CASE 9.5
Kawasaki Disease | Level 3

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1. What subjective and objective evidence supports the diagnosis of Kawasaki disease?

The current diagnostic criteria for Kawasaki disease consist of unexplained fever persisting for 5 days or more, with four or more primary clinical features that are present in this patient as subjective and objective findings. Although laboratory abnormalities are not required for a diagnosis of typical Kawasaki disease, some are highly suggestive of disease and are listed below.

SUBJECTIVE FINDINGS: A 23-month-old Chinese girl presented with the following:

- 7-day history of persistent fever
- 4-day history dry lips and red tongue
- 4-day history of nonbloody diarrhea (which is worsening)
- 1-day history maculopapular rash developing on her chest and abdomen

OBJECTIVE FINDINGS: On physical exam, patient has bilateral, nonexudative conjunctivitis, edema of the hands and feet, and diffused blanching macular rash over abdomen. Abnormal laboratory findings consistent with Kawasaki disease are leukocytosis (WBC count $26.7 \times 10^3/\mu L$), normocytic anemia (Hgb 10.1 g/dL, Hct 29.7%), thrombocytosis (platelets $877 \times 10^3/\mu L$), elevated CRP and ESR (20.2 mg/dL and 56 mm/hr, respectively), sterile pyuria (WBC count 16/hpf with negative bacteria on Gram stain), hypoalbuminemia (albumin 2.5 g/dL), and elevated serum aminotransaminases (AST/ALT 56/79 units/L). Furthermore, diagnostic tests to confirm Kawasaki disease, including chest x-ray, influenza, and respiratory syncytial virus, are negative.

Another possible etiology for the patient's clinical presentation, particularly worsening diarrhea, is gastroenteritis that can be caused by a virus or bacteria (including *Shigella*, *Campylobacter*, *E. coli*, and *Yersinia*). However, gastroenteritis is unlikely due to the marked CRP elevation. The diarrhea is also unlikely caused by *C. difficile* because the patient was not recently hospitalized or exposed to broad-spectrum antibiotics (excluding amoxicillin). Other infections, including pneumonia and pyelonephritis, may elevate WBC count; however, diagnostic work-up consisting of normal chest x-ray and urinalysis suggests otherwise.

2. What risk factors evident in this patient support the diagnosis of Kawasaki disease?

Ethnicity and young age are common risk factors for Kawasaki disease. The incidence is highest among children of Asian or Pacific Islander descent. In addition, up to 90% of cases occur in patients between 6 months and 5 years of age.

3. What additional diagnostic test would you recommend to rule out the common complications of Kawasaki disease?

Although a self-limiting disease, Kawasaki disease can progress to cardiac complications including coronary artery aneurysms, congestive heart failure, myocarditis, pericarditis, and arrhythmias. Coronary artery aneurysms, the major cardiac complication, occur in one-fourth of untreated children with Kawasaki disease versus 4% with therapy, emphasizing the importance of adequate treatment. Prompt initiation of appropriate therapy, particularly within 10 days of fever onset, may prevent cardiac morbidity progression and mortality. To ascertain the degree of cardiac involvement, an echocardiogram should be performed within 2 weeks after fever onset and repeated 6 to 8 weeks later to confirm therapeutic response.

4. Recommend and explain the benefit(s) of pharmacologic treatment during hospitalization and at discharge. Provide the therapeutic goals and monitoring plans for this patient.

Based on guidelines developed by the American Heart Association and the American Academy of Pediatrics, the standard therapy for Kawasaki disease is a single dose of intravenous immune globulin (IVIG) and high-dose aspirin initiated as soon as the diagnosis is made or within the first 10 days of illness. The benefits of IVIG are its anti-inflammatory properties to support resolution of fever and prevention of coronary artery aneurysm. Although it does not decrease the development of coronary abnormalities, aspirin is used for its additive anti-inflammatory and antiplatelet activities.

A single, high-dose infusion of IVIG at 2 g/kg (22 g infused over 8 to 12 hours for this patient), compared with low doses over 4 to 5 days, has been shown to produce a greater decrease in the duration of fever and length of hospital stay as well as faster resolution of laboratory findings for acute inflammation. In addition, for its anti-inflammatory and antiplatelet activities, high-dose aspirin 80 to 100 mg/kg/day administered orally (243 mg in this patient, which equates to 3 of 81 mg chewable tablets every 6 hours, not to exceed 4 g/day) is recommended until 48 to 72 hours after fever resolves. Alternatively, high-dose aspirin can be continued until 14 days after illness onset, with at least 48 to 72 hours after fever cessation. This is followed by low-dose aspirin 3 to 5 mg/kg/day (i.e., ~40 mg [½ of 81 mg chewable tablet] orally once daily) for its antiplatelet effect and is continued until resolution of ESR or platelet count or until 6 to 8 weeks after illness onset to rule out cardiac abnormalities. Aspirin, including the low-dose therapy, should be discontinued in patients with influenza or varicella infection to avoid Reye syndrome. Clopidogrel can be temporarily substituted for aspirin in this situation.

Additional medications to prevent thrombosis formation may be necessary if coronary involvement is present. At this time, none of the following medications are indicated in this patient. They should be considered based on the result of the echocardiogram and clinical progress. The use of antiplatelet, anticoagulation, or combination therapies will depend on the degree of coronary involvement. For mild, asymptomatic cases, low-dose aspirin is recommended. The addition of other antiplatelet drugs (e.g., clopidogrel or dipyridamole) to low-dose aspirin to further enhance activity may be more effective in moderate cases with evidence of enlarged coronary artery aneurysm. Anticoagulation using warfarin (with initial unfractionated heparin as bridge therapy), in combination with low-dose aspirin, is indicated when the risk of thrombosis is high, particularly in rapidly enlarging coronary aneurysms.