

# Cytokine Profiles of Macrophage Activation Syndrome Associated with Rheumatic Diseases

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**ABSTRACT. Objective.** To elucidate the cytokine profiles of macrophage activation syndrome (MAS) in relation to underlying rheumatic diseases and prognosis.

**Methods.** The clinical features and laboratory data of 18 patients with MAS and rheumatic diseases were retrospectively analyzed. Serum levels of macrophage colony-stimulating factor (M-CSF), interleukin 18 (IL-18), tumor necrosis factor- $\alpha$ , interleukin 6, interferon- $\gamma$ , ferritin, and  $\beta_2$ -microglobulin ( $\beta_2$ m) were measured. These data were compared between underlying diseases and between those who died and those who recovered.

**Results.** Of the 18 patients with MAS, 9 had underlying systemic lupus erythematosus (SLE), 7 had adult-onset Still's disease (AOSD), 1 had rheumatoid arthritis (RA), and 1 had antiphospholipid syndrome. Three patients with SLE and 1 patient with RA died. The serum M-CSF and IL-18 levels were substantially elevated in all the patients. In the patients with SLE, the M-CSF level was higher than the IL-18 level (median: 4879 vs 1341 pg/ml,  $p = 0.0054$ ), and it was the reverse in the patients with AOSD (5883 vs 228,350 pg/ml,  $p = 0.0017$ ). The serum M-CSF and  $\beta_2$ m levels were significantly higher in the patients who died than in those who recovered (M-CSF: 18,245 vs 3404 pg/ml,  $p = 0.019$ ;  $\beta_2$ m: 18.8 vs 5.4 mg/dl,  $p = 0.0058$ ).

**Conclusion.** The cytokine profiles associated with MAS differed between patients with SLE and patients with AOSD. The patients with SLE showed a prominent increase in serum M-CSF levels, as did the patients with AOSD in serum IL-18 level. Patients who died had higher serum M-CSF and  $\beta_2$ m levels, and this suggests that aggressive treatment for patients with MAS and these profiles should be promptly started. (First Release March 15 2010; J Rheumatol 2010;37:967-73; doi:10.3899/jrheum.090662)

## Key Indexing Terms:

MACROPHAGE ACTIVATION SYNDROME  
MACROPHAGE COLONY-STIMULATING FACTOR

CYTOKINES

INTERLEUKIN 18  
 $\beta_2$ -MICROGLOBULIN

Macrophage activation syndrome (MAS) is an uncommon but potentially life-threatening complication of rheumatic diseases. It is characterized by systemic inflammatory reaction, cytopenia, coagulopathy, and vital organ dysfunctions. In 1985, Hadchouel, *et al* first described 7 patients who developed these complications during the course of systemic juvenile idiopathic arthritis (JIA)<sup>1</sup>. The term MAS was proposed in 1993 in a followup report<sup>2</sup>.

Although considerable mortality of 15-60% has been observed in MAS<sup>3</sup>, and early diagnosis and immediate intervention are crucial, the recognition, diagnosis, and predicting the prognosis in the early phase are difficult. We aimed

to elucidate the cytokine profiles of MAS in relation to underlying rheumatic diseases and prognosis.

## MATERIALS AND METHODS

Clinical and laboratory data on 18 consecutive patients with MAS associated with rheumatic diseases, who were admitted to Tokyo Metropolitan Komagome Hospital from May 2000 to October 2007, were retrospectively analyzed.

MAS was defined as a condition meeting these criteria: systemic inflammatory response syndrome (SIRS), cytopenia of more than 2 blood cell series, and hyperferritinemia. The diagnosis of SIRS requires at least 2 of the following: body temperature of  $> 38$  or  $< 36^\circ\text{C}$ , heart rate of  $> 90/\text{min}$ , respiratory rate of  $> 20/\text{min}$ , and white blood cell count (WBC) of  $> 12,000$  or  $< 4000/\mu\text{l}$ <sup>4</sup>. Cytopenia was defined as neutrophil count of  $\leq 1.0 \times 10^3/\mu\text{l}$ , hemoglobin level of  $\leq 9$  g/dl, or platelet count of  $\leq 100 \times 10^3/\mu\text{l}$ , or a decrease to less than half of the patient's baseline level of each blood cell series. Hyperferritinemia was defined as a serum ferritin level  $\geq 1000$  ng/ml.

