AWARDSISENT. 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.

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.7-9 We suggest that KD be included on the list of causes of MAS.

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 nonvascular maculopapular rash, oral mucosal changes including a strawberry tongue with no buccal mucosa or pharynx exudes and no Koplak spots, 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 and subsequently had a normal echocardiogram. His infectious disease work-up including blood cultures, throat swab for group A beta 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 nonspecific 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 3 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

<table>
<thead>
<tr>
<th>Day</th>
<th>At Presentation</th>
<th>Onset MAS</th>
<th>48 Hours Later</th>
<th>At Discharge</th>
<th>2 Months Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count (4–10 × 10^9/L)</td>
<td>24.1 × 10^9/L (10^6/μL)</td>
<td>102 × 10^9/L (10^6/μL)</td>
<td>19.7 × 10^9/L (10^6/μL)</td>
<td>6.8 × 10^9/L (10^6/μL)</td>
<td>12.9 × 10^9/L (10^6/μL)</td>
</tr>
<tr>
<td>Polys (2.00–7.50 × 10^9/L)</td>
<td>20.5 × 10^9/L (10^6/μL)</td>
<td>2.68 × 10^9/L (10^6/μL)</td>
<td>14.43 × 10^9/L (10^6/μL)</td>
<td>5.04 × 10^9/L (10^6/μL)</td>
<td>11.1 × 10^9/L (10^6/μL)</td>
</tr>
<tr>
<td>Lymph (1.5–7.0 × 10^9/L)</td>
<td>0.96 × 10^9/L (10^6/μL)</td>
<td>0.20 × 10^9/L (10^6/μL)</td>
<td>0.93 × 10^9/L (10^6/μL)</td>
<td>1.02 × 10^9/L (10^6/μL)</td>
<td>1.3 × 10^9/L (10^6/μL)</td>
</tr>
<tr>
<td>Hemoglobin (120–160 g/L)</td>
<td>113 g/L (11.3 g/dL)</td>
<td>85 g/L (8.5 g/dL)</td>
<td>93 g/L (9.3 g/dL)</td>
<td>101 g/L (10.1 g/dL)</td>
<td>136 g/L (13.6 g/dL)</td>
</tr>
<tr>
<td>PLT (150–400 × 10^9/L)</td>
<td>623 × 10^9/L (6.23 × 10^12/μL)</td>
<td>104 × 10^9/L (1.04 × 10^12/μL)</td>
<td>133 × 10^9/L (1.33 × 10^12/μL)</td>
<td>464 × 10^9/L (4.64 × 10^12/μL)</td>
<td>293 × 10^9/L (2.93 × 10^12/μL)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (1–10 mm/hour)</td>
<td>118 mm/hour</td>
<td>70 mm/hour</td>
<td>53 mm/hour</td>
<td>36 mm/hour</td>
<td>1 mm/hour</td>
</tr>
<tr>
<td>AST (0–36 units/L)</td>
<td>105 units/L</td>
<td>2083 units/L</td>
<td>1339 units/L</td>
<td>96 units/L</td>
<td>26 units/L</td>
</tr>
<tr>
<td>ALT (0–40 units/L)</td>
<td>12 units/L</td>
<td>903 units/L</td>
<td>951 units/L</td>
<td>79 units/L</td>
<td>31 units/L</td>
</tr>
<tr>
<td>ALK phos (180–475 units/L)</td>
<td>N/A</td>
<td>339 units/L</td>
<td>247 units/L</td>
<td>111 units/L</td>
<td>51 units/L</td>
</tr>
<tr>
<td>Conjug. bili (0–2 μmol/L)</td>
<td>0 μmol/L (0 mg/dL)</td>
<td>10 μmol/L (0.58 mg/dL)</td>
<td>1 μmol/L (0.06 mg/dL)</td>
<td>0 μmol/L (0 mg/dL)</td>
<td>N/A</td>
</tr>
<tr>
<td>Unconj. bili (0–17 μmol/L)</td>
<td>0 μmol/L (0 mg/dL)</td>
<td>0 μmol/L (0 mg/dL)</td>
<td>0 μmol/L (0 mg/dL)</td>
<td>0 μmol/L (0 mg/dL)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ferritin (22.0–400 ng/L)</td>
<td>N/A</td>
<td>1156 μg/L</td>
<td>1236 μg/L</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>LDH (432–700 units/L)</td>
<td>N/A</td>
<td>29691 units/L</td>
<td>5062 units/L</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Fibrinogen (1.60–4.00 g/L)</td>
<td>N/A</td>
<td>5420 ng/L</td>
<td>1970 ng/L</td>
<td>N/A</td>
<td>429 ng/L</td>
</tr>
<tr>
<td>D-Dimer (0–499 ng/L)</td>
<td>N/A</td>
<td>252 μmol/L (223 mg/dL)</td>
<td>280 μmol/L (248 mg/dL)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Albumin (35–58 g/L)</td>
<td>28 g/L (2.8 g/dL)</td>
<td>110 g/L (11.0 g/dL)</td>
<td>110 g/L (11.0 g/dL)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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 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. 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. 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.

REFERENCES


### TABLE 2. Comparison of Patients With KD Who Developed MAS

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

IVMP indicates intravenous methylprednisolone; N/A, not available.
Are Children With Kawasaki Disease and Prolonged Fever at Risk for Macrophage Activation Syndrome?
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