Occult macrophage activation syndrome in systemic-onset juvenile idiopathic arthritic syndrome – a case report

Ping Zeng[1], Feng Li[2], Huasong Zeng[2]

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TABSTRACT

Macrophage activation syndrome (MAS) is a severe and life-threatening complication of rheumatic disorders in children. We described a 9-year-old girl in whom MAS developed as a complication of systemic juvenile idiopathic arthritis (S-JIA) at onset with obvious hemophagocytosis presented in the marrow. She suffered from high fever and generalized rash subsequently joints swelling for two weeks before admission. Physical examination revealed mild cervical lymphadenopathy and hepatosplenomegaly. Laboratory findings were: abnormal liver enzymes, increased triglyceride and ferritin levels, anemia .Hyperplasia of hemophagocytic macrophages was remarkable in her bone marrow. Methylprednisolone and cyclosporin therapy resulted in clinical and laboratory improvement. It is unusual that hemophagocytosis presented in the marrow at onset of So-JIA without obvious abnormal coagulation profile, thrombocytopenia and leucopenia. It seemed that MAS may be occult at onset of SJIA. It may be integral to the pathogenesis of SJIA. The proper cyclosporine serum lever at the onset of MAS is as high as 200-300 ng/ml.

Keywords: Macrophages; Arthritis; Juvenile idiopathic.

INTRODUCTION

Macrophage activation syndrome (MAS) is a severe and life-threatening complication of rheumatoid diseases, especially in systemic-onset idiopathic arthritic syndrome. MAS is characteristically similar to hemophagocytic lymphohistiocytosis (HLH) and involves abnormal liver or renal function, cytopenia, central nervous dysfunction, pneumonedema, hemorrhage, hepatosplenomegaly, lymphadenopathy, and persistent fever. Prognosis depends on prompt recognition and immediate treatment. However, MAS is difficult to diagnose due to a lack of diagnosis criteria; it differs from sepsis or other syndromes, especially at the initial stage.

Similar to other hemophagocytic syndromes, the preliminary guidelines of MAS posed in 2005 set three clinical criteria and four laboratory criteria as sensitive clinical features of MAS, which include decreased platelet count (≤262×10^9/L), elevated levels of aspartate aminotransferase (>59 U/L), decreased white blood cell count (≤4.0×10^9/L); hypofibrinogenemia (≤ 2.5g/L), central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, and coma), hemorrhages (purpura, easy bruising, and mucosal bleeding), and hepatomegaly (≥3 cm below the costal arch). A bone marrow aspirate may be required only in ambiguous cases to determine hemophagocytosis. In the present paper, we describe the case of a nine-year-old girl who developed MAS during systemic-onset juvenile idiopathic arthritis (So-JIA) treatment without typical clinical and laboratory test results aforementioned.Case ReportA nine-year old girl suffered from remittent high fever for two weeks with no reported coughing, vomiting, diarrhea, headache, and stomachache. Generalized salmon pink rash appeared on the fourth day of the fever, accompanied by itching, which subsided as the fever declined. Antibiotic drugs were not effective. Bacterial, fungal, and viral tests for Parvovirus B19 virus, Epstein-Barr virus, and adenovirus showed negative results in the laboratory. On the 13th day of fever, the girl complained of pain on the left knee joint, and the fifth articulationes metacarpophalangeae showed red swelling. The condition was suspected to be So-JIA, and the girl was admitted in the rheumatoid department.

Physical examination revealed mild hepatosplenomegaly. Pink-colored rashes were diffusely present on

1. Department of Allergy, Immunology and Rheumatology, Guangzhou Woman and Children's Medical Center, Guangzhou, China, 510120;
2. Department of Immunology and Rheumology, Guangzhou Children's Hospital, Guangzhou Woman and Children's Medical Center, Guangzhou Medical College, 510120,China