As for the diagnosis of the underlying rheumatic diseases, the 1997 revised American College of Rheumatology (ACR) criteria were adopted for systemic lupus erythematosus (SLE)<sup>5</sup>, the criteria of Yamaguchi, *et al* for adult-onset Still's disease (AOSD)<sup>6</sup>, the ACR criteria for rheumatoid arthritis (RA)<sup>7</sup>, and the 1998 Sapporo criteria for antiphospholipid syndrome (APS)<sup>8</sup>. The disease activity of SLE was evaluated using the SLE Disease Activity Index (SLEDAI)<sup>9</sup>.

Laboratory data and some clinical data were compared between underlying diseases and between those who died and those who recovered. For clinical data, these factors were analyzed: sex, age, diagnosis, duration of

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underlying diseases, SLEDAI score in the case of SLE, dose of prednisolone (PSL), newly administered medication within 3 months before the onset of MAS, and organ involvement, treatment, and outcome of MAS. For laboratory data, these factors were evaluated: peripheral WBC and platelet counts, hemoglobin level, erythrocyte sedimentation rate, and serum levels of ferritin,  $\beta_2$ -microglobulin ( $\beta_2m$ ), aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), leucine aminopeptidase, C-reactive protein, soluble interleukin-2 receptor, and cytokines including macrophage colony-stimulating factor (M-CSF), interleukin 18 (IL-18), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6), and interferon- $\gamma$  (IFN- $\gamma$ ). If previous data were available, then WBC, platelet counts, and hemoglobin level 1 week and 1 month prior to the onset of MAS were also analyzed.

**Immunoassay for cytokine levels.** The serum levels of M-CSF (R&D Systems, Abington, UK; lower limit of detection: 9 pg/ml), IL-18 (MBL, Nagoya, Japan; 12.5 pg/ml), TNF- $\alpha$  (R&D Systems; 0.12 pg/ml), IL-6 (R&D Systems; 0.70 pg/ml), and IFN- $\gamma$  (Beckman Coulter, France; 0.08 IU/ml) were measured using commercially available ELISA. The adopted data were those measured within 2 days after the onset of MAS.

**Statistical analysis.** The statistical differences in the marker levels between the 2 groups (M-CSF vs IL-18, SLE vs AOSD, and those who died vs those who recovered) were analyzed by Mann-Whitney U test. A *p* value < 0.05 was considered statistically significant.

## RESULTS

**Clinical features.** The patients' profiles are described in Table 1. Of 18 patients with MAS (female/male: 17/1; age: median 36 years, range 14-76; disease duration: median 1.5 years, range 0-36.0), the underlying diseases were SLE in 9 (8/1; 32, 14-76; 2.0, 0-36.0), AOSD in 7 (7/0; 36, 16-76; 0.25, 0-14.0), RA in 1 (1/0; 52; 2.6), and APS in 1 (1/0; 55; 33.0). Among them, 3 patients with SLE and 1 patient with RA died within 1 to 7 days after MAS developed. The patients who recovered from MAS were monitored for at least 5 months, except 2 patients who died of infection after recovering from MAS (Table 1). All the patients with SLE had a SLEDAI score of  $\geq 9$  (median 21, range 9-56), and had taken 0-53 (median 2) mg/d of prednisolone just before the onset of MAS. All the patients with AOSD were at the active phase that required hospitalization before MAS developed, and had taken 0-55 (26) mg/d PSL. Other than PSL, 2 patients had taken ibuprofen, 1 had taken leflunomide, mizoribine, and cyclosporin A, and another had taken ibuprofen, intravenous immunoglobulin (IVIg), and cyclo-

Table 1. Clinical features of 18 patients with macrophage activation syndrome (MAS).

