

Kawasaki Disease In A 15-Year-Old Adolescent

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It has been 28 years since Dr. Tomisaku Kawasaki originally described mucocutaneous lymph node syndrome, now known as Kawasaki disease.¹ First thought to be a benign self-limited febrile illness, Kawasaki disease today is recognized as the most common cause of acquired heart disease in children in the United States. It is almost exclusively an illness of young children — about 80 percent of patients are younger than 4 years — and the syndrome is unusual after 8 years of age.² The peak age of Kawasaki disease patients in Japan is from 9 to 11 months, with equal numbers of cases in the first and second years. Studies in the United States and Europe showed that a peak age of Kawasaki disease is 18 to 24 months, older than in Japan.³

Adult Kawasaki disease has received increased recognition, but early reports have been challenged as probably representing toxic shock syndrome instead. One review of 21 patients with adult Kawasaki disease reported in the English literature accepted only 10 cases as representing this syndrome.⁴

Case Report

A 15-year-old boy from the Dominican Republic, accompanied by his mother, came to the Jackson Memorial Hospital Emergency Department in Miami, Florida, complaining of a 6-day history of fever and rash. He previously had been seen in a local clinic, where a throat culture was done, and diphenhydramine and cefaclor were prescribed. He remained febrile and irritable and had headaches; he also complained of stiffness and pain in both hands. His medical history was unremarkable. The youngster denied any sexual contact, drug use, or any infectious exposures. No risk factors for human immunodeficiency virus were found. He said he had had no earlier arthritic episodes or exposure to other medications.

Upon admission his blood pressure was 90/60 mmHg, heart rate was 88 beats per minute, temperature 102.7°F, and respiratory rate 20/min. Bilateral conjunctival injection without secretion; erythema, swelling, and fissures of the lips; cervical lymphadenopathy; and a stiff neck were found on the physical examination. Findings on the cardiovascular examination were normal. The auscultation of the lungs showed crackles at the left anterior base. The abdomen was benign without hepatosplenomegaly. He had a maculopapular rash on the torso and extremities and swelling, tenderness, and redness of the proximal interphalangeal joints of both hands. Palms and soles were indurated and erythematous without skin desquamation. Pulses were present and normal in all four extremities, and no bruit was found. Genitalia were normal to inspection and palpation. He was somewhat lethargic, but no focal signs were found during the neurological examination.

Laboratory studies disclosed a white cell count of 17,900/mm³ with 77 percent polymorphonuclear leukocytes, 10 percent band forms, and no atypical lymphocytes; he had an elevated platelet count of 546,000 μ L, a hemoglobin of 13.1 g/dL, and a hematocrit of 40 percent. The erythrocyte sedimentation rate was 65 mm/h. Liver enzymes were aspartate aminotransferase 102 U/L, alanine aminotransferase 95 U/L, alkaline phosphatase 335 U/L. Antistreptolysin "O" titers were not elevated. Hepatitis B surface antigen, screening test for syphilis, and antinuclear antibody titer were negative, as were blood cultures. There were normal findings on a computerized tomogram of the brain, and results of a lumbar puncture were within normal limits. The chest radiograph showed a right middle lobe infiltrate without adenopathy; the heart size was normal. An initial working diagnosis of community-acquired pneumonia was made, specifically attributed to atypical organisms, such as mycoplasma and chlamydia, that can cause rash and adenopathy.

Stevens-Johnson syndrome was considered unlikely because the patient did not develop profuse exudate with pseudomembrane formation. The target lesions were biopsied and showed changes

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consistent with erythema multiforme, which can be found in association with *Mycoplasma pneumoniae*. The patient, however, did not respond to intravenous erythromycin. The possibility of drug reaction was disregarded because signs and symptoms preceded any medications.

Infectious mononucleosis was considered based on the clinical disease expressions — fever, lymphadenopathy, pharyngitis, malaise — but there were no atypical large lymphocytes in the blood smear, nor did he have lymphocytosis. Cerebral spinal fluid showed no increase in pressure or abnormal lymphocytes and elevated protein levels. Results of Epstein-Barr virus capsid antibody testing were inconclusive, and the patient had thrombocytosis instead of thrombocytopenia.

