in the bone marrow, leading to diagnosis of AAHS complicated with AOSD. The absolute neutrophil count was 0/mm^3 on May 12, which showed that neutropenia developed to agranulocytosis. She was given additional cyclosporine A (CsA) (trough level was maintained around 250 ng/ml) and 6 courses of plasmapheresis with granulocyte colony stimulating factor (G-CSF; 75 μg daily) support. Twelve days after diagnosis of agranulocytosis, on 23 May, the neutrophil count had increased to 800/mm^3 and the platelet count had increased to 10.6x10^4/mm^3, so G-CSF was discontinued. In good accordance with the improvement of clinical symptoms, hyperferritinemia and hypercytokinemia rapidly improved (Table I, and ferritin; 110 ng/ml on June 20). At that point, the patient could finally be discharged, taking 20mg of oral prednisolone and 100mg of oral CsA daily.

Table I. Serum levels of cytokines at various time points.

Variables	12 May	18 May	20 June	Normal range	Unit
TNF α	152.1	45.2	6.0	6-20	pg/ml
sTNFR1	9.5	6.1	4.2	0-2.5	pg/ml
sTNFR2	52.2	18.4	9.6	0-4.5	pg/ml
IL-18	1714	1056	152	80-170	pg/ml
IL-1β	1.837	0.524	0.328	0-0.567	pg/ml
IL-6	74.1	26.0	0	0-4	pg/ml
M-CSF	13270	6258	624	220-530	pg/ml

AAHS may result from several increased serum cytokine levels since these play a prominent role in triggering macrophage activation (5-8), and hyperferritinemia reflects the process of hemophagocytosis (2, 3, 7). However, serum cytokine levels were not examined at the diagnosis of AOSD in March, thus, the precise contribution of hemophagocytosis toward hypercytokinemia in this case remains obscure. In the case of AAHS, refractory to glucocroticoid therapy, the introduction of CsA and plasmapheresis leads to a significant effect (7-9). It is shown that major effects of CsA are mediated by the suppression of early steps in T-cell and macrophage activation, leading to failure to facilitate the transcription of early genes such as those encoding for cytokines (10), which may also be indicative in this patient.

This is a rare case report of AAHS complicated with AOSD and presenting severe laboratory abnormalities including agranulocytosis with hypercytokinemia. We suggest that plasmapheresis and CsA can be considered first-line treatments with glucocorticoid in life-threatening AAHS.

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Competing interests: none declared.

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