Patient	Age/Sex	Underlying Disease and Duration (m/*)	Organ Involvement	HPS	Treatment	Outcome
1	29 F	SLE (96/25)	Alveolar hemorrhage, pleural effusion, pericardial effusion, DIC	—	Pulsed mPSL + PSL (1.2 mg/kg)	Died
2	26 F	SLE (12/32)	GI bleeding, alveolar hemorrhage, PH, DIC, nephritis, blurred vision, altered mental status	NA	Pulsed mPSL + IVIg + CyA (3 mg/kg)	Died
3	18 F	SLE (4/56)	Cerebritis, nephritis, enteritis, pleural effusion, pericardial effusion	+	Pulsed mPSL	Died
4	32 F	SLE (12/54)	Interstitial pneumonia	—	Pulsed mPSL + PSL (1.2 mg/kg) → IVIg → CyA (5 mg/kg)	Recovered
5	76 F	SLE (7/18)	Interstitial pneumonia, pleural effusion, pericardial effusion	—	PSL (10 mg/d)	Recovered
6	35 F	SLE (24/36)	Pleural effusion	NA	Pulsed mPSL + PSL (1.2 mg/kg)	Recovered
7	14 M	SLE (0/9)	—	+	Pulsed mPSL + PSL (1.2 mg/kg)	Recovered
8	64 F	SLE (258/21)	Pleural effusion	—	Pulsed mPSL + PSL (5 mg/d) → IVIg	Recovered
9	64 F	SLE (432/21)	PH, pleural effusion, ascitis, renal failure, heart failure	—	PSL (1.2 mg/kg)	Recovered <sup>†</sup>
10	70 F	AOSD (3)	Interstitial pneumonia	+	Pulsed mPSL + PSL (1.2 mg/kg) + IVIg	Recovered <sup>††</sup>
11	16 F	AOSD (0)	Altered mental status	—	PSL (1.2 mg/kg) → IVIg → pulsed mPSL	Recovered
12	36 F	AOSD (3)	ARDS, peripheral neuropathy	+	Pulsed mPSL + PSL (1.2 mg/kg)	Recovered
13	30 F	AOSD (148)	Pleural effusion, pericardial effusion	NA	PSL (26 mg/d) + CyA (2.5 mg/kg) → pulsed mPSL	Recovered
14	36 F	AOSD (8)	Pleural effusion, nephritis, uveitis	NA	IPF (30 mg/kg) → PSL (1.2 mg/kg) → pulsed mPSL	Recovered
15	76 F	AOSD (1)	Pleural effusion	NA	IPF (30 mg/kg) → PSL (0.8 mg/kg) → pulsed mPSL → IVIg → CyA (3 mg/kg)	Recovered
16	31 F	AOSD (45)	Nephritis, colitis	NA	PSL (0.8 mg/kg for 3 days) → PSL (10 mg/d)	Recovered
17	52 F	RA (31)	ARDS, DIC, GI bleeding	NA	Pulsed mPSL	Died
18	55 F	APS (396)	GGO	NA	PSL (5 mg/d) + warfarin (2.5 mg/d)	Recovered

m: month; \* Systemic Lupus Erythematosus Disease Activity Index (SLEDAI); HPS: hemophagocytosis; AOSD: adult-onset Still's disease; RA: rheumatoid arthritis; APS: antiphospholipid syndrome; DIC: disseminated intravascular coagulopathy; GI: gastrointestinal; PH: pulmonary hypertension; ARDS: acute respiratory distress syndrome; GGO: ground-glass opacity in chest computed tomography; NA: not available; mPSL: methylprednisolone; PSL: prednisolone; IVIg: intravenous immunoglobulin; CyA: cyclosporin A; IPF: ibuprofen. <sup>†</sup> Died of cytomegalovirus infection 1 month after recovery from MAS. <sup>††</sup> Died of severe pneumonia complicated with tension pneumothorax 1.5 months after recovery from MAS.

sporin A, within 3 months before the onset of MAS. None of these medications was regarded as a trigger of MAS. Arthritis was active in a patient with RA who had taken no steroid. A patient with APS who was on a maintenance dose of 5 mg/d PSL and warfarin showed no obvious features of active APS.

