Kawasaki Disease

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Kawasaki disease is an acute, multisystem illness that predominantly affects young children and has been described throughout the world. The triphasic course includes an initial phase of acute illness marked by high fever, conjunctival injection, oral changes, and erythematous rash. The second, subacute, phase begins with a decline of the acute findings and proceeds with desquamation of rash, joint manifestations, thrombocytosis, and cardiac disease. Most deaths (1 to 2 percent of cases) occur in this phase, usually resulting from myocardial infarction. During the third phase all signs of clinical illness subside. The prognosis is related to the degree of cardiac involvement, and 14 to 20 percent of patients develop coronary artery aneurysms. Inhibition of platelet aggregation, combined with symptomatic relief and supportive measures, forms the cornerstone of therapy. Family physicians need to be aware of this illness, particularly since it can no longer be considered rare.

Case Report

A 22-month-old Japanese-American girl presented to the family practice clinic with a one-day history of temperature to 101° F. The history and physical examination were otherwise unremarkable, and the parents were reassured. The patient returned the following day with soft stools and a macular, erythematous rash on her back. By the third day of illness, the child was lethargic with a temperature to 105° F, diarrhea, and an erythema multiforme rash on her back, palms, soles, and axillae. Laboratory data included normal urinalysis and spinal fluid studies. The white blood cell count was 6,100/mm^3 with 3 percent segmented forms, 33 percent band forms, 5 percent metamyelocytes, and 1 percent myelocytes. Cultures were obtained from throat, urine, blood, and spinal fluid, and all were subsequently negative. Because of the excellent reliability of the parents, the child was sent home after temperature reduction improved her general appearance.

On the fourth day of illness, the patient had temperature elevation of 104° to 105° F and a mild conjunctivitis. On the following day she developed cracking of her lips, but her condition was otherwise unchanged. Repeat leukocyte count of 16,700/mm^3 included 31 percent segmented forms, 50 percent band forms, 3 percent metamyelocytes, and 1 percent myelocytes. Platelet count was 286,000/mm^3. By the sixth day, the continued fe-

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brile course (102° to 104° F) and signs of parental stress and fatigue led to admission of the child to the hospital. At that time she had bilateral bulbar conjunctivitis, cracked red lips, prominent tongue papillae, and the suggestion of edema on the dorsal side of her feet. The admitting diagnosis was probable Kawasaki disease, and studies were obtained to rule out viral illness, leptospirosis, and scarlet fever. Pediatric cardiology and infectious disease consultations were obtained.

During the one-week hospitalization other disease processes were ruled out. The patient remained febrile for 12 days, developed significant swelling of feet and hands in the second week of illness, and had a desquamating rash of fingers and toes beginning around day 10. Her sedimentation rates ranged from 45 to 113 mm/hr, and her platelet count reached 948,000/mm^3 on day 15 then gradually decreased. She also exhibited anemia (hemoglobin 10.2 to 11.0 g/100 mL), pyuria, tachycardia, and hypoalbuminemia. She was treated with aspirin (100 mg/kg/d initially then reduced to 30 mg/kg/d, and her course was stable. Though technically adequate M-mode and two-dimensional echocardiography revealed no coronary artery aneurysms, several consultants discussed the possibility of cardiac catheterization to "define the anatomy." Feeling that this invasive procedure was not warranted in this clinical situation, the primary care physicians decided against catheterization. An opportunity developed to discuss the child's illness with Dr. Kawasaki in Japan, who shared his belief that cardiac catheterization in this illness should be reserved for those patients for whom cardiovascular surgical procedures are being seriously considered and for patients showing clinical deterioration of cardiac function in whom echocardiography is inconclusive.

After discharge the patient continued to do well, with gradual resolution of all signs of acute illness. One week after discharge, however, two-dimensional echocardiogram revealed two coronary artery aneurysms. Once again, after extensive discussion with the family and several consultants, it was decided that cardiac catheterization would not significantly improve patient management. Currently, several months later, the patient continues to do well. Her coronary aneurysms have shown significant reduction in size; she remains on aspirin therapy, and she continues to be followed by the family medicine clinic.