Systemic-onset juvenile rheumatoid arthritis was part of the differential diagnosis, but the intermittent fever with rapid return to normal levels characteristic of Still disease was not evident, and neither his liver nor his spleen was enlarged. The throat culture for streptococci was negative and the antistreptolysin "O" titer was not elevated.

Therapy was begun with intravenous erythromycin and intravenous fluids for treatment of his right middle lobe pneumonia. The patient remained febrile for 2 days without any improvement. Given the constellation of symptoms — fever unresponsive to antibiotics, adenopathy, conjunctivitis, arthralgias, and rash — Kawasaki disease was seriously considered, and treatment with intravenous gamma globulin and acetylsalicylic acid was started.

An ophthalmologic examination showed anterior uveitis, and a biopsy of the skin showed changes consistent with erythema multiforme. An echocardiogram revealed a small pericardial effusion, an ejection fraction of 50 percent, and no coronary aneurysms. The fever resolved 24 hours after the treatment was started.

The patient was discharged home on close observation and acetylsalicylic acid therapy. He was seen in the cardiology clinic 2 weeks later, where a second echocardiogram showed diffuse dilatation of the coronary arteries. At that time he reported occasional fever, and his erythrocyte sedimentation rate was 99 mm/h. He was then readmitted for a second course of intravenous gamma globulin, a single infusion of 2 g/kg of body weight for 12 hours, acetylsalicylic acid

325 mg/d, dipyridamole 25 mg orally three times a day, bed rest, and observation. During this hospitalization he had mild diffuse abdominal pain without fever, guarding, or rebound. Also present was desquamation of the hands and feet. He was sent home with prescriptions for dipyridamole 25 mg orally three times a day and low-dose acetylsalicylic acid.

Discussion

The cause of Kawasaki disease is unknown. Epidemiologic evidence suggests an infectious cause. Several groups are investigating the role of group A streptococcus, as many features of Kawasaki disease are similar to those diseases associated with streptococcal exotoxins. Agents such as *Rickettsia*, skin commensals, and retroviruses have not been confirmed in studies.

Pathophysiology

The major pathologic feature of Kawasaki disease is an acute multisystem vasculitis affecting small and medium-sized musculoelastic arteries. Marked activation of the immune system occurs, with increased levels of circulating cytokines (interleukin 1, interleukin 6, tumor necrosis factor, interferon). Also seen are high levels of circulating soluble CD4 and CD8 antigen cells, polyclonal hypergammaglobulinemia, and high levels of immunoglobulin G and immunoglobulin M circulating immune complexes.⁴ Histologic examination shows perivasculitis with endothelial cell swelling, proliferation, and necrosis, as well as adhesion of polymorphonuclear leukocytes to the endothelium wall.

Clinical and laboratory features in Kawasaki disease are similar to those seen in diseases caused by bacterial toxins that act as superantigens, such as staphylococcal enterotoxins and streptococcal exotoxins. Superantigens are molecules that stimulate thymus-dependent (T) cells by binding to the T cell receptor outside the usual idiotypic site. They can, therefore, activate large numbers of T cells by this less-specific antigen-receptor interaction.

Diagnostic Criteria

Although there is no diagnostic test for Kawasaki disease, the symptoms can be classified into two groups: principal symptoms and other important symptoms or findings.⁵

The principal symptoms are as follows:

1. Fever persisting 5 days or more
2. Changes of peripheral extremities: reddening of palms and soles, indurative edema, and later membranous and desquamation from fingertips
3. Polymorphous exanthema
4. Bilateral conjunctival congestion
5. Changes of lips and oral cavity: reddening of lips, strawberry tongue, diffuse infection of oral and pharyngeal mucosa
6. Acute nonpurulent cervical lymphadenopathy

At least five of these six symptoms should be satisfied for diagnosis of Kawasaki disease.