When MAS developed, pulmonary involvements were observed in 15 patients; pleural, pericardial, or peritoneal effusion in 9; renal involvements in 5; neurological and gastrointestinal involvements in 4 each; disseminated intravascular coagulopathy (DIC) in 3; and uveitis in 1 (Table 1). Hemophagocytosis (HPS) was examined for 10 patients, and observed in 1 of 2 patients who died and in 3 of 8 patients who recovered (Table 1).

The numbers of vital organs involved were higher in those who died than in those who recovered (median 4 vs 1,  $p = 0.0079$ ). However, no differences were observed in age, duration of the underlying diseases, and PSL dose before the onset of MAS (Table 2).

**Treatment and outcome.** Treatment for MAS and its outcome are described in Table 1. Among the 9 patients with SLE, 7 took pulsed methylprednisolone (mPSL; 1000 mg/d for 3 consecutive days), 1 had an increased dose of 1.2

mg/kg/d PSL, and the other had only a maintained dose of 10 mg/d PSL. Three received additional IVIg (400 mg/kg/d for 5 consecutive days), and 2 of the 3 also had cyclosporin A (3 and 5 mg/kg/d). Eventually, 6 patients with SLE recovered from MAS including 1 with spontaneous remission, and 3 died of MAS. All the patients with SLE who died showed very rapid deterioration complicated by DIC and/or central nervous system involvements, and died 1, 6, and 7 days after MAS developed. Another patient with SLE died of cytomegalovirus infection 1 month after recovery from MAS.

Among the 7 patients with AOSD, 6 took pulsed mPSL and the other had an increased dose of 0.8 mg/kg/d PSL for 3 consecutive days. Three had IVIg and 2 took cyclosporin A in addition to steroids. All the patients with AOSD responded well to these therapies and none died of MAS. One patient died of pneumonia complicated by tension pneumothorax 1.5 months after recovery from MAS.

A patient with RA died of MAS complicated by adult respiratory distress syndrome and DIC despite pulsed mPSL therapy, 4 days after the MAS developed. A patient with APS showed spontaneous remission under a maintenance dose of 5 mg/d PSL.

Table 2. Clinical features and laboratory data of patients who died and patients who recovered. Figures are median (range).

Feature	Recovered	Died	p
No. of patients	14	4	
Underlying disease	6 SLE, 7 AOSD, 1 APS	3 SLE, 1 RA	
Age, yrs	36.0 (14–76)	27.5 (18–52)	0.14
Duration of underlying disease, mo	16.0 (0–432)	21.5 (4–96)	0.83
PSL dose at the onset of MAS, mg/day	5 (0–55)	5 (0–53)	0.92
No. organs involved	1 (0–4)	4 (3–5)	< 0.01
IL-18, pg/ml	141,093 (810–586,510)	5640 (1330–10,133)	0.46
M-CSF, pg/ml	3404 (1189–12,333)	18,245 (5554–428,424)	0.019
TNF- $\alpha$ , pg/ml	12.8 (2.6–100)	82.4 (23–133)	0.11
IL-6, pg/ml	63 (10–943)	113 (0–1102)	0.44
IFN- $\gamma$ , IU/ml	0.5 (0–55.2)	4.1 (1.9–10.4)	0.12
sIL-2R, U/ml	2427 (219–11,288)	6890 (3078–12,990)	0.15
WBC, / $\mu$ l	3700 (500–11,000)	4400 (1600–8600)	0.63
Hb, g/dl	8.1 (6.1–12)	5.1 (4.2–6.5)	< 0.01
PLT, $10^3/\mu$ l	62 (26–186)	26.5 (17–36)	< 0.01
$\beta_2$ m, mg/dl	5.4 (2.8–17.7)	18.8 (14.6–23.2)	< 0.01
Ferritin, ng/ml	8396 (1017–127,506)	49,667 (2184–257,407)	0.29
AST, IU/l	272 (60–987)	473 (154–1250)	0.46
ALT, IU/l	139 (40–926)	103 (38–351)	0.63
LDH, IU/l	867 (144–3028)	2499 (835–6475)	0.056
LAP, IU/l	1260 (387–4835)	834 (299–2010)	0.70
CRP, mg/dl	10.6 (0–21.9)	8.4 (1.8–17.4)	0.83
ESR, mm/h	77 (7–145)	54 (13–145)	0.16

