Successful gammaglobulin therapy for reactive hemophagocytosis in pregnant woman with serological positive for anti-SS-A/-B antibody

Hiroshi Fujita • Junji Tomiyama • Yamao Adachi^{*1)}, Hideki Kudo^{*2)}

case report

JAPANESE JOURNAL OF INFLAMMATION

A 28-year-old pregnant woman who was serologically positive for anti-SS-A/-B antibody developed reactive hemophagocytosis, and gammaglobulin therapy was very effective in treating it. This case showed the underlying not only pregnancy but also disease such as some infections and serological abnormality. We suspect that the possible involvement of an immunological disorder of pregnancy in the pathogenesis of the hemophagocytosis.

Rec. 9/16/1999, Acc. 10/6/1999, pp 374-378

key words : reactive hemophagocytosis, M-SCF, Sjögren's syndrome, pregnancy

Reactive hemophagocytosis is characterized by histiocyte activation, with prominent hemophagocytosis in the bone marrow and reticuloendothelial system. Its occurrence is usually associated with an underlying disease, such as a viral infection¹⁾, collagen disease²⁾, or malignant lymphoma³⁾. Systemic lupus erythematosus (SLE) sometimes becomes complicated by hemophagocytosis (acute lupus hemophagocytic syndrome). However, our case was not diagnosed as a typical collagen disease, and associated with serological positive for anti-SS-A/-B antibody during pregnancy.

Case Report

A 28-year-old female was referred to our hospital in 1998 because of a continuous high fever during pregnancy (17 weeks). Four days before admission she developed a remittent fever (>39 degree) that did not improve in response to the antibiotics she received at from another hospital. The day before admission, pancytopenia was detected at other hospital, and she was referred the following day. The patient had a history of rheumatic fever at 14 years of age and Guillain-Barré syndrome at 24 years of age. She was diagnosed as having a serological abnormality manifested by hypergammaglobulinemia (IgG : 2430 mg/dl), positivity for antinuclear antibody (1280×), and positivity for rheumatic factor (RA) since 18 years of age. However, neither clinical symptoms suggestive of SLE nor Sjögren's syndrome (sicca syndrome) were present prior to admis-

^{*1)} Department of Internal Medicine, ^{*2)} Department of Transfusion Medicine, Tokyo Metropolitan Bokutou General Hospital

Offprint requests to : H. Fujita Department of Internal Medicine, Tokyo Metropolitan Bokutou General Hospital, 4-23-15, Koutoubashi, Sumida, Tokyo, 130-8575, Japan, Tel : 81-3-3633-6151, Fax : 81-3-3633-6173

sion. Serum complement was normal, and anti-DNA antibody and LE tests were negative before admission. Physical examination revealed well-nourished and well-developed women. The pupils were equally round and reactive to light. The patient exhibited slight conjunctival injection, and the sclerae were anicteric. Blood pressure was 106/60 mmHg, and the pulse was regular, and 140/min and body temperature 39.5 degrees. On auscultation, the heart sounds were normal, and there were no heart murmurs. No rales were audible in the lung fields. Abdominal examination suggested no hepatosplenomegaly or tenderness. The fundus of the pregnant uterus was palpable in the lower abdomen. Rectal examination was normal. There was a skin rash on the face. There was no adenopathy, petechiae, jaundice, or tattoos. Kernig's sign was absent; deep tendon reflexes were intact and symmetrical. No focal motor deficits or cerebellar signs were present.

Ancillary studies on admission revealed a peripheral white blood cell (WBC) count of $1.0 \times 10^9/l$ (84% neutrophils, 13% lymphocytes, 3% atypical lymphocytes), a low platelet count ($82 \times 10^9/l$), and slightly low hemoglobin (10.5 g/dl). Serum iron was normal (690 $\mu g/l$, normal reference range: 60-200), but serum ferritin was increased (8318 pg/l, normal: 30-323). Folate and vitamin B12 were normal. The coagulation data showed a partial thromboplastin time of 49.9 sec, prothrombin time of 87% and fibrin degradation product (FDP) level of 40 ng/l. Fibrinogen was normal (3.28 g/l, normal: 2-4). D-dimer (9277 ng/ml, normal < 150), thrombin-antithrombin complex (TAT) (50.1 ng/ml, normal < 0.8) and $\alpha 2$ plasmin inhibitor (αbPI 5.6 $\mu g/ml$, normal < 3) were high. Serum glucose, BUN, and serum creatinine all were normal. Hyponatremia (Na 127 mEq/l and Cl 94