Other important symptoms or findings include the following:

1. Cardiovascular: prolonged PR-QT intervals, abnormal Q wave, low-voltage ST-T changes, arrhythmias, cardiomegaly on radiographs, pericardial effusion, coronary aneurysm
2. Gastrointestinal: diarrhea, vomiting, abdominal pain, hydrops of gall bladder, slight increase in serum transaminase
3. Blood: leukocytosis with shift to the left, thrombocytosis, increased erythrocyte sedimentation rate, positive C-reactive protein
4. Urine: proteinuria, increase of leukocytes in urine sediment
5. Skin: redness, small pustules, transverse furrows of the fingernails
6. Respiratory: cough, rhinorrhea, abnormal shadows on chest radiograph
7. Musculoskeletal: pain, swelling of the joints
8. Neurologic: pleocytosis of mononuclear cells in cerebral spinal fluid, convulsion

The rash of Kawasaki disease can take many forms: an urticarial exanthem with large erythematous plaques, a morbilliform maculopapular rash that might be multiform, i.e., target lesions, a scarlatiniform erythroderma, or, rarely, a fine micropustular form. It usually involves trunk and extremities.

Laboratory findings include leukocytosis, thrombocytosis, and elevated erythrocyte sedimentation rate. There is no antinuclear antibody or rheumatoid factor detectable. There are decreased circulating T8 suppressor cells and increased circulating activated T4 helper cells.

Clinical Course

The acute febrile phase lasts from 7 to 10 days. It is characterized by conjunctival injection, mouth and lip changes, rash, and lymphadenopathy.

The subacute phase lasts from 10 to 25 days. Fever, rash, and lymphadenopathy resolve, while irritability and anorexia persist. Desquamation of fingers and toes are typically seen, as are arthritis, arthralgia, myocardial dysfunction, and thrombocytosis.

The convalescent phase continues until the erythrocyte sedimentation rate returns to normal. Clinical signs disappear in 6 to 8 weeks, but occasionally a patient can experience clinical rebound, with recurrence of fever and clinical signs. This rebound is associated with an increased risk of coronary artery disease.²

The differential diagnosis includes scarlet fever, leptospirosis, toxic shock syndrome, juvenile rheumatoid arthritis, Epstein-Barr virus infection, measles, acrodynia, Rocky Mountain spotted fever, drug reaction, Stevens-Johnson syndrome, and other vasculitis syndromes.

Cardiovascular Manifestation

Cardiac involvement is the most important prognostic feature of Kawasaki disease. Myocarditis (by echocardiogram, not clinical) is found in 80 percent of cases, and coronary artery abnormalities develop in 15 to 25 percent of children who do not receive treatment. Aneurysms are divided into localized and giant saccular and are usually diagnosed by two-dimensional echocardiography. Between one-half and two-thirds of the aneurysms can resolve spontaneously,⁶ and resolution is directly proportional to the size of dilatation. Regression occurs by myointimal proliferation or by organization of the thrombus. The worst prognosis is for the giant aneurysms (maximum internal diameter of 8 mm or more). Myocardial infarction can occur early or many years after the acute illness.

Treatment

The conventional regimen has been a 4-day course of intravenous gamma globulin as a daily infusion of 400 mg/kg, together with 100 mg/kg/d of aspirin, through the 14th day of the illness, then 3 to 5 mg/kg/d. This regimen has proved safe and effective in preventing coronary artery lesions and reducing systemic inflammation.

Others have reported that a single infusion of gamma globulin of 2 g/kg is more effective than the standard 4-day regimen, suggesting that the single infusion regimen accelerated the resolution of systemic inflammation.⁷

Although Kawasaki disease often is a benign self-limiting illness, it is extremely important to consider this diagnosis early in the course of the illness, to institute appropriate therapy, and to remain alert for possible complications.

Currently the diagnosis rests solely on clinical grounds and on the exclusion of other diseases by appropriate laboratory studies. Kawasaki disease is rare after childhood, but several cases have been reported. Despite its rarity in an adolescent age group, it is important to consider Kawasaki disease in patients who have fever, rash, arthritis, and other findings, because of the potential that specific therapy can prevent death or chronic heart disease. Our patient fulfilled the criteria for Kawasaki disease even though he did not belong to the common age group affected by this disease process.

Serious morbidity and mortality can occur many years after the acute phase. Experience in treatment of Kawasaki disease is generally limited to the pediatric age group, but because high-dose intravenous gamma globulin and aspirin are safe and effective in reducing cardiac complications, it is essential that we be prepared to initiate treatment in patients with suspected Kawasaki disease, even when they do not fit the usual age group.

Family physicians are important in the care of patients in transition from childhood to adult-

hood, providing continuity of care during this time of physical growth and personality development. We should be alert and should seek specific information regarding childhood illnesses when evaluating acute cardiovascular symptoms in the young patient.

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