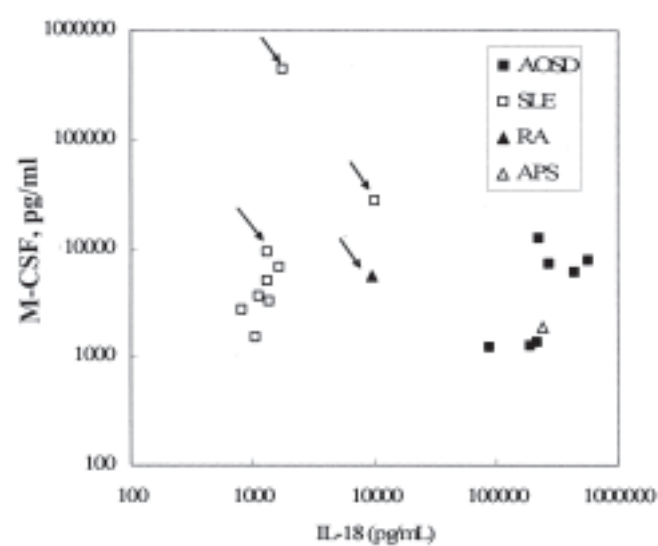
AOSD: adult-onset Still's disease; APS: antiphospholipid syndrome; RA: rheumatoid arthritis; PSL: prednisolone; MAS: macrophage activation syndrome; M-CSF: macrophage colony-stimulating factor; IFN- $\gamma$ : interferon- $\gamma$ ; sIL-2R: soluble interleukin 2 receptor;  $\beta_2$ m:  $\beta_2$ -microglobulin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; LAP: leucine aminopeptidase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SLE: systemic lupus erythematosus; IL-18: interleukin 18; TNF: tumor necrosis factor; WBC: white blood cell; Hb: hemoglobin; PLT: platelet.

*Serum cytokine levels and other laboratory data.* Serum M-CSF and IL-18 levels were markedly elevated in all the patients. The serum M-CSF level was higher than the serum IL-18 level in the patients with SLE (Table 3,  $p < 0.01$ ), and it was the reverse in the patients with AOSD (Table 3,  $p < 0.005$ ; Figure 1). The serum IL-18 level was significantly higher in the patients with AOSD than in the patients with SLE (Table 3,  $p < 0.001$ ) and the platelet count was lower in the patients with SLE than in the patients with AOSD (Table 3,  $p < 0.005$ ). The ferritin level was higher in patients with AOSD than in patients with SLE, although not significantly (Table 3,  $p = 0.05$ ). However, no difference was observed in the serum levels of M-CSF,  $\beta_2m$ , or the other laboratory markers. Serum M-CSF and IL-18 levels of patients with RA and APS are shown in Figure 1.

The serum M-CSF level was significantly higher in the patients who died than in those who recovered ( $p = 0.019$ ; Table 2, Figure 1). The patients who died also had higher serum  $\beta_2m$  levels ( $p < 0.01$ ), lower hemoglobin levels ( $p < 0.01$ ), and lower platelet counts ( $p < 0.01$ ; Table 2). The high serum  $\beta_2m$  level was not associated with renal impairment (data not shown). The LDH level was higher in patients who died, although not significantly (Table 2). No difference was observed in the serum levels of IL-18, ferritin, or other laboratory markers. When blood cell counts were analyzed, the counts of all blood cell series rapidly dropped within 1 week before the onset of MAS (Figure 2).

