Are Children With Kawasaki Disease and Prolonged Fever at Risk for Macrophage Activation Syndrome?

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ABSTRACT. Kawasaki disease (KD) patients are known to be at increased risk for coronary artery lesions. We present evidence of another possible complication associated with KD: macrophage activation syndrome (MAS). In this case, a patient with KD and prolonged fever developed MAS. This case is of particular interest because of the late age of onset and recurrent nature of KD as well as the complication of MAS. We also present a review of the literature that supports the inclusion of MAS as an infrequent complication of KD. *Pediatrics* 2003;112:e495–e497. URL: http://www.pediatrics.org/cgi/content/full/112/6/e495; *Kawasaki disease, macrophage activation syndrome, hemophagocytosis, intravenous immunoglobulin.*

ABBREVIATIONS. KD, Kawasaki disease; IVIG, intravenous immunoglobulin; ASA, acetylsalicylic acid; MAS, macrophage activation syndrome; LDH, lactate dehydrogenase.

Kawasaki disease (KD) is an acute multisystemic vasculitis of the small and medium-sized arteries characterized by high fever for >4 days and 4 of the following: polymorphous exanthem; bilateral nonpurulent conjunctival injections; changes to the lips or oral cavity; changes to the extremities; and cervical lymphadenopathy.[1–3] The treatment of KD with intravenous immunoglobulin (IVIG) and high-dose acetylsalicylic acid (ASA) has been shown to decrease the morbidity associated with KD including cardiac aneurysms.[1–3]

Macrophage activation syndrome (MAS) (hemophagocytosis) is caused by excessive activation and proliferation of macrophages that occurs secondary to a diverse group of diseases including infections, neoplasms, hematologic conditions, and rheumatic disorders.[4] MAS is characterized by persistent fever, cytopenia, liver dysfunction, hepatosplenomegaly and frequently hyperferritinemia, elevated serum lactate dehydrogenase (LDH), hypofibrinogenemia, and hypertriglyceridemia.[5,6]

In this report we present a 9-year-old child with KD complicated by MAS. This case is of particular interest because of the complication of MAS, which has only rarely been reported to occur secondary to KD.[7–9] We suggest that KD be included on the list of causes of MAS.

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Received for publication Jun 6, 2003; accepted Aug 12, 2003.
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HISTORY

A previously healthy 9-year-old boy with a normal developmental history and up-to-date immunizations presented to the Hospital for Sick Children with a fever for 13 days, nonpurulent conjunctival injections, a nonspecific diffuse nonvesicular maculopapular rash, oral mucosal changes including a strawberry tongue with no buccal mucosa or pharynx exudates and no Koplik spots, mild swelling and erythema of his hands and feet, slightly tender unilateral cervical lymphadenopathy (~1.5–2 cm) with no other lymphadenopathy, and a II/VI systolic flow murmur. He was diagnosed with KD and treated with IVIG and high-dose ASA and subsequently had a normal echocardiogram. His infectious disease work-up including blood cultures, throat swab for group A β hemolytic streptococci, and virology studies for Epstein-Barr virus, parvovirus, cytomegalovirus, and herpes simplex virus were all negative. His symptoms quickly resolved, and he was afebrile for 48 hours and discharged on low-dose ASA.

Three days later, he presented to the Hospital for Sick Children with fever, nonpurulent conjunctival injections, a nonvesicular maculopapular rash, oral mucosal changes including a strawberry tongue, mild swelling and erythema of his hands and feet (and the dorsum of his hands now showed periungual desquamation), and unilateral cervical lymphadenopathy (>3 cm). He again was treated with IVIG and high-dose ASA but did not respond. The next day he remained febrile with a temperature of 39.7°C, and he developed a macular rash. He was treated with 1000 mg of methylprednisolone for 3 days and improved clinically over those days. After the completion of the methylprednisolone, he was still febrile and was started on a one-time dose of 60 mg of prednisone followed by 20 mg 3 times daily. Although he still felt unwell, he remained afebrile for 24 hours after the first dose of oral steroids.

Forty-eight hours after the oral steroids, the patient was febrile with a worsening purpuric rash (although seen in KD most likely due to thrombocytopenia) and a palpable liver edge 3 cm below the costal margin. He appeared unwell, and a chest radiograph was done that showed normal lungs and heart with no mediastinal masses. An ultrasound revealed mild hepatosplenomegaly with no masses. Laboratory findings included elevated liver enzymes and LDH, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and cytopenia (Table 1).

