



# Prolonged Fever and Intravenous Immunoglobulin Resistance in Kawasaki Disease: Should Macrophage Activation Syndrome Be Considered?

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## Abstract

**Introduction:** Macrophage activation syndrome (MAS) is a rare and potentially fatal complication of Kawasaki disease (KD). Typically, MAS presents as the exacerbation of KD, manifested by prolonged fever and resistance to treatment. Early and accurate diagnosis might be challenging due to overlapping features of MAS and intravenous immunoglobulin (IVIG)-resistant KD and lack of validated diagnostic criteria.

**Case Presentation:** In this article, we report four cases of KD with prolonged fever that were eventually diagnosed and treated as MAS. Three cases were boys and one infant was a girl. The mean age of the cases was 29 months. Three cases had typical and one case had atypical KD. Two cases had abnormal findings in echocardiography and three cases had hepatomegaly. In laboratory evaluation, all of them had thrombocytopenia, increased liver enzymes, and hyperferritinemia. All the patients were treated with intravenous high-dose methylprednisolone (pulse therapy) after IVIG therapy, two cases with oral cyclosporine, and one case with infliximab. There was no mortality in our cases, and in long-term follow-up, all the patients had normal clinical, laboratory, and echocardiography findings.

**Conclusions:** KD resistant to IVIG and sustained fever have high diagnostic values in MAS with underlying KD.

**Keywords:** Kawasaki Disease, Macrophage Activation Syndrome, Prolonged Fever, Pancytopenia, Serum Ferritin

## 1. Introduction

Macrophage activation syndrome (MAS) is a rare and potentially fatal complication of infections, malignancies, and autoimmune disorders (1). It presents with high and persistent fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, impaired liver function, coagulopathy, and central nervous system dysfunction following inappropriate activation of macrophages and T lymphocytes and resulting in increased cytokine production (2). The near resemblance between MAS and a group of disorders called hemophagocytic lymphohistiocytosis (HLH) has led to MAS being used to describe secondary HLH; in some studies, MAS and HLH have been considered as a single abnormality (1, 2).

In the pediatric population, MAS is mostly reported in patients with systemic-onset juvenile idiopathic arthritis

and systemic lupus erythematosus and less commonly, in association with Kawasaki disease (KD) (3-5).

KD, also called mucocutaneous lymph node syndrome, is an acute, self-limiting, small-vessel vasculitis with an unknown etiology that affects children less than five years of age and is characterized by prolonged fever of unknown origin for five days, bilateral conjunctival injection, oropharyngeal mucous membranes changes, erythema and edema or periungual desquamation, polymorphous rash, and cervical lymphadenopathy (6).

Typically, MAS presents as the exacerbation of KD, manifested by prolonged fever, rash, and resistance to intravenous immunoglobulin (IVIG) (7). However, other reasons should be considered for prolonged or relapsing fever after IVIG therapy in KD, such as fever as a complication of IVIG therapy and other diagnoses (subacute infections or systemic juvenile idiopathic arthritis). Early and correct di-

agnosis of MAS is challenging due to overlapping features of MAS and IVIG-resistant KD, as well as lack of validated diagnostic criteria (8, 9). In this article, we report four cases of KD with prolonged fever that were eventually diagnosed and treated as MAS.

## 2. Case Presentation

During three years, 218 cases of KD were admitted to Children's Medical Center, Pediatrics Center of Excellence as a tertiary referral center in Tehran, Iran. Four cases (1.8%) complicated by confirmed MAS. The main clinical and laboratory data of these cases have been compared in Table 1. We presented all MAS cases in detail.

### 2.1. Case 1

A 22-month-old boy was admitted with a 20-day history of fever and skin lesions since the 14th day of fever. On physical examination, we found a disseminated maculopapular skin rash. Laboratory tests showed leukocytosis and increased erythrocyte sedimentation rate (ESR) and C-reactive-protein (CRP). Liver function tests were normal. Antistreptolysin O titer, antinuclear antibodies, and rheumatoid factor were negative. Abdominal ultrasound revealed mild hepatomegaly. Right and left coronary artery (RCA and LCA) ectasia was observed on echocardiography. The patient was diagnosed with KD and was treated with a single infusion of 2 g/kg IVIG and high-dose acetylsalicylic acid (ASA). He was discharged after resolution of fever with instructions to use ASA.

One week after discharge, the child was readmitted with recurrence of fever and skin rash. On physical examination, he had disseminated rash, desquamation, strawberry tongue, left submandibular lymphadenopathy, and splenomegaly. Laboratory investigation showed pancytopenia, hyperferritinemia, and elevated transaminases. RCA and LCA dilatation was evident in echocardiography. The patient was treated with a second infusion of IVIG for refractory KD. However, the fever did not resolve, MAS was suspected, and bone marrow aspiration was performed to rule out malignancy, showing evidence of hemophagocytosis. The patient was treated with pulse methylprednisolone, cyclophosphamide, and oral cyclosporine (5 mg/kg). Fever and other manifestations resolved and the laboratory indices returned to normal. The patient was discharged with instructions to use prednisolone and cyclosporine and remained well during the follow-up period.

