

# Systemic onset juvenile idiopathic arthritis with macrophage activation syndrome and coronary artery dilatation misdiagnosed as Kawasaki disease

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**SUMMARY:** Keskindemirci G, Aktay-Ayaz N, Melikoğlu N, Bornaun H, Aydoğmuş Ç, Aldemir E, Aydoğan G. Systemic onset juvenile idiopathic arthritis with macrophage activation syndrome and coronary artery dilatation misdiagnosed as Kawasaki disease. Turk J Pediatr 2015; 57: 518-521.

Systemic onset juvenile idiopathic arthritis (SoJIA) is characterized by arthritis, fever and visceral organ involvement including hepatosplenomegaly, lymphadenopathy and serositis. This is a case of SoJIA misdiagnosed as Kawasaki disease (KD) and developed macrophage activation syndrome (MAS) secondary to Epstein-Barr virus (EBV) infection. It is presented to point out the conditions that may come along. First of all, SoJIA should be kept in mind while making the differential diagnosis of coronary arterial ectasias and dilatations usually seen in vasculitic diseases like KD. Second, as a very fatal complication MAS should always be considered while following a patient with the diagnosis of SoJIA. Infections like EBV may be the potential triggers for development of MAS especially in immunosuppressed patients.

*Key words:* EBV infection, MAS, SoJIA.

Systemic onset juvenile idiopathic arthritis (SoJIA) is characterized by arthritis, fever and visceral organ involvement including hepatosplenomegaly, lymphadenopathy and serositis. The characteristic occurrence of fever is daily or twice a day lasting at least two weeks. The fever peaks especially at the evening and with a typical rash; salmon like erythema. Macrophage activation syndrome is a rare and fatal complication of SoJIA<sup>1</sup>. Although typical for Kawasaki disease (KD), coronary artery involvement had been reported in SoJIA<sup>2,3</sup>. The incomplete and atypical presentations of KD put it into the first order in the differential diagnosis of SoJIA. Here, we report a patient with SoJIA who was misdiagnosed as KD due to the coronary artery dilatation accompanying prolonged fever and then developed macrophage activation syndrome secondary to Epstein-Barr virus infection.

## Case Report

A 2-year-old boy attended the pediatric rheumatology out-patient clinic with fever, joint swelling and a faint rash. From his previous history, it was learned that he had been treated as incomplete KD by 2 g/kg/day of IVIG and 80 mg/kg/day of aspirin at a general pediatrics clinic. He had been febrile for 24 days and fever was peaking two to three times a day. There, he had a faint rash, arthralgia and lymphadenopathy during follow-up period. But he had no conjunctivitis or extremity changes. It was learned that his lips were becoming red as his temperature increases. At that time, he had elevated inflammatory markers. Microbiological work-up had been performed and no etiology to clarify the fever had been found. At his echocardiography, left coronary artery dilatation had been detected and he had been accepted as incomplete KD by his former pediatrician. But due to unresponsiveness of his

complaints and persistence of high acute-phase response with this treatment protocol, he had been sent to our pediatric rheumatology unit for further diagnostic evaluation. When he was first seen at our out-patient clinic, arthritis of both wrists and knees were noticed. He was internalized to pediatric rheumatology clinic and his temperature charts were closely followed. He had two peaks of fever a day with salmon colored rash over his chest. On his physical examination, cervical lymphadenopathy and hepatosplenomegaly were remarkable. Peeling of fingers, conjunctivitis and crackles of lips were not detected. His hemoglobin was 9.1 g/dl, leukocyte count was 32000/ $\mu$ l, platelet count was 582000/ $\mu$ l, erythrocyte sedimentation rate (ESR) was 84 mm/hr, C-reactive protein was 57 mg/L. Echocardiography was performed. He had dilatation of left main coronary and left anterior descending arteries (Table I). At abdominal ultrasound presence of hepatosplenomegaly was confirmed. Bone marrow aspiration was done and exclusion of infiltrating malignant diseases were made. He was diagnosed as SoJIA with dilated coronary arteries. Oral methotrexate of 15 mg/m<sup>2</sup>/week and pulse steroid of three doses of 30 mg/kg/day with an anti-aggregating dose of aspirin were commenced. His fever subsided and laboratory values began to decline. Pain had subsided and range of motion in the affected joints had been gained back. After one week of afebrile period, fever and generalized lymphadenopathy recurred. His ESR was 31 mm/hr, CRP level was 24 mg/L, leukocyte count was 18000/mm<sup>3</sup>, thrombocyte count was 80000/mm<sup>3</sup>, ferritin level was 6800 ng/ml, triglyceride level was 174 mg/dl, fibrinogen was 96 mg/dl, D-dimer was 3100 ng/ml. Although the diagnosis of macrophage activation syndrome was made, a biopsy of cervical lymph node was performed due to the suspicion of lymphoma. Pathological evaluation pointed out to changes related to EBV infection. Serological tests for EBV were re-tested. EBV-VCA IgM ve EBV-early antigen IgM were positive, which were negative at the beginning of the hospitalization period. Bone marrow aspiration was repeated and hemophagocytosis was detected (Fig. 1). The diagnosis was SoJIA with macrophage activation syndrome secondary to EBV infection. Pulse methylprednisolon from 30 mg/kg/day for 3 days and cyclosporin 5 mg/kg/day were

commenced. But during follow-up, with the tapering of the steroid dose, arthritis and fever recurred. Anti-IL1 therapy (anakinra 2 mg/kg/day) was started alongside with cyclosporin, methotrexate and prednisolon (1 mg/kg/day) treatment. He was well without fever and rash, also his arthritis went in to remission. Even though, still with high z-scores, coronary dilatation began to regress at his follow-up echocardiographic evaluations. Now, he is under only anakinra treatment without any clinical signs nor symptoms of activation for 6 months.