The patient again was treated with a 1000-mg methylprednisolone pulse for 3 days. A blood smear showed atypical lymphocytes. A bone marrow aspirate showed no evidence of malignancy but indicated hemophagocytosis. The patient recovered and was released 5 days later. On his 2-month follow-up visit he was asymptomatic on a tapering dose of prednisone. He is currently well and off all medications with no cardiac sequelae as shown by echocardiogram.

DISCUSSION

KD is characterized by fever of >4 days. Refractory or recurrent fever occurs in 10% of patients with KD despite treatment with IVIG and is associated with a higher risk for coronary artery lesions.[10–12]

TABLE 1. Changes in Laboratory Values During Course of Illness

Day	At Presentation	Onset MAS	48 Hours Later	At Discharge	2 Months Later
White blood count (4–10 10^9/L)	24.1 × 10^9/L (10^3/μl)	10.2 × 10^9/L (10^3/μl)	19.7 × 10^9/L (10^3/μl)	6.8 × 10^9/L (10^3/μl)	12.9 × 10^9/L (10^3/μl)
Polys (2.00–7.50 10^9/L)	20.5 × 10^9/L (10^3/μl)	2.68 × 10^9/L (10^3/μl)	14.43 × 10^9/L (10^3/μl)	5.04 × 10^9/L (10^3/μl)	11.1× 10^9/L (10^3/μl)
Lymph (1.5–7.0 10^9/L)	0.96 × 10^9/L (10^3/μl)	0.20 × 10^9/L (10^3/μl)	0.93 × 10^9/L (10^3/μl)	1.02 × 10^9/L (10^3/μl)	1.3 × 10^9/L (10^3/μl)
Hemoglobin (120–160 g/L)	113 g/L (11.3 g/dL)	85 g/L (8.5 g/dL)	93 g/L (9.3 g/dL)	101 g/L (10.1 g/dL)	136 g/L (13.6 g/dL)
PLT (150–400 10^9/L)	623 × 10^9/L (10^3/μl)	104 × 10^9/L (10^3/μl)	133 × 10^9/L (10^3/μl)	464 × 10^9/L (10^3/μl)	293 × 10^9/L (10^3/μl)
Erythrocyte sedimentation rate (1–10 mm/hour)	118 mm/hour	70 mm/hour	53 mm/hour	36 mm/hour	1 mm/hour
AST (0–36 units/L)	105 units/L	2083 units/L	1339 units/L	96 units/L	26 units/L
ALT (0–40 units/L)	12 units/L	903 units/L	951 units/L	79 units/L	31 units/L
ALK Phos (180–475 units/L)	121 units/L	339 units/L	247 units/L	111 units/L	51 units/L
Conj. bili (0–2 μmol/L)	0 μmol/L (0 mg/dL)	10 μmol/L (0.58 mg/dL)	1 μmol/L (0.06 mg/dL)	0 μmol/L (0 mg/dL)	N/A
Unconj. bili (0–17 μmol/L)	0 μmol/L (0 mg/dL)	0 μmol/L (0 mg/dL)	0 μmol/L (0 mg/dL)	1 μmol/L (0.06 mg/dL)	N/A
LDH (432–700 units/L)	N/A	29691 units/L	5062 units/L	N/A	N/A
Ferritin (22.0–400 μg/L)	N/A	1156 μg/L	1256 μg/L	N/A	N/A
Fibrinogin (1.60–4.00 g/L)	N/A	0.47 g/L	0.76 g/L	4.41 g/L	N/A
D-Dimer (0–499 ng/L)	N/A	5420 ng/L	1970 ng/L	2160 ng/L	429 ng/L
Triglyceride (0.40–1.30 mmol/L)	N/A	2.52 mmol/L (223 mg/dL)	2.80 mmol/L (248 mg/dL)	N/A	N/A
Albumin (33–58 g/L)	N/A	28 g/L (2.8 g/dL)	23 g/L (2.3 g/dL)	N/A	N/A

Laboratory values with normal SI unit values in brackets are shown. N/A indicates not available; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALK phos, alkaline phosphatase; PLT, platelet; conj. bili, conjugated bilirubin; unconj. bili, unconjugated bilirubin.

The suggested treatment for persistent fever, refractory to ≥2 infusions of IVIG, is intravenous steroid pulse therapy.[11–13] Although KD patients with prolonged fever are at increased risk for coronary artery lesions, there is no evidence to suggest an increased risk to develop other complications. We described a patient with KD who had persistent fever unresponsive to IVIG who developed MAS.