### DISCUSSION

The pathogenesis of MAS remains incompletely under-



*Figure 1.* Serum macrophage colony-stimulating factor (M-CSF) and interleukin 18 levels in macrophage activation syndrome (MAS) patients with rheumatic diseases. Patients who died (arrows) had higher serum M-CSF level. AOSD: adult-onset Still’s disease; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; APS: antiphospholipid syndrome.

stood. Most of the hypotheses have been derived from observations in primary hemophagocytic lymphohistiocytosis (HLH). Recently there is increasing evidence that impaired natural killer (NK) cell function is responsible for the development of MAS<sup>10,11</sup>. The inability of NK cells and cytotoxic T lymphocytes to efficiently terminate the immune response would lead to sustained activation and

*Table 3.* Laboratory data of SLE and AOSD patients. Figures are median (range).

Feature	SLE	AOSD	p
IL-18, pg/ml	1341 (810–10,133)	228,350 (87,883–586,510)	< 0.001
M-CSF, pg/ml	4879 (1497–428,424)	5883 (1189–12,333)	0.43
TNF- $\alpha$ , pg/ml	23.0 (4.3–133)	17.6 (2.6–100)	0.95
IL-6, pg/ml	25 (0–12.9)	142 (45–943)	0.12
IFN- $\gamma$ , IU/ml	2.4 (0–12.9)	0.5 (0–55.2)	0.20
sIL-2R, U/ml	2803 (1306–12,990)	2602 (219–11,288)	0.49
WBC, / $\mu$ l	1700 (500–8600)	4700 (250–11,000)	0.064
Hb, g/dl	6.8 (6.0–11.6)	7.6 (6.2–10.4)	0.27
PLT, $10^3/\mu$ l	37 (20–62)	72 (46–186)	< 0.005
$\beta_2m$ , mg/dl	11.1 (4.1–23.2)	5.2 (2.8–8.5)	0.081
Ferritin, ng/ml	3270 (1017–257,407)	38,277 (7986–12,506)	0.05
AST, IU/l	530 (60–1250)	271 (72–328)	0.12
ALT, IU/l	150 (38–926)	114 (40–269)	0.56
LDH, IU/l	998 (144–6475)	696 (372–3028)	0.63
LAP, IU/l	982 (299–2315)	2049 (722–2895)	0.12
CRP, mg/dl	7.3 (0–21.9)	11.2 (6.5–15.2)	0.10
ESR, mm/h	45 (7–145)	86 (11–128)	0.19

AOSD: adult-onset Still’s disease; M-CSF: macrophage colony-stimulating factor; IFN- $\gamma$ : interferon- $\gamma$ ; sIL-2R: soluble interleukin 2 receptor;  $\beta_2m$ :  $\beta_2$ -microglobulin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; LAP: leucine aminopeptidase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SLE: systemic lupus erythematosus; IL-18: interleukin 18; TNF: tumor necrosis factor; WBC: white blood cell; Hb: hemoglobin; PLT: platelet.



