A 12-Week-Old Male with a 10-Day History of Fever

Sima Thakkar Bhatt, MD; Joseph R. Hageman, MD; Allison Bartlett, MD; and Kalyani Trivedi, MD

Abstract

Kawasaki disease (KD) is a self-limited vasculitis that can have significant morbidity and even mortality if not identified and treated early. The purpose of this case study is to highlight the importance of keeping KD in the differential diagnosis, even if all clinical criteria are not met. This is especially true in children younger than 1 year of age, who are more likely to have an incomplete or atypical presentation. The patient in this study is a 12-week-old African-American male with no significant past medical history who presented with a 10-day history of fever up to 105°F. An echocardiogram shortly after admission demonstrated normal cardiac structure and function with evidence of coronary artery abnormalities. Diagnosis of KD (treatment with intravenous immunoglobulin, aspirin, and a tumor necrosis factor-alpha inhibitor) and follow-up imaging are detailed. Treatment of KD in the acute phase is aimed at preventing coronary thrombosis and aneurysm formation.
A 12-week-old African-American male with no significant past medical history presented with a 10-day history of fever up to 105° F. The patient was admitted to a referring hospital 9 days prior, where a blood culture, urine culture, and respiratory viral panel (RVP) were negative. No lumbar puncture was done at that time. He received ceftriaxone until he was culture-negative for 48 hours. He was discharged home after 3 days. On the day of discharge, he spiked another fever at home to 104° F, which resulted in his mother bringing him back to the referring hospital. Another blood culture was drawn and he was given a dose of ceftriaxone and readmitted. He was discharged 3 days later and was brought to the emergency department (ED) at our institution 1 day later for continued fever. The boy’s mother reported that he improved with scheduled acetaminophen but never had an afebrile 24-hour period.

Past history and pregnancy were unremarkable. The patient had received his first set of immunizations. Review of systems was positive for fever, irritability, and neck rash and was negative for conjunctivitis, decreased urine output, rhinorrhea, cough, decreased oral intake, and changes in stool.

Upon examination in the ED, vital signs were: temperature 40.1° C, pulse 170, BP 108/59 mm Hg, respirations 44, and oxygen saturation 99% on room air. The patient was irritable and inconsolable when held by his mother. He had dry mucous membranes, clear oropharynx, no conjunctival injection or eye discharge, and anterior fontanelle was soft and flat. The neck was supple and without lymphadenopathy. Cardiac exam was normal and capillary refill was less than 2 seconds. Lungs were clear to auscultation bilaterally and abdominal exam was unremarkable. He had a rash in the skin fold of his neck with no dermatologic changes of his hands or feet.

Significant lab results included white blood cell (WBC) count of 27.9 (x10³/µL), hemoglobin of 6.9 g/dL with hematocrit of 20.9% and a mean corpuscular volume of 75 fL. Platelet count was 654 (x10³/µL). Albumin was 2.7 g/dL and C-reactive protein (CRP) was 275 mg/L. The catheterized urinalysis (UA) was significant for 3 to 5 WBCs per high-power field with no bacteria, leukocyte esterase, or nitrites. Cerebrospinal fluid (CSF) results included 3 red blood cells, 2 white blood cells, glucose 65 mg/dL, and protein 25 mg/dL. A lab test was performed.
Diagnosis:
Kawasaki Disease

An echocardiogram shortly after admission demonstrated normal cardiac structure and function with evidence of coronary artery abnormalities. The left main coronary artery (LMCA) was 3.4 mm (z-score 4.40) in diameter, the left anterior descending artery (LAD) was 3 mm (z-score 2.68), and the right coronary artery (RCA) was 3.1 mm (z-score 5.79) (Figures 1-4). Based on the atypical Kawasaki algorithm (Figure 5), the patient was treated presumptively for Kawasaki disease (KD) with intravenous immunoglobulin (IVIG) at 2 gm/kg over 10 hours and aspirin at 80 mg/kg/day. The day of presentation to our institution was the patient’s tenth day of symptoms, and treatment by day 10 of fever is associated with improved outcomes when compared with delayed therapy.\(^1\)

He initially defervesced, but within 8 hours of completing his IVIG dose, the patient had recurrence of fever. He was given another 2 mg/kg dose of IVIG but again had recurrence of fever. Finally, he received treatment with a tumor necrosis factor-alpha (TNF-alpha) inhibitor (infliximab), after which he remained afebrile. His infectious work-up was negative. At the time of discharge, he was noted to have peeling of his hands and feet.