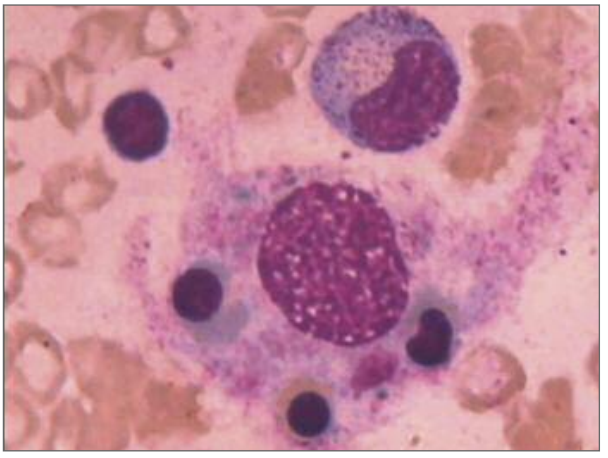

FIGURE 1. Bone marrow biopsy section shows macrophage hemophagocytosis.

her abdomen, face, neck, and anus. The left fifth articulationes metacarpophalangeae swelled. Laboratory tests for rheumatoid factor, anti-streptolysin O, and antinuclear antibody were all negative. Liver function and lipid metabolism was abnormal. Leukocyte count was high but the hemoglobin level was only 8.6 g/l. Erythrocyte sedimentation rate (ESR) increased to 109 mm/hr, and C-reactive protein (CRP) was 156 mg/l. Ferritin reached up to 1,500 ng/ml. NK cell level decreased to 3%. Coom's test was negative. The bone marrow aspirate biopsy showed macrophage hemophagocytosis, as presented in Figure 1, and the histocyte level was 3%. Skin biopsy only showed cutaneous allergic reaction. The detailed laboratory findings are presented in Table I.

The girl has no family history of HLH. She was

TABLE I. LABORATORY VALUES ON WEEK1~ 10 OF THE PATIENT'S HOSPITALIZATION

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
Hemoglobin(g/L)	80	90	91	92	84	89	87	85	87	88
White blood cells($\times 10^9$/L)	21.3	23.5	25.8	22.3	26.1	16.4	22.9	22.3	15.7	27.7
Polymorphonuclear cells, %	70	86	89	85	80	79	81	80	80	83
Platelets	358	364	317	354	367	458	276	323	433	415
*ESR(Westergren method), mm/hour	109	69	120			110	108	48	92	112
*CRP level, mg/liter (normal <3)	156	27	76.5	62	67.6	119	84	96	29.5	35
Ferritin, ng/ml (normal 15–200)	>1500					>1500	>1500	>1500	>1500	>1500
*ALT U/L	51	56		25		30	142	83	36	24
Triglycerides, mmol/L (normal 0.23–1.7)	1.4	2.48		1.52		2.31	2.16	1.87	3.23	2.86
*LDH U/L (normal 126–294)	1772	1502		787		616	726	623	459	415
*TB µmmol/L (normal 2~17)	4.8	3.6		4.2		2.3	3.9	4.9	3.5	4.7
Albumin, gm/dl (normal 3.5–5)	30.9	28.5		28.5		31.7	33.3	32.2	31.6	32.5
D-Dimer mg/L (normal <0.3)	2	2	0.3			0.7	0.7	0.5	0.4	<0.3
*FIB g/L normal 2~4	3	2	3.38			3.73	3.89	3.74	3.52	4.37
Prothrombin Time normal 10.4~14s	14.80				11.6	12.4	12.7	12.1		11.8
*PTT(normal 23~35)	30.70				21.00	24.60	25.8	21.4		23.6
INR(normal 0.75~1.25)	1.20				0.93	1.00	1.03	0.97		0.95

*ESR=erythrocyte sedimentation rate; CRP= C-reactive protein; ALT=alanine aminotransferase; FIB=fibrinogen
PTT=Partial Thromboplastin Time; TB= Total bilirubin.

