CAS CLINIQUE/CASE REPORT
MACROPHAGE ACTIVATION SYNDROME IN A PATIENT WITH SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS INITIALLY TREATED FOR ATYPICAL KAWASAKI DISEASE
A Case-Based Review

Essa HARIRI1, Rawan DEMACHKIEH2, Ahmad NAJA1, Ahmad HACHEM3, Gerard WAKIM2


ABSTRACT • Systemic-onset juvenile idiopathic arthritis (SoJIA) is the most common rheumatic disorder in children and its presentation can mimic atypical Kawasaki disease. The diagnosis of SoJIA is often challenging and children are often diagnosed and treated for Kawasaki disease initially, especially after an unremitting fever lasting for several days. This fact can delay the treatment of SoJIA as incorrect treatment with intravenous immunoglobulins (IVIG) is being given and this may probably lead to a worse outcome in those individuals. This is a case of a 12-month-old infant who was initially treated for atypical Kawasaki instead of a SoJIA presenting with a macrophage activating syndrome (MAS). We also present a review of the literature that supports the diagnosis of SoJIA presenting with MAS.

Keywords: systemic onset-juvenile idiopathic arthritis; atypical Kawasaki; macrophage activating syndrome; coronary artery dilatation; corticosteroids

INTRODUCTION

Macrophage activating syndrome (MAS) is a potentially life-threatening condition caused by dysregulation in macrophage-lymphocyte interaction, and it manifests as a high-grade fever, disturbed liver function, pancytopenia, and central nervous manifestations. MAS has been associated with several conditions such as drugs, infections, Kawasaki and rheumatic diseases, specifically systemic onset juvenile idiopathic arthritis (SoJIA). Kawasaki disease (KD), previously known as mucocutaneous lymph node syndrome, is the most common vasculitis and major cause of acquired heart disease in infants that presents acutely with an unknown etiology and self-limited course [1]. Another type known as atypical KD is characterized with an unusual presentation not fulfilling the diagnostic criteria of KD and is more common in infants [2]. The main conflict that arises is that the initial presentation of atypical KD is similar to that of SoJIA, and both entities share common laboratory findings from an elevated CRP and ESR, thrombocytosis, anemia, leukocytosis leading to a confusion with respect to diagnosis [3]. Herein, we report a case of a 12-month-old male child with undiagnosed SoJIA presenting with MAS and initially treated for atypical KD refractory to intravenous immunoglobulin (IVIG) treatment, along with a literature review.

CASE REPORT

A previously healthy 12-month-old male child with up-to-date vaccinations presented to our hospital for a three-day history of high-grade fever (up to 40°C), non-productive cough, somnolence, vomiting, oliguria, and decreased appetite. There was no history of a similar episode and family history was significant for Crohn’s disease as well as juvenile and rheumatoid arthritis on the maternal side. However, the child had developed an urticarial rash five months ago localized to the extremities which lasted for
one week without any treatment. Upon arrival his vital signs were: heart rate: 152 beats/min, respiratory rate: 30 breaths/min and a temperature of 38.7°C. Physical examination showed erythematous and bulging tympanic membranes with a slightly distended abdomen and mild tenderness. Furthermore, no skin rashes, lymphadenopathy or redness and inflammation of joints were reported. Initial laboratory workup revealed anemia, thrombocytopenia, and hyponatremia with evidence of systemic inflammation and infection (Table I).

The child was managed for pyrexia of unknown origin, and differential diagnoses of meningitis, pneumonia, EBV and CMV were considered. Blood and urine cultures were negative for any organism. A lumbar puncture was contraindicated due to the low platelet count, and the infant was admitted and treated with IV ceftriaxone (100 mg/kg/day) for the presumptive diagnosis of meningitis. An abdominal ultrasound was performed and revealed hepatosplenomegaly with multiple mesenteric lymph nodes.

On the 8th day of admission, bilateral conjunctivitis was observed and diagnosed as anterior uveitis. The infant also continued to experience daily intermittent fever during the first 8 days (Fig. 1), remained lethargic with a decreased appetite, and spent most of the day sleeping. He had episodes of non-bloody and non-mucoid diarrhea that were self-limited, and stool analysis were germ and blood free.

Serology tests were negative for: CMV, EBV, adeno-virus, parvovirus, ANA, RF, Anti-CCP, Anti-Scl, Anti-Sm, Anti-SS A/B, Anti-RNP, Anti-DNA and Anti-Jo. As a result, a differential diagnosis of atypical KD and SoJIA was made.