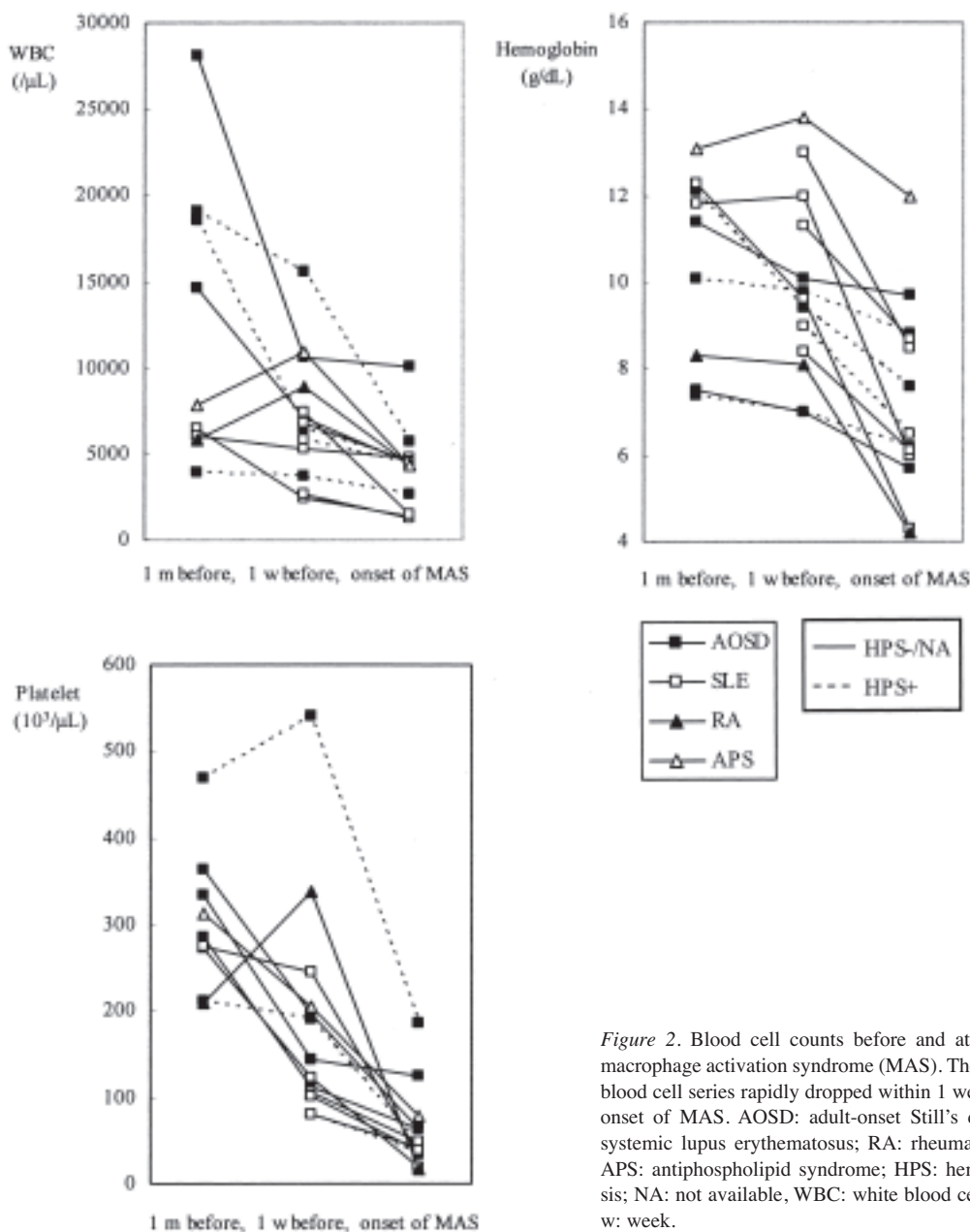


Figure 2. Blood cell counts before and at the onset of macrophage activation syndrome (MAS). The counts of all blood cell series rapidly dropped within 1 week before the onset of MAS. AOSD: adult-onset Still's disease; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; APS: antiphospholipid syndrome; HPS: hemophagocytosis; NA: not available, WBC: white blood cell. m: month; w: week.

proliferation of lymphocytes and macrophages, and overproduction of cytokines. This may result in widespread tissue damage and HPS<sup>12</sup>.

One study demonstrated reduced perforin expression in NK cells and in CD8+ cytotoxic T lymphocytes in patients with active systemic JIA compared with polyarticular JIA and healthy controls<sup>13</sup>. Perforin is a protein that mediates cytotoxic activity of NK cells and T lymphocytes, and thus reduced perforin expression results in impaired cytolytic function of these cells. Another recent study showed that defective phosphorylation of IL-18 receptor  $\beta$  disables NK cells' capability to upregulate perforin in systemic JIA<sup>14</sup>. Impaired differentiation and cytotoxicity of NK cells in SLE

have also been reported<sup>15</sup>. Any patients with impaired NK cell function might have the potential to develop MAS.