mEq/l) and hypokalemia (3.3 mEq/l) were noted. Liver function tests yielded the following findings: AST, 128 U/l (normal < 40); ALT, 37 U/l (normal < 50); γ GTP, 38 U/l (normal < 65); total bilirubin, 20 $\mu mol/l$ (normal: 3.4-17); albumin, 35 g/l (normal: 36-51); alkaline phosphatase, 120 U/l (normal: 60-320). LDH was 1028 IU/l (normal: 100-215), and extremely high. C-reactive protein was positive (9.2 mg/dl, normal < 0.4). Bone marrow study revealed slightly hypoplastic marrow with characteristic features of reactive hemophagocytosis. The hemophagocytic histiocytes had ingested granulocytes, erythrocytes, erythroblasts, and platelets. Histiocytes were increased in the bone marrow (8.4% of the total cell count). There was no evidence of malignancy or chromosomal abnormalities in the bone marrow cells.

The chest radiograph revealed slight cardiomegaly. An electrocardiogram showed sinus tachycardia with no ST-T changes. An echocardiogram showed normal left ventricular function with no valvular disease. Serology revealed normal gammaglobulinemia (IgG: 1119 mg/dl, IgA: 318 mg/dl, IgM: 47 mg/dl), with positivity for RA test, high antinuclear antibody (640 $\times$, speckled type), and positivity for anti-SS-A and SS-B antibodies. The levels of C3, C4 and CH50 were normal. Scintigraphy of the salivary glands and sialography were not performed because she was pregnant. The tear was secreted normally. Clinical manifestations of Sjögren's syndrome were not noted.

Repeated blood, urine, and stool cultures were all negative. Bacterial and fungal cultures of sputum were negative. Serum endotoxin was almost normal (10.2 pg/ml, measured by the Endospecy method), and β -glucan was also normal. There was no serological evidence of

Fig. 1 Clinical course of the patient with reactive hemophagocytosis
Intravenous gammaglobulin therapy was performed for five days.

recent infection with Epstein-Barr virus (by the fluorescence antibody method [FA] and by enzyme-linked immunosorbent assay [ELISA]), cytomegalovirus (by ELISA), herpes simplex (by ELISA), herpes zoster (by ELISA) or parvo B 19 virus (by ELISA). PCR examination for EB virus failed to detect any genomes in the bone marrow cells.

No primary disorder causing the reactive hemophagocytosis was detected only a serological disorder manifested by the presence of anti-SS-A/SS-B antibody. We could not use granulocyte colony stimulating factor (G-CSF) and steroids because of pregnancy. The patient was treated by intravenous administration of

gammaglobulin (5 g/day, five days), and this was followed by rapid improvement of the thrombocytopenia and leukopenia and coagulation disorder concomitant with suppression of the hemophagocytic histiocytes and decreases in serum ferritin and LDH levels (Fig. 1). WBC count at day 27 was $3.5 \times 10^9/L$ (54% neutrophils, 36% lymphocytes, 10% monocyte). This improved state has been maintained ever since the administration of the gammaglobulin, and healthy baby was born approximately 23 weeks after treatment.

Discussion

(1) The cause of pyrexia

We diagnosed the cause of the pyrexia as reactive hemophagocytic syndrome (HPS), because this case satisfied all of the criteria of HPS. Typical HPS is manifested by ① continuous high fever, ② pancytopenia, ③ increased serum LDH, ④ increased serum ferritin, ⑤ increased histiocytes in the bone marrow, and ⑥ hemophagocytic features in the reticuloendothelial system, including the bone marrow and lymph nodes⁴⁾. In our case, however, the cause of the HPS was not very clear. Reactive HPS is known to be induced by ① viral infections, ② malignancy, including malignant lymphoma, and ③ collagen disease, such as systemic lupus erythematosus (SLE).