On the 10th day of admission, an echocardiogram revealed a left and right coronary artery dilatation (3-4 mm) and mild dilatation of the left ventricle (Fig. 2). Therefore, a diagnosis of atypical KD was hypothesized based on a prolonged fever for more than 5 days associated with one clinical diagnostic criteria (bilateral conjunctivitis), coronary artery dilatation, increased CRP and ESR with a complementary laboratory criteria – anemia. After checking for the absence of thrombocytopenia, the patient was treated with a first dose of IVIG (2 gram/kg) along with a high dose of aspirin (100 mg/kg/day), and fever returned to normal shortly before peaking again. Afterwards, another infusion of IVIG (2 gram/kg) was given due to the recurrence of fever, but the child did not show improvement and continued to have high grade fever spikes. Echocardiogram and abdominal ultrasounds were repeated and the results remained unchanged. The persistence of fever with two doses of IVIG and lack of further clinical criteria to support the diagnosis of atypical Kawasaki raised the suspicion of SoJIA, and aspirin dose was shifted to an antiplatelet dose (3-5 mg/kg/day).

On the 15th day of hospitalization, and after receiving IVIG with no alleviation of pyrexia, a bone marrow aspirate was obtained and revealed rare hemophagocytic bodies with no evidence of underlying malignancies. However, since the patient fulfilled both HLH-2004 criteria [4] as well as Ravelli et al. criteria [5], he was diagnosed to

### Table I

**Laboratory investigations during hospital stay and follow-up**

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<th>Day 3</th>
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<td>10.17</td>
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<td>Urine WBC</td>
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*IVIG infusion, **Steroids treatment, †discharge, Hb: hemoglobin, WBC: white blood cells, N: neutrophils, PLT: platelets, CRP: C-reactive protein, ESR: erythrocyt e sedimentation rate, ALT: alanine transaminase, AST: aspartate transaminase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, TG: triglyceride
have MAS and subsequently, 1 mg/kg/day of prednisone was initiated once daily, and a significant clinical improvement was observed with no remitting fever. The anterior uveitis persisted and treatment with prednisolone acetate ophthalmic suspension drops was initiated with the prednisone dose increased to 2 mg/kg/day.

The child was discharged after one week, and follow-up with the ophthalmologist two weeks later has shown resolution of the anterior uveitis. Hence, prednisone dose was tapered off over the following three-week period. Echocardiography then revealed an improvement in the coronary artery dilation, and the child is currently on follow-up for the last four months with no recurrence of fever.

DISCUSSION

The diagnosis and management of a fever of unknown origin is one of the most difficult yet common cases facing pediatricians. KD and juvenile idiopathic arthritis (JIA) are two major causes of prolonged and refractory fever in children not sought early by physicians and considered as diagnoses of exclusion. JIA is the most common chronic rheumatologic disease affecting children and considered a major cause of pain, depressed growth and mobility restriction in this age group [6]. It usually starts as general systemic symptoms that include sore throat, fever, lymphadenopathy, hepatosplenomegaly and recurrent salmon-colored rash [7]. These symptoms may precede the involvement of the joints and the development of arthritis that may not appear until months or even years after the pyrexia begins, hence delaying the diagnosis [7]. Common laboratory abnormalities include anemia, leukocytosis elevated ESR, and children are usually ANA and RF negative.

MAS, known as reactive haemophagocytic lymphohistiocytosis, occurs in 6-7% of children with SoJIA, with a reported mortality rate of 20-30% [8], and about one-third of patients with active SoJIA may have mild, subclinical MAS [9]. It was first described by Hachouel et al. in 1985 [10], and is believed to be triggered by bacterial or viral infections (Hepatitis A, varicella zoster virus, EBV virus, etc.), or by the use of non-steroidal anti-
inflammatory drugs (NSAIDs), methotrexate, gold salts or sulfasalazine [11]. The onset of MAS is usually in the early stages of SoJIA and can commonly be the initial presentation of this disease [12]. Until now, there are no definite or validated diagnostic criteria for MAS, and establishing early diagnosis is often difficult [5]. Typically, patients who develop MAS present with persistent unremitting fever, rash, jaundice, lymphadenopathy, hepatosplenomegaly, mental status changes, and laboratory analyses show coagulopathy with fall in at least two of three blood cell lines, elevated prothrombin time (pTT) and partial thromboplastin time (pPT), reduced fibrinogen and raised D-dimer levels, low erythrocyte sedimentation rate (ESR) and elevated serum liver enzyme values which can terminate in acute liver failure, coma and multiple organ failure.

