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 disorders, 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 associated with S-JRA in Koreans, and the first one, in which hemophagocytic macrophages were proven in bone marrow.

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. 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
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).

The patient described here showed typical clinical and laboratory features of MAS, which changed dramatically after the initiation of immunosuppressive treatment (Fig. 3-5).

Table 1. Cases of macrophage activation syndrome in Koreans

| Sex/age          | Underlying disease | Disease duration | Hemoglobin (g/dL) | White blood cell (× 10^9/L) | Platelet (× 10^11/L) | ESR (mm/hr) | Bleeding time (min) | Prothrombin time (sec) | aPTT (sec) | Fibrinogen (mg/dL) | AST (IU/L) | ALT (IU/L) | ALP (IU/L) | GGT (IU/L) | Triglyceride (mg/dL) | Ferritin (ng/mL) | Treatment               | Possible triggers | Clinical course  |
|------------------|--------------------|------------------|-------------------|-----------------------------|----------------------|-------------|---------------------|------------------------|------------|-------------------|-------------|-------------|-------------|-------------|---------------------|--------------------|------------------------|-----------------|-----------------|
| Kim et al. (1988)* | Male/9 yr S-JRA    | 7 yr             | NA                | NA                          | 60                   | NA          | >10                  | 18                     | 77.6       | NA                | NA          | NA          | NA          | NA          | NA                  | NA                | FFP, Methylprednisolone, IVIG, Cyclosporin | Pneumonia, Sulfasalazine, Aspirin | Recovered       |
| Park et al. (1998) | Female/13 yr S-JRA | 8 yr             | 7.6               | 4.5                         | 157→51               | 36          | NA                  | 20.5                   | 66         | 40                | 244         | 97          | 97          | NA          | NA                  | 6,345             | Methylprednisolone | Salicylates, Naproxen, Ibuprofen | Expired         |
| Present case     | Male/13 months S-JRA | 3 months        | 6.9               | 6.1                         | 55                   | 17          | NA                  | 21.2                   | 37.4       | 31.2              | 2,090       | 560         | 2,751       | 227         | 326                 | 28,589            | Fresh frozen plasma, IVIG, Intravenous immunoglobulin | | 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.

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).
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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