EB virus is the most frequent agent in reactive HPS, so called virus-associated hemophagocytic syndrome (VAHS). No serological evidence of recent EB virus infection was found in our case and PCR for EB virus in the bone marrow cells was negative. There were no increases in IgM to other viruses. Occasionally, bacterial and fungal infection are accompanied by HPS⁵⁾, in our case all of the cultures were negative. Nevertheless, it is impossible to completely rule out the possibility that a infection

Table 1 Serum cytokine levels before and after gammaglobulin therapy
Serum TNF α , IFN γ , IL-6, M-CSF and GM-CSF were measured by ELISA. Serum IL-2 and IL-1 β were measured by RIA.

	Treatment with γ globulin	
	day 0	day 27
IFN γ (IU/ml)	19.3	<0.1
IL-1 β (pg/ml)	<10	<10
IL-2 (U/ml)	<0.8	<0.8
IL-6 (pg/ml)	81.7	1.1
TNF α (pg/ml)	<5	<5
GM-CSF (pg/ml)	<8	<8
M-CSF (pg/ml)	<10000	1240

induced the HPS, but we have no direct evidence of microorganisms involved.

Malignant lymphoma is a common disease in malignancy-associated hemophagocytic syndrome (MAHS), but there was no lymphadenopathy or infiltration by lymphoma cells or other malignant cells, including leukemia, in the bone marrow in our case.

HPS occurs in association with collagen diseases, especially SLE. In our case, there was no evidence of typical SLE, or any other collagen disease. The patient did not have the sicca syndrome, but she was anti-SS-A, B antibodies. This subclinical, serological Sjögren's syndrome may be based on the occurrence of HPS. We suspect that she did not reveal typical symptoms of Sjögren's syndrome because of her young age, and that clinical symptoms may occur in the future.

Because it still remained positive for anti-nuclear antibody (640 $\times$) and anti-SS-A, B antibodies after her labor, we considered that gammaglobulin therapy and pregnancy did not affect these serological disorders.

(2) Relationship between hemophagocytosis and pregnancy

Is there a possibility that pregnancy may be based on the induction of HPS? There have

been very few reports on HPS and pregnancy. Macrophage-colony stimulating factor (M-CSF) is a characteristic cytokine that plays an essential role in placenta maintenance⁶⁾. In fact, the level of serum M-CSF and circulating monocytes increase during the pregnancy⁷⁾. M-CSF stimulates macrophage activation. HPS is a pathological condition that causes increases in serum cytokine level and results macrophage activation. We measured the serum cytokine levels in our case, and the results are shown in **Table 1**. Inteferon γ (IFN γ), interleukin 6 (IL-6), and M-CSF were higher on admission (day 0) than after treatment (day 27). M-CSF was still high after treatment, because M-CSF is related to pregnancy. Thus, increased M-CSF due to pregnancy may promote the occurrence of HPS.

(3) Therapy for hemophagocytosis complicated with pregnancy

Therapies for HPS consist of ① steroids¹⁾, ② gammaglobulins⁷⁾, ③ immunosuppressors⁸⁾, ④ anti-cancer drugs, such as etoposide⁹⁾, ⑤ bone marrow transplantation¹⁰⁾, and peripheral blood stem cell transplantation¹¹⁾. We selected gammaglobulin therapy because of the pregnancy. Other therapies can affect the condition of fetus. So we did not perform them. Nor did we use G-CSF to treat the neutropenia, even though neutropenia was a risk factor for severe further infections, because G-CSF may induce fetal congenital abnormalities. We consider gammaglobulin therapy to have been very effective, because the high fever resolved and the hematological data except anemia improved after therapy. We consider that it still remained anemic after treatment of gammaglobulin, because of pregnancy. 6 months after labor, the hemoglobin level increased up to 12 g/dl. In addition, cytokine levels such as those IFN γ , IL-6, and M-CSF, decreased after gam-

maglobulin treatment (Table 1). This is the first case report of a pregnant woman with serological Sjögren's syndrome and HPS in whom gammaglobulin therapy was beneficial in treating the HPS.

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