Evaluation of macrophage activation syndrome associated with systemic juvenile idiopathic arthritis: single center experience over a one-year period

Kenan Barut¹, Gözde Yücel², Ada Bulut Sinoplu², Sezgin Şahin¹, Amra Adroviç¹, Özgür Kasapçopur¹

¹Department of Pediatrics, Division of Pediatric Rheumatology, Istanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

²Department of Pediatrics, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Abstract

Aim: This study aimed to evaluate the demographic, clinical, laboratory properties of patients with macrophage activation syndrome and treatment outcomes.

Material and Methods: The data of the patients who were diagnosed with macrophage activation syndrome secondary to systemic juvenile idiopathic arthritis between June 2013-May 2014 were evaluated by screening patient records.

Results: Ten patients with macrophage activation syndrome were followed up in one year. The mean age at the time of diagnosis was found to be 7.6±4.5 years. The most common clinical finding at presentation (80%) was increased body temperature. Hepatosplenomegaly was found in half of the patients. The most common hematological finding (90%) was anemia. The mean erythrocyte sedimentation rate was found to be 71.8±36.2 mm/h, whereas it was measured to be lower (31.2±25.2 mm/h) at the time of the diagnosis of macrophage activation syndrome. Increased ferritin level was found in all of our patients (the mean ferritin level was found to be 23 957±15 525 ng/mL). Hypertriglyceridemia was found in nine patients (90%). The mean triglyceride level was found to be 397±332 mg/dL. Systemic steroid treatment was administered to all patients. Cyclosporine A was given to eight patients (80%), canakinumab was given to four patients (40%) and anakinra was given to five patients (50%). Plasmapheresis was performed in two patients. Improvement was found in all patients except for one patient. The patient in whom no improvement was observed showed a chronic course.

Conclusions: The diagnosis of macrophage activation syndrome should be considered in presence of sudden disturbance in general condition, resistant high fever and systemic inflammation findings in children with active rheumatic disease. Complete recovery can be provided with early and efficient treatment in macrophage activation syndrome which develops secondary to systemic juvenile idiopathic arthritis. (Türk Pediatri Ars 2015; 50: 206-10)

Keywords: Juvenile idiopathic arthritis, macrophage activation syndrome, systemic

Introduction

Juvenile idiopathic arthritis (JIA) is an autoimmune chronic arthritis with an onset before the age of 16 years which persists for more than six weeks. According to the classification of the "International League of Associations for Rheumatology" (ILAR), it has seven different subtypes and systemic juvenile idiopathic arthritis (SJIA) is one of these subtypes. Systemic juvenile idiopathic arthritis in childhood is the equivalent of adult-onset Still's disease. Prolonged fever and rash are among the most important clinical findings of SJIA. Fever makes a peak once or twice a day and pinky erythematous rash more frequent on the trunk which may improve in a short time, lymphadenopathy, hepatosplenomegaly and serositis may accompany (1).

While systemic findings predominate in the beginning of the disease, arthritis may occur subsequently in a significant portion of the patients. The most important compli-

cation of this disease is macrophage activation syndrome (MAS). Macrophage activation syndrome is acquired, secondary phagocytosis which is encountered in the course of rheumatic diseases. The main clinical findings include prolonged fever, hepatosplenomegaly, rapidly developing pancytopenia and increased transaminases, sudden decrease in erythrocyte sedimentation rate (ESR), abnormal coagulation tests, hypofibrinogenemia, hypertriglyceridemia and hyperferritinemia. Demonstration of hemophagocytosis which is a characteristic change on bone marrow aspirate helps to make the diagnosis. In addition, hemophagocytic infiltrations may also occur in organs including lymph node, liver and spleen (2).

The same clinical findings may also be observed in hemophagocytic lymphohistiocytosis (HLH) and are named as "primary form of the disease". Macrophage activation syndrome which occurs secondary to other diseases is known as secondary hemophagocytosis. Although it is

Address for Correspondence: Kenan Barut, E-mail: drkenanbarut@hotmail.com

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mostly named as MAS by rheumatologists, it is also known as reactive or secondary HLH (3).