In this case, we present a patient with SoJIA presenting initially with MAS and treated for a considerable period of time as incomplete KD due to the presence of coronary artery dilatation. In fact, clinical features in patients with SoJIA, particularly in the initial stages, closely resemble KD. Both illnesses will present with fever, rash, thrombocytopenia, and increased inflammatory markers. Therefore, it is not surprising that most SoJIA patients with coronary artery dilatation were all initially classified as KD or incomplete KD and treated with multiple doses of IVIG. Differentiation from KD is important for three reasons: to hasten institution of appropriate treatment, to determine long-term prognosis, and most importantly to avoid multiple courses of IVIG due to suspected refractory KD. This would dramatically increase expenditure given the exorbitant costs of IVIG in addition to exposing the patient to potential harms of blood products. Such is demonstrated in our patient as well as other reports in literature [12, 13], where multiple courses of IVIG would be potentially delaying therapy in this subset of SoJIA patients that need to be treated more aggressively. However, Shin et al. had suggested that the implications of misdiagnosing SoJIA patients as KD were minimal since IVIG treatment would be beneficial in SoJIA patients as well [14]. In our patient, because the prolonged fever was unexplained, incomplete KD was considered, especially with the presence of certain laboratory parameters (anemia, hypoalbuminemia, elevated liver enzymes) and abnormal echocardiography. It is well recognized that some patients do not fulfill the classic diagnostic criteria of KD termed ‘incomplete’ or ‘atypical’ KD, and the diagnosis is often based on echocardiographic findings of coronary artery abnormalities and laboratory findings according to the American Heart Association guidelines [15]. It should be considered in all children with prolonged fever for ≥ 5 days associated with 2 or 3 of the principal clinical features of KD [16, 17].

The pattern of fever described as intermittent is more typical to SoJIA than KD that usually has a remittent type of fever, while thrombocytopenia along with hepatosplenomegaly may exclude the diagnosis of KD. Besides, uveitis is not an uncommon feature of JIA and is found in 12% of all types [18], thus the presence of uveitis does not favor the diagnosis of KD in our patient. Additionally, KD itself remains an acute, self-limiting illness, and evidence of systemic inflammation is more persistent in SoJIA than usually observed in KD.

Hence, this patient has JIA undiagnosed previously with a family history of arthritis and Crohn’s disease, and the ongoing fever that responded to steroids with absence of response to a combination of IVIG and aspirin. The patient’s initial presentation of SoJIA appeared as a complication of MAS in a milder form because he had thrombocytopenia, anemia, deranged liver function tests, increased lactate dehydrogenase (LDH), pTT and D-dimers, hypertriglyceridemia, hyponatremia with hepatosplenomegaly and dilated cardiac ventricles. Besides, prompt recognition of MAS as a severe complication associated with SoJIA is mandatory, treatment with high doses of corticosteroids as first line therapy has been shown to be effective, followed by cyclosporine A if no response to steroids is evident within 24-48 hours [8, 19]. Fortunately, our patient recovered from it early with a low dose of corticosteroids despite the unfavorable prognosis of MAS.

Besides, the diagnosis of MAS is usually confirmed by the demonstration of hemophagocytosis in the bone marrow. However, the sensitivity of hemophagocytosis was 83% in one study, with a specificity of only 60% [21]. Hence, in several instances of MAS [6], the bone marrow aspirate does not show hemophagocytosis, which is not demonstrable in the initial stages of the disease, and repeating bone marrow aspirate over time may eventually demonstrate hemophagocytosis. Furthermore, although a decline in fibrinogen is expected in MAS, high fibrinogen does not exclude this diagnosis, where a case study on nine patients with MAS found one patient with elevated fibrinogen [10]. On the other hand, the child’s age made the examination difficult to determine whether there was joint pain and to confirm the presence of arthritis. In addition, the development of arthritis before 2 years of age is usually uncommon. Therefore, MAS in our case is the initial presentation of an underlying, undiagnosed JIA. Since JIA can be a chronic, intermittent or transient disease, a close follow-up of the child is warranted to ensure proper management and avoid progression of this disease.

**CONCLUSION**

Similar to our case, there are several reports in literature where an initial incorrect diagnosis of incomplete Kawasaki is established in a patient with a prolonged fever of unknown origin, followed by the diagnosis of SoJIA, with or without a complication of MAS [12, 20-23]. Hence, even if guidelines may aid physicians towards the diagnosis of incomplete KD, it remains difficult to establish the diagnosis of KD and differentiate it from SoJIA due to overlapping features and absence of specific laboratory markers. All in all, given the prognosis of MAS and its prevalence in SoJIA, a high index of suspicion is needed in a patient with prolonged unremitting fever, coagulopathies, pancytopenia and hepatosplenomegaly to initiate proper treatment and avoid fatal outcomes.
REFERENCES