In our study, we showed a clear association of the high serum M-CSF and  $\beta_2\text{m}$  levels with a poor prognosis. M-CSF is secreted by monocytes and partly by activated CD8+ T cells, stimulates mononuclear phagocytes, and may play a key role in tissue damage, which may lead to the most severe clinical features of MAS.  $\beta_2\text{m}$  is a light-chain molecule of the major histocompatibility complex class I antigens, and is found on the surface membrane of almost all nucleated cells. It is particularly plentiful on WBC. An increased serum level of  $\beta_2\text{m}$  has been found to be of prognostic relevance in a wide variety of hematological malignancies.

nancies<sup>16</sup>. In patients with MAS, the elevation of the serum M-CSF and  $\beta_2$ m levels would reflect the excessive activation of lymphocytes and macrophages.

We observed the difference in cytokine profiles between patients with SLE and patients with AOSD. The patients with SLE showed a prominent increase in serum M-CSF levels, as did the patients with AOSD in serum IL-18 levels. This suggests different pathophysiologic mechanisms of MAS between patients with SLE and patients with AOSD, possibly regarding NK cell function. The mechanisms of MAS in different rheumatic diseases need to be further investigated.

There are no common diagnostic criteria for MAS so far. We adopted 3 features as MAS criteria for our study: SIRS, cytopenia in more than 2 series, and elevated serum ferritin level, not including histological evidence of HPS. Bone marrow aspirate or biopsy may not always show HPS<sup>17,18</sup>. Indeed, in a report, a patient with a previously normal bone marrow showed clear evidence of HPS a few days later by autopsy<sup>19</sup>. In addition, although liver, lymph node, or spleen may show HPS more frequently than bone marrow, their biopsies are often difficult in patients with profound thrombocytopenia or DIC<sup>17,18</sup>. Neither preliminary diagnostic guidelines for MAS complicating systemic JIA<sup>20</sup> nor those for MAS complicating juvenile SLE<sup>21</sup> require evidence of HPS in the presence of the typical clinical and laboratory features of MAS.

As for the ferritin level, we adopted a diagnostic criterion for secondary HPS proposed by Imashuku, which set  $\geq 1000$  ng/ml<sup>22</sup>. Another study set a ferritin level of  $\geq 10,000$  ng/ml for diagnosing MAS complicating JIA<sup>23</sup>. In our study, the patients with SLE had lower ferritin levels than the patients with AOSD, and 2 of the 9 patients with SLE (both of whom had clear findings of HPS and one of whom died) had peak ferritin levels of 2184 and 3095 ng/ml, respectively. Further, the Histiocyte Society set ferritin levels of  $\geq 500$  ng/ml as one of the diagnostic criteria for HLH in its revised guidelines (HLH-2004)<sup>24</sup>, and the preliminary diagnostic guidelines for MAS complicating juvenile SLE also set a ferritin level of  $\geq 500$  ng/ml<sup>21</sup>.

In terms of cytopenia, we added the extent of decrease to less than half of the patient's baseline level to the previously proposed threshold value of each blood cell series for HPS<sup>20,25</sup>. The importance of progressive cytopenia rather than the absolute counts in making an early diagnosis has been emphasized<sup>17,19</sup>. The baseline counts vary from patient to patient according to underlying active rheumatic diseases, and a significant drop in blood cell counts, even though not to the threshold value, should not be dismissed as irrelevant<sup>19</sup>.

The cytokine profiles of MAS differed between patients with SLE and patients with AOSD, and between those who died and those who recovered. The patients with SLE showed a prominent increase in serum M-CSF level, as did

the patients with AOSD in serum IL-18 level. As high serum M-CSF and  $\beta_2$ m levels were considered to be important and useful predictors for fatal MAS, aggressive treatment for patients with these profiles should be promptly started. We hope that it is further investigated in a larger patient population.

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