### 2.2. Case 2

A 5.5-year-old boy was hospitalized with complaints of a 2-day fever, lethargy, delirium, loss of appetite, vom-

iting, abdominal pain, and tachypnea. On physical examination, the patient was icteric and had erythematous lips, disseminated erythematous maculopapular lesions, and bilateral non-purulent conjunctivitis. Laboratory tests demonstrated increased ESR and CRP, elevated transaminases, and direct hyperbilirubinemia. The patient was stabilized and was treated with clindamycin and cloxacillin as he was suspected of toxic shock syndrome. However, the patient gradually developed loss of consciousness, hypotension, and periorbital edema. He was transferred to the intensive care unit (ICU) and treated with dopamine.

Although the consciousness improved, the patient remained febrile and mucocutaneous symptoms persisted. Gallbladder hydrops was observed on ultrasound and dilation of the coronary arteries was reported in echocardiography. The patient was diagnosed with KD and was treated with 2 g/kg IVIG and ASA. Following treatment, the patient remained febrile and laboratory tests showed leukopenia, thrombocytopenia, low ESR, high CRP, hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia. MAS with underlying KD was diagnosed and the patient was treated for three days with 30 mg/kg/d methylprednisolone and 5 mg/kg infliximab. He was discharged after resolution of fever with oral cyclosporine and prednisone. Laboratory and echocardiographic investigations in follow-up visits showed normal results.

### 2.3. Case 3

The patient was a 7-month-old female with a one-month history of fever, skin rash, vomiting, and non-bloody diarrhea. KD was suspected, and the patient received 2 g/kg IVIG two weeks after onset of fever. On physical examination, the patient was febrile and had edema in the lower extremities, bilateral cervical lymphadenopathy, hepatomegaly, disseminated erythematous rash, desquamation, strawberry tongue, chapped lips, and bilateral non-purulent conjunctivitis.

Laboratory findings were leukopenia, thrombocytopenia, low ESR, elevated CRP, elevated transaminases, hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia. Therefore, MAS was diagnosed, and the patient was treated with 2 g/kg IVIG and 30 mg/kg/d methylprednisolone for three days. After improvement of the general condition and resolution of fever, the patient was discharged with oral prednisone and ASA. On follow-up, no recurrence of fever was observed and laboratory tests returned to normal. Follow-up echocardiography was also normal.

### 2.4. Case 4

A 5-year-old boy was referred to our hospital with loss of consciousness and fever from 10 days ago. He had been

**Table 1.** Clinical Manifestations, Laboratory Data and Treatment in Four Cases of Kawasaki Disease Complicated with Macrophage Activation Syndrome

	Case 1	Case 2	Case 3	Case 4
Age	22 months	5.5 years	7 months	5 years
Gender	Male	Male	Female	Male
Prolonged fever	+	+	+	+
Rash	+	+	+	+
Conjunctivitis	-	+	+	+
Lips and tongue changes	+	+	+	+
Lymphadenopathy	+	-	+	-
Hepatomegaly	+	+	+	-
Extremity changes	-	+	+	+
Loss of consciousness	-	+	-	+
Desquamation	+	-	+	-
WBC, /L	$4.9 \times 10^9$	$10.6 \times 10^9$	$18.4 \times 10^9$	$4.06 \times 10^9$
HB, g/dL	7.1	7.2	10.4	10.9
PLT, /mm <sup>3</sup>	$142 \times 10^3$	$44 \times 10^3$	$31 \times 10^3$	71000
ESR, mm/h	41	17	6	12
CRP, mg/dL	120	232	38.6	115
ALT, U/L	779	90	58	117
AST, U/L	893	86	368	73
ALKP, U/L	930	368	687	879
Na, mmol/L	130	-	-	133
Ferritin, ng/mL	1506	1868	23248	890
Fibrinogen, mg/dL	323	242	77	166
TG, mg/dL	131	356	438	143
Echocardiography	Aneurysm dilation (LMCA,LCA) + dilation (RCA)	Dilation (LAD, LCX) + pericardial effusion	Normal	Normal
Treatment	IVIG+ methylprednisolone pulse+ cyclophosphamide + cyclosporine	IVIG+ methylprednisolone pulse + cyclosporine + Infliximab	IVIG+ methylprednisolone pulse	IVIG+ methylprednisolone pulse

under treatment of isolated room in another hospital with the diagnosis of meningococemic meningitis because of central nervous system manifestations, rashes, pancytopenia, and ill condition. After five days, his condition was aggravated. Thus, acyclovir had been added to the antibiotic regimen with the possibility of herpes encephalitis.

