INTRODUCTION

There are various extra-articular manifestations in juvenile rheumatoid arthritis (JRA), like rheumatoid arthritis (RA). And macrophage activation syndrome (MAS) is one of the life-threatening complications of systemic onset JRA. It is associated with excessive activation and uncontrolled proliferation of T lymphocytes and macrophages (1). This condition occurs in a heterogeneous group of diseases including infectious, neoplastic, hematologic and rheumatic disorders (2). The clinical findings of MAS are acute and dramatic. Typically, patients become acutely ill at presentation with non-remitting high fever, pancytopenia and impaired liver and renal function tests, elevated triglyceride and serum ferritin levels. Bone marrow biopsy showed hyperplasia of histiocytes with active hemophagocytosis. He was diagnosed as MAS associated with juvenile rheumatoid arthritis and managed with high-dose corticosteroids initially, but clinical symptoms and laboratory findings did not improve immediately. Finally, he completely recovered after treatment with cyclosporine A (3 mg/kg/day).

CASE REPORT

A 29-yr-old man visited our clinic due to fever and jaundice for one month. Three days ago, he visited the local clinic and took oral prednisolone 20 mg but his symptoms and elevated liver enzyme did not improve. He had been diagnosed with systemic onset JRA 16 yr ago. Physical and laboratory results showed hepatosplenomegaly, high fever, pancytopenia and impaired liver and renal function tests, elevated triglyceride and serum ferritin levels. Bone marrow biopsy showed hyperplasia of histiocytes with active hemophagocytosis. He was diagnosed as MAS associated with juvenile rheumatoid arthritis and managed with high-dose corticosteroids initially, but clinical symptoms and laboratory findings did not improve immediately. Finally, he completely recovered after treatment with cyclosporine A (3 mg/kg/day).

Key Words: Macrophage activation syndrome; Arthritis, Juvenile Rheumatoid; Cyclosporine

Macrophage activation syndrome (MAS) is one of the serious complications of juvenile rheumatoid arthritis (JRA) and recently, cyclosporine A has been found to be effective in patients with corticosteroid-resistant MAS. A 29-yr-old male was admitted with high fever and jaundice for one month. He was diagnosed as juvenile arthritis 16 yr ago. Physical and laboratory results showed hepatosplenomegaly, high fever, pancytopenia and impaired liver and renal function tests, elevated triglyceride and serum ferritin levels. Bone marrow biopsy showed hyperplasia of histiocytes with active hemophagocytosis. He was diagnosed as MAS associated with juvenile rheumatoid arthritis and managed with high-dose corticosteroids initially, but clinical symptoms and laboratory findings did not improve immediately. Finally, he completely recovered after treatment with cyclosporine A (3 mg/kg/day).

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INTRODUCTION

There are various extra-articular manifestations in juvenile rheumatoid arthritis (JRA), like rheumatoid arthritis (RA). And macrophage activation syndrome (MAS) is one of the life-threatening complications of systemic onset JRA. It is associated with excessive activation and uncontrolled proliferation of T lymphocytes and macrophages (1). This condition occurs in a heterogeneous group of diseases including infectious, neoplastic, hematologic and rheumatic disorders (2). The clinical findings of MAS are acute and dramatic. Typically, patients become acutely ill at presentation with non-remitting high fever, hepatosplenomegaly, lymphadenopathy, severe cytopenia, liver disease, and intravascular coagulation.

To our knowledge, a case of MAS associated with juvenile rheumatoid arthritis has not been reported in Korea. We present MAS in a patient with JRA successfully treated with cyclosporine A.
rate was 2 mm/hr and C-reactive protein was 5.25 mg/dL (0-0.3). Coagulation tests and disseminated intravascular coagulation profiles showed prothrombin time of 97%, activated partial thromboplastin time 37 sec (normal control 27 sec), fibrinogen 219 mg/dL, fibrin degradation product 10.6 µg/mL (normal<5), antithrombin III 120% and D-dimer 13.51 mg/L (normal<1.0). Serological tests for viral infections, such as Epstein-Barr virus, cytomegalovirus and herpes simplex virus, revealed no sign of recent infections. Bacterial cultures of blood and urine were all negative. Bone marrow aspiration and biopsy showed marked increased histiocytes with active hemophagocytosis (Fig. 2). We diagnosed him as having macrophage activation syndrome associated with JRA. Intravenous pulsed methylprednisolone (1 g/day) was administered followed high-dose oral prednisolone (1 mg/kg/day). However, his symptoms and clinical signs did not improve. Fever was sustained and abnormal laboratory findings such as pancytopenia and impaired liver and renal function were not corrected. Then, oral cyclosporine A (CsA, 3 mg/kg/day) was added, and on next day after treatment with cyclosporine A, fever disappeared. After 5 days, pancytopenia recovered with white blood cell count 5,800/µL (neutrophil 67.1%), hemoglobin 9.1 g/dL, hematocrit 26.1% and platelet count 58,000/µL. Deteriorations of liver and renal function were also normalized with AST 10 IU/L, ALT 24 IU/L, total bilirubin 0.85 mg/dL, BUN 26.5 mg/dL and Cr 1.10 mg/dL, and serum ferritin decreased to 1,500 ng/mL.