A full-body magnetic resonance angiogram (MRA) did not show any other vessel abnormalities, and follow-up echocardiogram immediately prior to discharge showed mild improvement in the size of the coronary vasculature. The LMCA was 2.5 mm (z-score 1.75), LAD was 2.1 mm (z-score 2.98), and RCA was 1.3 mm (z-score -0.44). The patient was maintained on low-dose aspirin at the time of discharge. Repeat echocardiogram 5 months later showed the LMCA measured 2.3 mm (z-score 0.51), the LAD measured 2 mm (z-score 1.44), and the RCA measured 1.5 mm (z-score -0.43).

DISCUSSION
KD is an acute systemic vasculitis with a predilection for coronary arteries.\(^1\) It is the leading cause of acquired heart disease in children in developed countries. The United States has an annual incidence rate of 15 to 20 cases per 100,000 children younger than 5 years of age.\(^4\) Rates are substantially higher in those of Asian ethnicity, suggesting a genetic susceptibility.\(^1\) There is also a higher incidence in males than females, with a ratio of 1.5:1. The etiology for KD is unknown. It is self-limited, with seasonal peaks in the winter and spring, and it likely has an infectious etiology.
KD is a clinical diagnosis (Table 1) and can be especially difficult to diagnose in children younger than age 1 year and older than 9 years, as they are more likely to present with incomplete KD (Figure 1). This often leads to a delay in diagnosis and therapy. There are numerous case reports in the literature of atypical or incomplete KD being diagnosed only after giant coronary artery aneurysms are detected on echocardiography or on autopsy.

Incomplete KD should be considered in all children with unexplained fever lasting 5 days associated with two or more of the principal clinical features of KD, as well as in any infant aged younger than 6 months with fever lasting at least 7 days and laboratory evidence of considerable systemic inflammation (erythrocyte sedimentation rate $\geq 40$ mm/hr or CRP $> 3$ mg/dL) if no other explanation for the febrile illness exists (Figure 5).

Treatment of KD in the acute phase is aimed at preventing coronary thrombosis and aneurysm formation. In those who develop aneurysms, long-term antiplatelet therapy should be initiated to prevent myocardial ischemia or infarction. Treatment in the acute phase consists of high-dose IVIG and aspirin. Patients who have persistence of fever or recurrence within 36 hours after IVIG infusion are considered IVIG-resistant. The
optimal rescue therapy for these patients remains controversial, and treatment options include a second dose of IVIG, 3 days of intravenous methylprednisolone, cyclophosphamide, methotrexate, plasma exchange, or a TNF- 
alpha inhibitor. Patients who are IVIG-resistant have an increased risk for development of coronary artery aneurysm.

Coronary artery aneurysms develop in 18% to 23% of children with KD who are untreated, whereas the rate decreases to 3% to 5% for those who receive treatment with IVIG within 10 days of fever onset.4,6 Risk factors for developing coronary artery disease include male sex, age of younger than 1 year, fever lasting more than 10 days, and IVIG refractoriness.6 Although the coronary arteries are most likely to be involved in KD, other medium-sized vessels throughout the body are also involved occasionally. Angiographic resolution of aneurysms occurs in 50% of arterial segments, but there is a persistent histological and functional abnormality that may be associated with coronary stenosis.1

Coronary artery aneurysms are classified as small (< 5 mm internal diameter), medium (5 mm to 8 mm internal diameter), or giant (> 8 mm internal diameter).1 Coronary artery lesions are classified by diameter of greater than 2.5 standard deviations above the mean for body surface area (z-score ≥ to 2.5).1

CONCLUSION
Kawasaki disease is a self-limited vasculitis that can have significant morbidity and even mortality if not identified and treated early. It is very important to keep this disease in the differential diagnosis, even if all clinical criteria are not met. This is especially true in children younger than 1 year of age, as they are more likely to have an incomplete or atypical presentation.

REFERENCES