healthy before febris. She was diagnosed of So-JIA and MAS after one week of admission and treated with methylprednisolone (10 mg/kg/d for three days, switched to oral methylprednisolone, 1 mg/kg/d) and oral cyclosporine (3 mg/kg/d). Clinical and several laboratory findings improved, as evidenced by normal temperature and decrease of ESR and CRP. Second (after one week) bone marrow aspiration biopsy showed that macrophages nearly disappeared. However, this state lasted only one week. Febris recurred, and the intermittent temperature ranged from 37.5 °C to 39 °C. CTX (8 mg/kg iv drip for 2 days) was administered. The condition persisted, and administration of NSAIDS appeared ineffective. Physical examination found nothing special except mycotic stomatitis. Antifungal agents were used, although laboratory tests for fungi were negative. Mycotic stomatitis was eventually treated, but fever remission was not successful. Further laboratory tests for bacteria, virus, and fungi still showed negative results. ESR, FER, and CRP increased. The girl turned pale and weaker on the 7th week after admission. Fever was persistent, arthralgia increased, and hemorrhage intermittently occurred. ESR dropped to 48 mm/hr, and ALT increased to 142 U/l. LDH was measured to be 726 U/l, D-Dimer was 0.7 mg/l, FER was >1,500, hemoglobin was 8 g/l, and NK cell measurement was 1%. The third bone marrow aspiration biopsy revealed macrophage hemophagocytosis and numerous hemophagocytic cells, and histocyte level of 3.5%. Serum level of cyclosporine was 123.2 ng/ml.

MAS was diagnosed again on the 8th week. Treatment with high-dose methylprednisolone (20 mg/kg/ /day) was promptly implemented and continued for three consecutive days, then switched to dexamethasone 10 mg/m2d for one week and methylprednisone 1.6 mg/kg/d for two weeks then decreased progressively. Cyclosporine dose was increased to 5 mg/kg/d to maintain a serum level ranging from 200 ng/ml to 300 ng/ml. Intravenous immunoglobin (IVIG) was given simultaneously at a dose of 1.0 g/kg/d for three days. The protocol was effective. Clinical symptoms improved; temperature returned to normal, rashes disappeared, arthralgia was relieved, and CRP dropped to 35. Currently, the girl is being followed up monthly as an outpatient in our unit. Her condition seems improved.

DISCUSSION

Hadchouel et al. first described MAS and associated it with So-JIA in 1985[1]; Stephan et al. proposed the term MAS in 1993[2]. More than 100 MAS cases have been reported worldwide (English literature)[3]. The mortality rate is about 8% to 22%[4,5]. Currently, MAS is widely recognized as a severe and potentially fatal complication of So-JIA. The prognosis depends on early recognition and immediate treatment. However, diagnosis of MAS is difficult and confusing because formal and universally accepted criteria have not been established. Clinicians usually use the HLH criteria for MAS in practice as both are heterogeneous diseases, but all come from histiocytic disorder and recognized as a subtype of HLH[6].

The patient described in this paper showed clinical features of So-JIA, which include fever for at least two weeks, hepatosplenomegaly, pink-colored rashes, and arthritis[21]. So-JIA diagnosis is not easy to establish because symptoms pointing to arthritis may appear after half a year or longer. The girl complained of pain in the left knee joint, and the fifth articulationes metacarpophalangeae showed red swelling on the 13th day of fever. Thus, the diagnosis of So-JIA was made without taking infections and tumors into account. The patient did not show MAS criteria (three clinical and four laboratory criteria) at the initial stage, which are based on the preliminary diagnostics guideline set in 2005[7]. However, hemophagocytosis found in the marrow supported diagnosis of MAS when the girl was admitted. In addition, the clinical and laboratory findings indicated four other criteria indicating HLH recommended in 2005 and 1991[8,9], which include fever, hyperferritinemia, decreased or absent NK cell activity, and splenomegaly. Based on 5/8 criteria for diagnosis of HLH and So-JIA, the girl was confirmed to have MAS. Hemophagocytosis in the marrow at the onset of So-JIA, as well as thrombocytopenia and leucopenia, was unusual.

MAS is fulminant. A review of the cases reported in the literature indicates that MAS usually occurs during So-JIA treatment. Typical clinical features defining MAS are persistently high fever, mucosal bleeding, neurological abnormalities (headache, irritability, lethargy, seizures, coma), pulmonary failure, cardiac and renal involvement, generalized lymphadenopathy, hepatosplenomegaly, and the presence of rashes or petechiae or purpura due to thrombocytopenia. Laboratory findings include coagulation abnormalities (DIC, prolonged PT, and PTT), drop in the sedimentation rate from hypofibrinogenia, pancytopenia, high levels of ferritin, high levels of liver enzymes and low levels of albumin due