**DISCUSSION**

In 1985, Hadchouel et al. reported that seven children with JRA had a syndrome characterized by hemorrhage and neurologic, hepatic, hematologic, and metabolic manifestations (4). In 1993 Stephan et al. introduced the term MAS in follow-up report originating from the same center (5). Recently, it is recognized that MAS belongs to secondary hemophagocytic syndromes, histiocytic disorders associated with an underlying systemic disease (6). Although MAS is most common in JRA, it can occur in patients with other rheumatic
disorders such as adult-onset Still’s disease, Behcet’s disease and systemic lupus erythematosus. Trigger factors are drugs (aspirin, nonsteroidal anti-inflammatory drugs, gold preparations, methotrexate, tumor necrosis factor blocking agents) and viral infections, particularly Epstein-Barr virus and herpes virus family (1).

The diagnostic hallmark of MAS is macrophage’s hemophagocytosis in the bone marrow. The sensitivity and specificity of the main components of the clinical and laboratory features of MAS were recently determined (7). Eighty-eight patients with JRA who had 109 episodes diagnosed as MAS were compared with control patients who had 35 episodes of disease flare. The variables that showed the highest sensitivity and specificity for MAS were the following: serum ferritin $\geq 10,000$ ng/mL, triglycerides $\leq 160$ mg/dL, SGOT $\geq 40$ IU/mL, fibrinogen $\leq 250$ mg/dL, SGPT $\geq 40$ IU/mL, $\gamma$-glutamyl transferase $\geq 40$ IU/mL, platelet count $\leq 150,000$/µL, bone marrow aspirate showing macrophage hemophagocytosis, hepatomegaly, and splenomegaly. Variables that did not prove sufficiently sensitive and specific included fever $\geq 38^\circ C$, lymphadenopathies, neurological manifestations, arthritis, rash, hemorrhages, WBC $\leq 4,000$/µL, ESR $\leq 50$ mm/hr, LDH $\geq 900$ IU/mL, bilirubin $\geq 1.2$ mg/dL, and serum sodium $\leq 130$ mEq/L. In our case, the patient had all components that showed the highest sensitivity and specificity for MAS, mentioned above.

The pathogenesis of MAS is still unclear. It has been explained that the over-activated T lymphocytes and macrophages are found in various organ (2), and perforin deficiency and some cytokines such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin (IL)-1, IL-6, and interferon (IFN)-$\gamma$ are playing roles in the pathogenesis of MAS (8, 9). Perforin is a cytotoxic protein that lymphocytes secrete to kill virus-infected cells and has a function that control the lymphocyte proliferation (10). Therefore, the perforin deficiency may lead to persistent lymphocyte activation.

MAS is associated with significant morbidity and mortality in JRA. Therefore, early recognition and prompt management are very important. It has been suggested that the initial treatment of choice in MAS is high-dose corticosteroid. But, MAS may appear to be corticosteroid resistant. Recently, cyclosporine A proved effective in treating severe or corticosteroid-resistant MAS (5, 11, 12). In most patients with MAS described by Mouy et al. (11) and Ravelli et al. (12), fever resolved within 24 hr and laboratory abnormalities within a few days. Cyclosporine A is a cyclic polypeptide immunosuppressant. The mechanism of action of cyclosporine A is not fully known. However, it is believed to exert its major effects by the early steps in T-cell activation. In addition, it may inhibit the production of IL-2 and IFN-$\gamma$ and the expression of the receptor site for IL-2 on T lymphocytes. Cyclosporine A has also been shown to inhibit expression of inducible nitric oxide (NO) synthase and cyclooxygenase-2 in macrophages, leading to decreased production of NO and prostaglandin E2 (13). Furthermore, cyclosporine A inhibits the expression of key cell surface co-stimulatory molecules. Thus, it can alter the antigen-presenting function of dendritic cells for T cell activation (14). In several cases of MAS, increased serum levels of TNF-$\alpha$ have been reported (5) and TNF-$\alpha$ is thought to play a central role in the pathogenesis of MAS. From this point of view, it has been hypothesized that anti-TNF-$\alpha$ agents may be effective therapy for MAS. Prahala et al. (15) described a patient with MAS and JRA successfully treated with the anti-TNF-$\alpha$ agent, etanercept.

The present case shows that MAS is a severe complication of JRA and is dramatically recovered after management with cyclosporine A. When high fever with pancytopenia, and multiorgan dysfunction develop in a patient with JRA, MAS should be considered. To our knowledge, this is the first case report of MAS in a patient with JRA in Korea.

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