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Macrophage Activation Syndrome in a Child with Systemic Juvenile Rheumatoid Arthritis

Macrophage activation syndrome (MAS) is a rare and potentially fatal complication of rheumatic disorders in children. We describe a 13-month-old boy in whom MAS developed as a complication of systemic juvenile rheumatoid arthritis (S-JRA). He suffered from fever and generalized rash followed by multiple joints swelling for four months before admission. Physical examination revealed cervical lymphadenopathy and hepatosplenomegaly. Laboratory findings were: abnormal liver enzymes, increased triglyceride and ferritin levels, coagulopathies resembling disseminated intravascular coagulation, anemia and thrombocytopenia. Hyperplasia of hemophagocytic macrophages was remarkable in his bone marrow. Methylprednisolone and cyclosporin therapy resulted in clinical and laboratory improvements. This is the third case of MAS associated with S-JRA in Koreans, and the first one, in which hemophagocytic macrophages were proven in bone marrow.

Key Words : *Macrophages; Arthritis, Juvenile Rheumatoid*

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INTRODUCTION

Macrophage activation syndrome (MAS) is a clinical entity characterized by serious liver diseases, hematologic abnormalities, coagulopathy resembling disseminated intravascular coagulation, and neurologic involvement. MAS is known to be a severe and potentially life-threatening complication of rheumatic disorder, especially systemic juvenile rheumatoid arthritis (S-JRA) (1).

MAS is a rarely-occurring disorder, and only sporadic case reports or several studies with relatively small number of patients are available in the literature (2-4). In Korea, only two cases of MAS associated with S-JRA have been reported (5, 6). Here we describe a 13-month-old boy, in whom MAS developed as a complication of S-JRA. This is the third case of MAS in Koreans, and the first one, in which hemophagocytic macrophages were proven in bone marrow (BM).

CASE REPORT

A 13-month-old boy, who had suffered from fever, generalized rash, and multiple joints swelling for four months, visited pediatric rheumatology clinic. At admission, fever, which had shown an intermittent high pattern, nearly subsided, but salmon pink-colored rheumatoid rash was diffusely present on his abdomen. His hands, lower legs and feet were bilaterally swelled with the involvement of metacarpal and proximal interphalangeal joints of second fingers, knee joints, and fifth toes (Fig. 1). Physical examination revealed cervical lymphadenopathy and hepatosplenomegaly. Under the diagnosis of S-JRA, he had been treated with aspirin (100 mg/kg for nine days) and ibuprofen at local hospital until one week before admission.

Laboratory results of rheumatoid factor, anti-streptolysin O, lupus anticoagulant, and antinuclear antibody were all negative. Complement and immunoglobulin data were: C3, 199 mg/dL; C4, 33.5 mg/dL; IgG, 766 mg/dL; IgA, 112 mg/dL; and IgM, 81.5 mg/dL. There was no evidence of viral infection or hepatitis. Other laboratory findings at admission are presented in Table 1.

Bone marrow (BM) examination, which was performed as a further work-up of hematologic abnormalities showed normocellular marrow with a cellularity of 90%. Granulocytic and megakaryocytic lineages were normal in maturation, but erythroid lineage was hypoplastic. Benign-looking macrophages were remarkably increased, and some of them showed hemophagocytic features. Their presence was confirmed with CD68 immunostain (Fig. 2).

He was diagnosed as having MAS. Immunosuppressive therapy with methylprednisolone (2 mg/kg/day for three days, and switched to oral prednisolone) and cyclosporin (2.5 mg/kg/day, under continuous medication) was started from the third and the ninth hospital days, respectively. Clinical and laboratory findings improved with decreased hepatomegaly and joints swelling at the time of discharge (Fig. 3-5). He has remained stable without relapse of MAS during the follow-up period of six months.

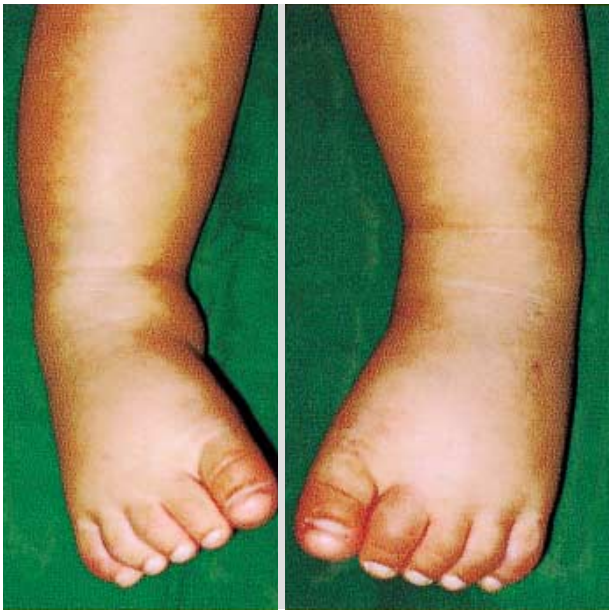

Fig. 1. Swelling of both lower legs and feet.