to impaired liver function, high levels of triglycerides, and phagocytosis of elements derived from bone marrow (hematophagocytic histiocytes) or other organs[3,10-12]. Preliminary criteria of MAS as recommended by Ravelli in 2002 and 2005[12,13] include persistent high fever, hepatosplenomegaly, bleeding, and neurologic dysfunction. Laboratory criteria include pancytopenia (WBC <4.0×10^9, Plt <262×10^9) or hyperferritinemia, high levels of liver enzymes (ALT >59 U/l), and hypofibrinogenia (<2.5 g/l). Clinical manifestation of MAS is occult. It is hard to diagnose, and it differs from the onset of So-JIA without taking a biopsy of bone marrow. The evolution of leukocyte and platelet counts is showed in the Table I. Throughout the onset of the disease, the leukocyte count was higher than 20×10^9/l, and platelet count was normal or slightly elevated. In a recent cohort study aimed at identifying features distinguishing MAS in So-JIA from familial hemophagocytic lymphohistiocytosis and virus-associated HLH, a substantial number of patients diagnosed with MAS showed values for white blood cells (84%), neutrophils (77%), platelets (26%), and fibrinogen (71%), which were within or above the normal range[22]. The occurrence of MAS at the initial stage of So-JIA should be noted. Genetic evaluation could potentially help early diagnosis and treatment. Mutations in genes involved in cytolytic pathways are increasingly being recognized in children who develop MAS as part of So-JIA23. Identification of these mutations may assist in future MAS diagnosis.

The efficiencies of corticosteroid and cyclosporine were confirmed in literature[14-19]. Corticosteroids inhibit the production of CD95 ligand and differentiation of dendritic cell to suppress the cytokine storm[16]. Pharmacological studies considered that the immunosuppressant cyclosporine can inhibit T-cell activation, suppress the production of IL-6, IL-1, and TNF-a, and thereby stop macrophage activation[18,19]. Currently, a standard treatment protocol for MAS is still lacking. Our experience in this case confirmed the effectiveness of methylprednisone and cyclosporine therapy. The girl was sensitive to methylprednisone and cyclosporine during the first two weeks of treatment. However, the average dose of corticosteroid and low dose of cyclosporine could not control the factor that contributed to MAS recurrence. Results point out that the appropriate cyclosporine serum level during the onset of MAS should be as high as 200 ng/ml to 300 ng/ml. IVIG may play a crucial role in the treatment of recurrent MAS. The mechanism proposed is through the ability of IVIG to induce expression of inhibitory FcgRIIB receptor on effector cells, thereby counteracting the activation responses triggered by FcgRIIB engagement in macrophages and other immune-competent cells[20]. Based on our experience, IVIG treatment is effective.

Currently, knowledge regarding the use of biological agents in so-JIA complicated by MAS is limited. The role of IL-1, IL-6, and TNF as important mediators in the inflammatory cascade of So-JIA has been demonstrated. Case reports of TNF blockade (etanercept) and IL-1 blocking agents (Anakinra) therapy in MAS are mixed: some have reported successful treatment, whereas others have described the development of MAS after the initiation of etanercept and Anakinra therapy for patients with sJIA[24-30]. However, more cases of So-JIA-associated MAS have been reported where patients largely benefit from Anakinra treatment after inadequate response to corticosteroids and CsA[31-33]. In a large case series of 46 So-JIA patients treated with Anakinra at disease onset, results show that Anakinra is a potential MAS trigger in five children at doses of 1 mgkg^{-1} to 2 mgkg^{-1} per day. However, dose escalation of Anakinra often appears to help control MAS, and permanent discontinuation of Anakinra proved unnecessary for any of the children[34]. Future therapeutic protocols for the treatment of MAS as part of So-JIA will potentially include a combination of high-dose corticosteroids, CsA, and anti-pro-inflammatory cytokine treatment, such as blockade of IL-1.

CORRESPONDENCE TO
Huasong Zeng
Department of Immunology and Rheumology, Guangzhou Children's Hospital, Guangzhou Woman and Children's Medical Center, Guangzhou Medical College, PRC,
318 Renminzhong Road, Guangzhou, 510120, PR. China
Fax: 86-20-81858962, 81861654
Tel: 86-20-81330702, 81330703, 81330704; 86-20-81906481
E-mail: zenghuasongcn@163.com

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