Our patient had clinical evidence of KD based on a persistent high fever, nonpurulent conjunctival injections, a nonspecific diffuse nonvesicular maculopapular rash, oral mucosal changes including a strawberry tongue, mild swelling and erythema of his hands and feet followed by desquamation the dorsum of his hands, and slightly tender unilateral cervical adenopathy (<1.5 cm). The disease was refractory to IVIG, which occurs in up to 10% of patients but was responsive to corticosteroid therapy. Immediately before discharge, the patient again became unwell and developed MAS. The diagnosis of MAS was based on hepatosplenomegaly, hyperferritinemia, abnormal serum acyl-transferases, elevated serum LDH, hypofibrinogenemia, hypertriglyceridemia, and rapidly falling hemoglobin and platelet count. The only classic finding he did not have was the documentation of a falling erythrocyte sedimentation rate, most likely because of neutralization of red blood count zeta potential by immunoglobulin G (secondary to IVIG), causing an artificial elevation of erythrocyte sedimentation rate.[4,14]

As can be seen, our case is strikingly similar to the previously published reports with persistent fever despite treatment with IVIG.[7–9] As illustrated in Table 2, all 3 earlier reported cases of MAS associated with KD had prolonged or recurrent fever that required multiple treatments of IVIG before the onset of MAS.[7–9] Two of the previously reported cases had bone marrow evidence of hemophagocytosis,[8,9] whereas 1 had liver biopsy evidence.[7] All patients developed hepatosplenomegaly, hyperferritinemia, and abnormal acyl-transferases as seen in our patient. Of interest, this case, as well as 1 of the previous described cases (6-year-old)[7] and another recently reported case (10-year-old girl),[15] all occurred in older children.

In this case, the patient responded to corticosteroid therapy; however, often other therapies are required to treat MAS, a potentially life-threatening complication. Patients with KD and MAS have been treated with corticosteroids and etoposide (VP16) and granulocyte colony-stimulating factor[7,8]; or granulocyte colony-stimulating factor[9] alone. Others have shown that cyclosporine can be used effectively in the treatment of MAS occurring in children with juvenile rheumatoid arthritis in both life-threatening and less-severe presentations of MAS.[16]

One of the earliest large series of cases of MAS in patients with systemic-onset juvenile idiopathic arthritis, a disease known to be associated with MAS, referred to this entity as a consumptive coagulopathy rather than MAS.[14] These cases would now be referred to as cases of MAS seen in association with systemic-onset juvenile idiopathic arthritis.[14,16] Similarly, as this and previous case reports have shown,

TABLE 2. Comparison of Patients With KD Who Developed MAS

Patient	1 (Ohga et al[9])	2 (Kaneko et al[8])	3 (Al-Eid et al[7])	4 (Present Case)
Age	32 mos	12 mos	6 y	9 y
Gender	Male	Female	Male	Male
Days to MAS	21	24	20	23
Number of courses of IVIG	3	5	2	2
Corticosteroid	None	None	1 course of IVMP	2 courses of IVMP followed by oral therapy
Laboratory evidence of MAS				
Cytopenia	Yes	Yes	Yes	Yes
Hyperferritinemia	Yes	Yes	Yes	Yes
Elevated LDH	Yes	N/A	Yes	Yes
Elevated acyl-transferases	N/A	Yes	Yes	Yes
Hypofibrinogenemia	No	N/A	Yes	Yes
Hypertriglyceridemia	N/A	N/A	Yes	Yes
Evidence of MAS by biopsy	Bone marrow	Bone marrow	Liver	Bone marrow

IVMP indicates intravenous methylprednisolone; N/A, not available.

the laboratory values seen in MAS may be mistaken with those seen in disseminated intravascular coagulation (also a known complication of KD). It is possible that children with KD who have become acutely unwell and thought to have disseminated intravascular coagulation may have had unrecognized MAS.[7–9] Therefore, MAS may be a more frequently under-recognized complication of KD. Early recognition and treatment of MAS is imperative to avoid a fatal outcome in severe cases.[16] We suggest that MAS should be considered in children with KD who have recurrent fever and multiple treatments with IVIG and high-dose ASA when hepatosplenomegaly with abnormal laboratory findings such as cytopenia, liver dysfunction, hyperferritinemia, elevated serum LDH, hypofibrinogenemia, and hypertriglyceridemia are present.

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Pediatrics 2003;112;e495

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