In primary HLH, dysfunction mutations in the genes encoding perforin, Munc13-4, syntaxin11 protein play a role in etiopathogenesis. Pathogenesis of HLH and MAS may be explained by uncontrolled activities of macrophages and dendritic cells as a result of these mutations (4, 5). In one study, syntaxin was reported in all exon analyses and heterozygous mutation was reported in the genes encoding Munc13-4 proteins in 5 of 14 subjects who developed MAS due to SJIA. These genes were found to have mutation in four (13.7%) of 29 SJIA patients who did not develop MAS (6).

Macrophage activation syndrome occurs most commonly as a complication of SJIA among rheumatic diseases. It has been reported that the frequency of marked MAS is roughly 10%, but it is known that the frequency of MAS which is not reflected in clinical practice reaches up to 30-40% (7, 8). Association with MAS has also been reported in systemic lupus erythematosus (SLE), Kawasaki disease and other vasculitides in addition to systemic JIA (9-11).

In treatment of macrophage activation syndrome, extensive high dose corticosteroid treatment is used in the beginning to control the findings. In addition, cyclosporin A treatment is used as immunosuppressive treatment. Etoposide treatment is used in primary HLH. It is rarely used in cases of MAS related with SJIA (12). Intravenous immunoglobulin (IVIG) treatment which was preferred more frequently in the past is currently applied in some severe cases (12). In maintenance treatment or in rare cases where activity findings can not be suppressed with classical treatment, anti-interleukin-1 (anti IL-1) or IL-6 treatment is used. Anakinra (IL-1 α ve beta inhibition), kanakinumab (IL-1 beta inhibition) and tosilizumab (IL-6 inhibition) are biological drugs used for this purpose (12).

This study aimed to evaluate the demographic, clinical and laboratory features and treatment results of patients with MAS related with SJIA and emphasized that the complication of MAS may be an urgent condition in patients with untreated chronic active SJIA.

Material and Methods

The patients who developed MAS secondary to SJIA and were examined in Istanbul University, Cerrahpaşa Medical Faculty, Department of Pediatrics, Division of Rheumatology during a one-year period (June 2013 and May 2014) were included in the study. All patients were diagnosed with SJIA according to ILAR diagnostic criteria. The diag-

nosis of MAS was made according to the diagnostic criteria of 'The Paediatric Rheumatology International Trials Organisation' (PRINTO) (1). Only the data of the patients who were diagnosed with MAS secondary to SJIA were obtained from their files and evaluated. Patients with MAS secondary to other infectious or malign diseases and patients with primary hemophagocytosis were not included in the study.

Statistical analysis

Statistical Package for the Social Sciences 14.0 program (SPSS Inc.; Chicago, IL, USA) was used for analysis of the ratios and mean values in this study.

Results

Ten patients were diagnosed with MAS in our clinic in the last one year (Table 1). Six (60%) of these patients were female and four (40%) were male. The primary disease in all patients was SJIA. The mean age at the time of onset of the primary disease was found to be 6.05 ± 4.5 years (range: 1.5-15 years). The mean age of occurrence of MAS was found to be 7.6 ± 4.5 years (range: 1.5-17.5 years). When the clinical findings were examined, persistent high fever was found in eight (80%) patients. Generalized lymphadenopathy was found in one patient (10%), hepatomegaly was found in six patients (60%) and splenomegaly was found in five patients (50%). When the laboratory findings were examined, leukopenia was found in two (20%) patients. The mean leukocyte count was found to be $21\ 820 \pm 17\ 395/\text{mm}^3$ (2 100-54 500/ mm^3). Reduced hemoglobin was found in nine (90%) of our patients. The mean hemoglobin level was measured to be 8.6 ± 1.8 g/dL (6.6-11.2 g/dL). Thrombocytopenia was found in six patients (60%) and the mean platelet count was measured to be $221\ 000 \pm 207\ 000/\text{mm}^3$ (35 000-512 000/ mm^3). Reduced erythrocyte sedimentation rate (ESR) was found in seven (70%) patients at the time of diagnosis of MAS. The mean ESR was found to be 71.8 ± 36.2 mm/h (18-120 mm/h) at the time of diagnosis of SJIA and 31.2 ± 25.2 mm/h (range: 1-90 mm/h) at the time of onset of the clinical picture of MAS. Elevated transaminase levels were found in eight (80%) of our patients and elevated aspartate aminotransferase (AST) level was more frequent. The median AST level was found to be 100 IU/L (9-1 690 IU/L) and the median alanine aminotransferase (ALT) level was found to be 66 IU/L (13-840 IU/L). Lactate dehydrogenase (LDH) was increased in nine (90%) patients and the median LDH level was found to be 1 160 IU/L (402-11 710 IU/L). Hypertriglyceridemia was found in nine (90%) patients and the mean triglyceride level was found to be 397 ± 332 mg/dL (78-1 260 mg/dL). Hyponatremia was found in two patients (20%) and the mean sodium value was found to be