On admission, meticulous physical examination revealed bilateral non-purulent conjunctivitis, disseminated skin rash, hands and feet edema, and strawberry tongue. Accordingly, previous drugs such as antibiotics and acyclovir were discontinued and the patient underwent treatment with IVIG and high-dose ASA for KD. Nevertheless, the general condition, loss of consciousness, and fever did not resolve, and laboratory investigations showed pancytopenia, low ESR, elevated CRP, increased transaminases, ele-

vated serum lactate dehydrogenase (LDH), hyperferritinemia, hypofibrinogenemia, and hypertriglyceridemia. The results of echocardiography and abdominal ultrasound were normal.

Accordingly, MAS was diagnosed and the patient was treated with three days of methylprednisolone pulse. The general condition and laboratory tests improved on the following days, and the patient was discharged with low-dose ASA and prednisolone. Subsequent follow-up proved satisfactory.

### 3. Discussion

MAS is a relatively rare complication of rheumatologic and inflammatory diseases, and its incidence in children

with KD is estimated at 1.1% - 1.9% (5, 7). In our study, the incidence rate of MAS was 1.8%. If not managed on time, MAS can result in multiorgan failure and mortality (1, 2). However, some clinical and laboratory manifestations of KD and MAS overlap, which makes diagnosis challenging (8).

Ravelli et al. described hepatomegaly, hemorrhage, central nervous system dysfunction, hypofibrinogenemia ( $\leq 2.5$  g/L), decreased leukocyte count ( $\leq 4 \times 10^9$ /L), decreased platelet (PLT) count ( $\leq 262 \times 10^9$ /L), increased alanine aminotransferase (AST) ( $> 59$  U/L), and evidence of macrophage hemophagocytosis in bone marrow aspiration as diagnostic indicators of MAS with the underlying systemic juvenile idiopathic arthritis (1). In this report, complete diagnosis of MAS in all the four cases was based on these criteria.

In the present report, all the four patients were resistant to IVIG treatment, manifested by persistent or recrudescence fever after the first IVIG infusion. Moreover, all had hypofibrinogenemia, decreased PLT count, and increased AST. Garcia-Pavon et al. reviewed the characteristics of 69 cases of KD complicated with MAS. Hypofibrinogenemia, decreased PLT count, and increased AST were reported in 85%, 87%, and 94% of patients, respectively (8).

Lack of response to fever treatment in patients with KD is one of the risk factors for subsequent coronary artery abnormalities (10). Furthermore, MAS is also accompanied by prolonged fever (11). In the present report, low-grade coronary artery involvement was observed in two of the four patients. Cardiac involvement was not severe and improved after treatment. Similar results were reported by Wang et al. (7). It seems that despite risk factors for coronary artery involvement, such as prolonged fever and IVIG resistance, MAS might modify the cardiac involvements in KD. Further studies are needed to prove this hypothesis.

In our patients, delay in clinical manifestations of KD was observed after a prolonged fever simultaneous with ill condition due to MAS. Trigger factors such as primary infections might cause sustained fever. Furthermore, some researchers believe that MAS is caused by decreased ability to control some infections (12).

Cellular and molecular evidence supported MAS only in one case, and no bone marrow aspiration was performed in the three other cases. Based on prior studies, despite the rise in the prevalence of hemophagocytosis in MAS cases with underlying KD, this factor cannot be considered as a definite diagnostic clue (1, 7).

Some common treatments of MAS include steroids, cyclosporine A, IVIG, etoposide, and methotrexate. However, steroids are the first line of treatment and almost half of MAS cases are treated by administering steroids alone (7). In our report, although laboratory findings and clinical

symptoms were improved in all the four cases after receiving IVIG and ASA (cyclosporine was also prescribed in two cases), but the definitive treatment was achieved after the administration of methylprednisolone.

Physicians generally consider and follow up complications of coronary artery in patients with KD, while MAS should not be neglected as a complication with high mortality. In this report, by introducing four children with KD resistant to IVIG along with sustained fever, we highlighted the high diagnostic value of these two risk factors in MAS with underlying KD.

In conclusion, although lower ESR (in comparison with other inflammatory diseases) supports MAS as an important diagnostic clue, this reduction may not be observed in KD because of receiving IVIG. Changes in blood cells (particularly thrombocytopenia), increased liver enzymes, hyperferritinemia, sustained fever, hepatosplenomegaly, resistance to IVIG, and the possibility of MAS incidence should be considered in KD cases.

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## Footnotes

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