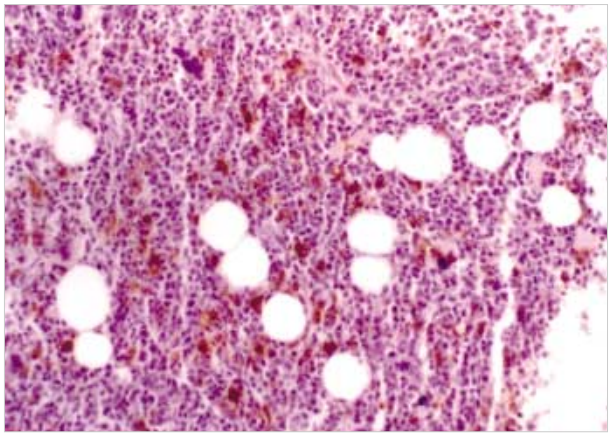

Fig. 2. Bone marrow biopsy section shows increased numbers of diffusely distributed and minimally clustered macrophages (CD68 immunostain, ×200).

DISCUSSION

In 1985, Hadchouel et al. described seven patients who showed unique clinical features with hematologic, neurologic, and hepatic abnormalities in association with S-JRA (7, 8). Since they suggested the term MAS in 1993, MAS has been commonly used to identify the hemophagocytic syndrome that may develop in children with chronic rheumatic diseases, particularly S-JRA (9).

MAS is a potentially fulminant disorder, and occurs during the clinical course of underlying S-JRA characterized by repetitive disease flares. It is thus very important to differentiate the onset of MAS from a flare of the disease, as they have different treatments and prognoses. Clinically, the patterns of fever and skin rash are somewhat different, although both of the diseases share lymphadenopathy and hepatosplenomegaly (1). From the aspect of laboratory findings, decreases of blood cells, erythrocyte sedimentation rate, and fibrinogen present striking contrasts to S-JRA. Hypertriglyceridemia, elevated liver enzymes, and abnormal coagulation profile are consistently found. Hyperferritinemia greater than 10,000 ng/mL is known to be also remarkable heralding MAS development, thus making early and aggressive immunosuppression possible (4, 10, 11).

Table 1. Cases of macrophage activation syndrome in Koreans

	Kim et al. (1988)*	Park et al. (1998)	Present case
Sex/age	Male/9 yr	Female/13 yr	Male/13 months
Underlying disease	S-JRA	S-JRA	S-JRA
Disease duration	7 yr	8 yr	3 months
Hemoglobin (g/dL)	NA	7.6	6.9
White blood cell ($\times 10^9$/L)	NA	4.5	6.1
Platelet ($\times 10^9$/L)	60	157→51	55
ESR (mm/hr)	NA	36	17
Bleeding time (min)	>10	NA	NA
Prothrombin time (sec)	18	20.5	21.2
aPTT (sec)	77.6	66	37.4
Fibrinogen (mg/dL)	NA	40	31.2
FDP (μg/mL)	80	20	>20
AST (IU/L)	NA	244	2,090
ALT (IU/L)	NA	97	560
LDH (IU/L)	NA	6,345	7,880
ALP (IU/L)	NA	NA	2,751
GGT (IU/L)	NA	NA	227
Triglyceride (mg/dL)	NA	NA	326
Ferritin (ng/mL)	NA	NA	28,589
Treatment	FFP, Antibiotics	Methylprednisolone, IVIG	Methylprednisolone, Cyclosporin
Possible triggers	Pneumonia Salicylates	Sulfasalazine Naproxen	Aspirin Ibuprofen
Clinical course	Recovered	Expired	Recovered

*In this case, detailed laboratory data on liver function and complete blood cell count except platelet count was unavailable at the onset of coagulopathy. ESR, erythrocyte sedimentation rate; aPTT, activated partial thromboplastin time; FDP, fibrin degradation product; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; S-JRA, systemic juvenile rheumatoid arthritis; NA, not available; FFP, fresh frozen plasma; IVIG, intravenous immunoglobulin.

The patient described here showed typical clinical and laboratory features of MAS, which changed dramatically after the initiation of immunosuppressive treatment (Fig. 3-5). To our knowledge, two cases of MAS were previously reported in Koreans (5, 6). Three cases including our case are summarized in Table 1. Although they were all pediatric patients suffering from S-JRA, MAS can also develop in other rheumatic disorders as well as in adults (2, 4).