Table 1. Demographic, clinical and laboratory features of the subjects with macrophage activation syndrome

Demographic properties		
Gender, n, (%)	Female	6 (60%)
	Male	4 (40%)
Age of onset of SJIA (years)		6.05±4.5 (1.5-15)
Mean age at the time of the diagnosis of MAS (years)		7.6±4.5 (1.5-17.5)
Clinical findings, n, (%)		
Persistent high fever		8 (80%)
Splenomegaly		5 (50%)
Hepatomegaly		6 (60%)
Lymphadenomegaly		1 (10%)
Laboratory findings		
Anemia		9 (90%), Hb mean 8.6±1.8 g/dL
Leukopenia		2 (20%), mean 21 820±17 395/mm ³
Thrombocytopenia		(60%), mean 221 000±207 000/mm ³
Mean ESR at the time of the diagnosis of SJIA		71.8±36.2 mm/h, (18-120 mm/h)
Mean ESR at the time of the diagnosis of MAS		31.2±25.2 mm/h, (1-90 mm/h)
Elevated transaminases,	AST	Mean 100 IU/L, (9-1 690 IU/L)
	ALT	Mean 66 IU/L, (13-840 IU/L)
Hypertriglyceridemia		9 (90 %), Mean 397±332 mg/dL (78-1 260 mg/dL)
Hypofibrinogenemia		4 (40%), Mean 321.4±252 mg/dL (70-800 mg/dL)
Increased ferritin		10 (100%), Mean 23 957±15 525 ng/mL (3 000-46 130)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; MAS: macrophage activation syndrome; SJIA: systemic juvenile idiopathic arthritis

135±4.2 mmol/L (128-140 mmol/L). Hypoalbuminemia was found in five patients (50%) and the mean albumin value was found to be 2.8±0.7 g/L. Reduced fibrinogen was found in four patients (40%) and the mean fibrinogen value was found to be 321.4±252 mg/dL (70-800 mg/dL). Increased D-dimer was found in all our patients. Although abnormal coagulation tests were found in seven (70%) patients, it was clinically manifested only in one patient as bleeding in the oral mucosa. Increased ferritin level was found in all patients. The mean ferritin value was found to be 23 957±15 525 ng/mL (3 000-46 130 ng/mL). Bone marrow aspiration was performed in five of our patients and hemophagocytosis was found in two (40%) of these patients. Central nervous system involvement was not found in any of our patients. Cardiovascular and respiratory tract involvement was found only in one patient as pericarditis and respiratory distress related with pericarditis. Moderate renal failure was found only in one patient and signs of dehydration were present in only one patient. The clinical and laboratory findings of renal failure improved after fluid treatment. None of our patients had complaints of active arthritis. Therefore, no case of arthritis with a tendency to improvement was found. Systemic steroid treatment was administered to all our patients. Cyclosporin A was given to eight patients (80%), kanakinumab was

given to four patients (40%) and anakinra treatment was given to five patients (50%). Plasmapheresis was applied in two patients. Clinical improvement was observed in all patients except for one patients after these therapies and acute phase reactants and ferritin levels returned to normal levels. Only one patient showed recurrent MAS attacks and MAS became chronic in this patient. Hemophagocytic lymphohistiocytosis was considered in this patient, but the genetic analyses were found to be normal. All patients survived.