## Discussion

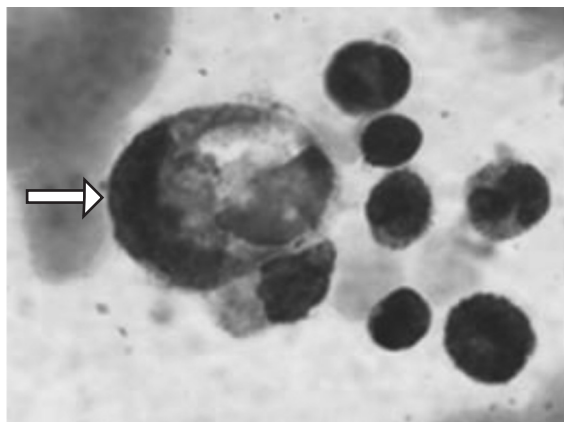
Kawasaki disease is a systemic vasculitis of early childhood, that may cause inflammation of the walls of medium-sized arteries especially, the coronary arteries. Fever of 5 days duration accompanied with 4 of the 5 clinical features like conjunctivitis, lymphadenopathy, polymorphic rash, oral mucosal changes and extremity changes are needed for the diagnosis<sup>4</sup>. Sometimes not all the criteria are coming in view, these patients are usually less than 1 year or older than 5 years. They are usually accepted as incomplete KD patients<sup>5</sup>. Our patients was a 2-year-old boy. Although he had fever and a faint maculopapular rash, his lymphadenopathy was not confined to only cervical region. He had echocardiographic changes at the beginning of the disease. Even though, he was not fulfilling the criteria of KD, he was diagnosed as incomplete KD. As he was unresponsive to IVIG and salycylate treatment, his former pediatrician fell into doubt. After his consultation with our pediatric rheumatology team, his fever was monitored very closely. It was seen that, unlike KD, he had only one or two peaks of fever unresponsive to antipyretics. The course and duration of fever, organomegaly, salmon-colored rash, arthritis and high inflammatory markers brought the diagnosis of SoJIA to our attention.

The clinical features of patients with SoJIA, may mimic the signs and symptoms of KD<sup>3</sup>. Both should be considered in the differential diagnosis of prolonged fever, rash and lymphadenopathy. Infections at a genetically susceptible individual were hypothesized as triggering factors for these diseases. Also an exaggerated immune response was accused for the clinical features of KD and SoJIA<sup>6</sup>.

**Table I.** Echocardiographic Evaluation of the Patient's Coronary Arteries

Left main coronary artery	Left anterior descending artery	Right coronary artery
3,4 mm	2.9 mm	2.6 mm
z score:3.23	z score:4.83	z score:2.3

When the literature was reviewed, it was seen that, Binstadt, et al.<sup>2</sup> had reported 5 out of 12 SoJIA patients with coronary artery dilatation. Neither KD, nor SoJIA has a specific diagnostic test. The diagnosis is concluded by clinical features<sup>7,8</sup>. So, from the concomitant clinical features of our patient, the coronary arterial involvement was attributed to SoJIA. SoJIA is the most severe subtype of JIA with characteristic fever, rash and visceral organ involvement. One of the most important complication of SoJIA is MAS. MAS is an excessive activation of the immune system with cytokine storm leading to fever, hepatosplenomegaly, lymphadenopathy, cytopenias, hyperferritinemia and disseminated intravascular coagulation<sup>1,9,10</sup>. It may accompany a series of rheumatic diseases. An infectious agent may be a trigger for MAS. Herpes family viruses, including EBV and cytomegalovirus, are frequent causes of infection-associated hemophagocytosis<sup>11</sup>. At the beginning of hospitalization in rheumatology unit, our case was responsive to systemic high dose steroids and methotrexate treatment, but during follow-up, possibly by the triggering effect of EBV, secondary hemophagocytosis ensued. By close follow-up of his clinical features and monitoring the laboratory data, the diagnosis of macrophage activation syndrome was made



**Fig. 1.** Histopathological evaluation of bone marrow aspiration showing hemophagocytosis of erythrocytes and leukocytes (marked with arrow).

at the very beginning of the scene. It is crucial to recognize MAS early because it can be fatal when the diagnosis is delayed. As the initial therapy for MAS is high dose pulse-steroid and cyclosporin<sup>12-14</sup> the clinical features of our patient were held down with this treatment modality. But as the dose of steroids was tapered, systemic JIA symptoms re-appeared. In order to avoid the unwanted effects of steroids and assure clinical remission, anti-IL1 therapy was started. Anti-IL1 treatment is accepted as a potential remission inducing treatment for both SoJIA and MAS. Moreover, early antagonism of IL-1 is accepted as an alternative first-line therapy by both consensus treatment plans of Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the new recommendations of ACR<sup>9,14</sup>. The fever, rash, arthritis and organomegaly subsided in our patient following anakinra treatment.

This is a case of systemic juvenile idiopathic arthritis misdiagnosed as KD and developed MAS secondary to EBV infection. It is presented to point out to few extraordinary conditions that may come along. First of all, SoJIA should be kept in mind while making the differential diagnosis of coronary arterial ectasias and dilatations usually seen in vasculitic diseases like KD. Second, as a very fatal complication MAS should be always considered while following a patient with the diagnosis of SoJIA. Third, an infectious cause may trigger MAS in an immune-dysregulated patient due to either a disease itself, like SoJIA, or due to the immunosuppressive treatment. Fourth, when the initial therapy is not enough to hold down the inflammation, a key cytokine, anti-IL1 blockage may help to keep the clinical signs and symptoms under control.

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