The pathognomonic feature of MAS is numerous well dif-

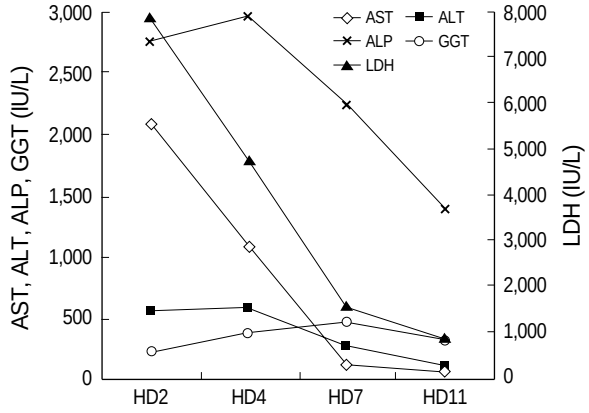

Fig. 3. Laboratory findings of liver enzymes during hospital days. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; LDH, lactate dehydrogenase; HD, hospital day.

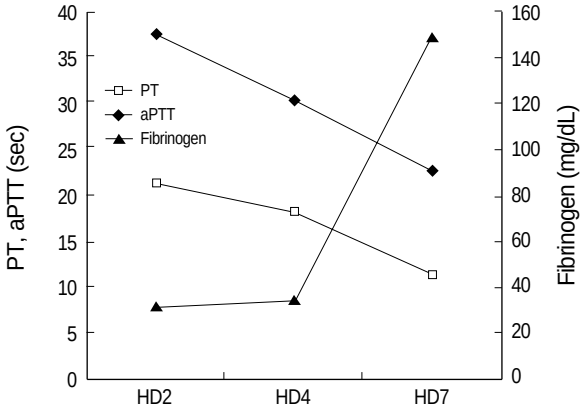

Fig. 4. Laboratory findings of PT, aPTT, and fibrinogen during hospital days. PT, prothrombin time; aPTT, activted partial thromboplastin time; HD, hospital day.

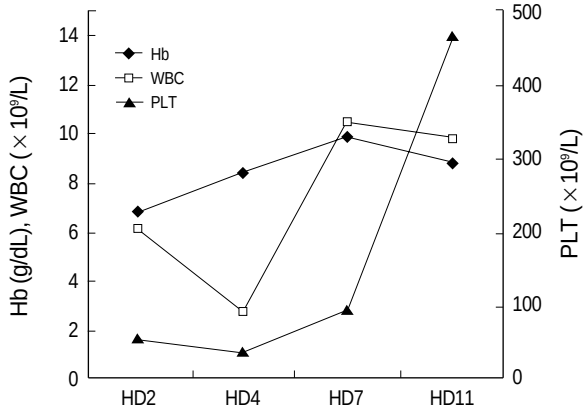

Fig. 5. Laboratory findings of complete blood cell counts during hospital days. At the third hospital day, red blood cell was transfused. Hb, hemoglobin; WBC, white blood cell; PLT, platelet; HD, hospital day.

ferentiated macrophages actively phagocytosing hematopoietic elements in BM. Hemophagocytic macrophages can also be found in spleen or lymph nodes. BM examination, however, may reveal false negative result related to a sampling error or the timing of aspiration during disease course (1, 2, 4). Accordingly, morphologic confirmation is not a prerequisite for the diagnosis of MAS. BM study was not performed in both of the previous Korean cases. However, coagulopathies resembling disseminated intravascular coagulation as well as other laboratory or clinical findings support their diagnoses of MAS.

Although the mechanism of MAS is still poorly understood, it is known that cytokine storm plays a major role. T cell or natural killer cell dysfunction may lead to uncontrolled macrophage activation, and increased levels of many cytokines, representatively tumor necrosis factor-alpha or interferon-gamma, released by macrophages or T cells initiate systemic hemophagocytosis (9, 11-13). At molecular level, dysfunctional perforin was recently suggested as a possible cause of this condition (11, 14).

Triggering episodes like infections or medications may precede the onset of MAS, and they have been reported in at least 58% to 88.9% of patients (1, 2). The possibility of triggers also existed in all of the three Korean cases (Table 1). In the patient by Kim et al., there was a history of infection and salicylates medication four to six weeks prior to the onset of coagulopathy (5). The other two patients by Park et al. and by us recently received anti-inflammatory drugs (6).

With regard to nomenclature, the term reactive hemophagocytic lymphohistiocytosis is interchangeably used with MAS (1, 15). Although MAS is widely used in the field of rheumatology, this is relatively unfamiliar to specialists in other fields such as infectious disease or hematology. MAS is even not included in the recently proposed classification of histiocytic disorders (16, 17). Some researchers insisted that MAS should belong to the category of secondary hemophagocytic syndrome likewise infection or malignancy-associated ones, and the term rheumatic disease-associated hemophagocytic syndrome is preferable to MAS (18-20). We agree with their opinion in that such unifying criteria would be beneficial for investigating etiologic relationships or developing treatment strategies among the related disorders.

In summary, we report a case of MAS in a 13-month-old boy suffering from S-JRA. His clinical and laboratory features were typical of MAS, and his clinical course improved after immunosuppressive therapy with methylprednisolone and cyclosporin. This is the third case of MAS in Koreans, and the first one, in which hemophagocytic macrophages were proven in BM.

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