Discussion

Macrophage activation syndrome is a serious and urgent disease which may be fatal. It occurs because of rheumatic diseases characterized with uncontrolled inflammation. Macrophage activation syndrome cases secondary to systemic lupus erythematosus and Kawasaki disease have been reported, though MAS frequently occurs secondary to SJIA (12-14).

Macrophage activation syndrome occurred secondary to SJIA in all patients in our study. In the last one year, no case of MAS secondary to another rheumatic disease was found.

Macrophage activation syndrome may be triggered as a complication of an underlying disease without any triggering factor or in relation with any infection, drug change, drug side effect or initiation of biological drugs (15). No triggering factor was found in any of our patients in our study. The underlying cause in all of the patients was evaluated to be uncontrolled rheumatic disease.

When the multi-center study conducted by Minoia et al. (2) and our study were compared in terms of gender distribution, the female/male ratio was found to be (57.5%/42.5%) and (60%/40%), respectively. These ratios were found to be compatible. When the clinical data were evaluated in the same study, prolonged fever was found in 341 (96%) patients, hepatomegaly was found in 245 (70%) patients, splenomegaly was found in 201 (57.9%) patients and lymphadenopathy was found in 178 (51.4%) patients. In our patient, prolonged high fever was found in eight (80%) patients, splenomegaly was found in five (50%) patients, hepatomegaly was found in six (60%) patients and lymphadenopathy was found in one (10%) patient.

The significant laboratory findings in MAS include pancytopenia, increased transaminases, hypertriglyceridemia, hyperferritinemia, increased LDH, hypoalbuminemia, increased D-dimer, reduced ESR and reduced sodium level (2). In our study, anemia was found in nine patients (90%), thrombocytopenia was found in six patients (60%) and leukopenia was found in two patients (20%). Elevated transaminase levels (mostly increased AST) were found in eight patients (80%), hyperferritinemia was found in all patients, hypertriglyceridemia was found in nine patients (90%), increased LDH was found in nine patients (90%) and increased D-dimer was found in all patients. Sudden reduction in ESR which is higher in primary disease at the time of the diagnosis of MAS was found in seven (70%) of our patients. A significant increase in ferritin levels has been reported in patients with MAS. In the study of Minoia et al. (2), the ferritin level was found to reach up to 21 975 ng/mL at most. In our study, a very high ferritin level (46 130 ng/mL) was found. This very significant increase in the ferritin value is important in terms of development of MAS in our clinical follow-up.

Hemophagocytosis on bone marrow aspirate is a characteristic finding for MAS (16). Bone marrow aspiration could be performed in five of our patients and hemophagocytosis cell was observed in two (40%) of them. In treatment, corticosteroids, cyclosporin and IVIG are used primarily. Anti-IL-1 drugs are used in some resistant cases (17). In our study, extensive high dose corticosteroid treatment was given to all patients for the initial control of the disease and oral corticosteroid as maintenance treatment was given subsequently. Cyclosporin A was given in addition to corticosteroids in eight (80%) patients. Plasma-

pheresis was applied in two patients who showed a severe course. Biological drugs were preferred as maintenance treatment. With this purpose, kanakinumab was given to four patients and anakinra was given to five patients. All of our cases could be controlled with these treatment options except for one case.

In conclusion, the diagnosis of MAS should be considered in presence of disrupted general well-being which occurs suddenly, persistent high fever and systemic inflammation findings in children with active rheumatic disease. Sudden reduction in erythrocyte sedimentation rate, extremely increased ferritin value and cytopenia are the laboratory data which would support the diagnosis of MAS strongly. The clinical findings and laboratory variables should be meticulously monitored in all patients with active rheumatism including especially systemic JIA.

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