Discussion

Kawasaki disease was called mucocutaneous lymph node syndrome when first reported in the Japanese literature in 1967.[1] The first comprehensive review of the illness appeared in this country in 1974.[2] Earlier cases may have been confused with infantile periarteritis nodosa,[2,3] "unusual" measles,[3] or atypical rheumatic fever.[3] Most early reports in the United States came from Hawaii,[3-6] but recent outbreaks have been described in New York[7] and Massachusetts[7,8] as well as in Hawaii.[9] This syndrome has been recognized in South Korea, Canada, Mexico, Hungary, Switzerland, West Germany, England, the Netherlands, Kuwait, the Philippines, Australia, Spain, France, Jamaica, Italy, Greece, Sweden, Turkey, Scotland, and Belgium.[10]

Eighty percent of cases occur in children under four years of age, and 50 percent occur in children under two years of age. Isolated reports of adults with this disease have appeared.[11,12] The male to female ratio is 1.5 to 1, and the disease is most prevalent in Japanese children and in Hawaiian children of Japanese ancestry.[3] Caucasian children appear to be underrepresented. The Japanese have surveyed over 24,000 patients and have found no clear genetic marker or geographic, dietary, environmental, or seasonal pattern. More recent data indicate a frequent history of an antecedent, primarily respiratory illness, and an increased risk in children of middle and upper socioeconomic status.[7] Neither person-to-person transmission nor common source exposure has been demonstrated. The disease is no longer considered rare, having a yearly incidence of over 20 cases per 100,000 children in Hawaii. In recent outbreaks in Boston and New York, incidence rates rose to more than 150 per 100,000 in a three- to four-month period.[3]

The diagnosis of Kawasaki disease can be made only when a patient fulfills five of the six criteria (Table 1) and other possible illnesses are excluded. More than 90 percent of patients fulfill all of the first five criteria. Lymph node enlargement is present in only about 50 percent.[3] The course of the disease has been described as triphasic.[3,5,6,10,13] The initial phase, lasting one to two weeks, is marked by an acutely ill child with abrupt onset of spiking fevers often exceeding 40° C (104° F). Conjunctival injection, lymph node enlargement, oral changes, erythematous rash of variable charac-

Table 1. Diagnostic Criteria for Kawasaki Disease

1. Fever for more than five days
2. Conjunctival injection
3. Changes in the mouth
   - Erythema, fissuring, and crusting of lips
   - Diffuse oropharyngeal erythema
   - "Strawberry" tongue
4. Changes in the peripheral extremities
   - Induration of hands and feet
   - Erythema of palms and soles
   - Desquamation of tips of fingers and toes roughly two weeks from onset of illness
   - Transverse grooves across fingernails two to three months after onset of illness
5. Erythematous rash
6. Cervical lymph node mass over 1.5 cm in diameter

ter, and firm swelling of hands and feet are usually seen in this stage. Associated features during the first two stages may include pyuria and urethritis, arthralgias and arthritis, irritability, lethargy, aseptic meningitis, diarrhea, myocarditis, abdominal pain, obstructive jaundice, and pericardial effusion.[5] Cough has also been described,[8] as has anterior uveitis.[13]

The second, or subacute, stage usually begins on day 10 to 12 and lasts for two to five weeks. This stage begins with a gradual decline in fever, lymphadenopathy, and acute illness, while desquamation of the rash, joint manifestations, thrombocytosis, and cardiac disease become prominent. This stage is the most critical, and of the 1 to 2 percent of deaths (usually due to myocardial infarction), 70 percent occur 15 to 45 days after the onset of fever. The third, or convalescent, stage usually begins around day 25 and lasts until the sedimentation rate is normal. During this phase, all signs of clinical illness disappear.

Laboratory findings commonly found include leukocytosis (on occasion greater than 30,000/mm^3) with "left shift," elevated sedimentation rate and C-reactive protein, and thrombocytosis (commencing during the second phase of illness, commonly exceeding 1,000,000/mm^3, and usually falling to normal around day 30). Other laboratory findings may include anemia, pyuria, proteinuria, microscopic hematuria, spinal fluid lymphocytic pleocytosis, hyperbilirubinemia, elevation of transaminases, elevated serum immunoglobulins and complement, and hypoalbuminemia. Laboratory tests for viral, bacterial, protozoan, and rheumatologic illnesses typically are negative. Differential diagnostic considerations include scarlet fever (streptococcal or staphylococcal), rheumatic fever, leptospirosis, staphylococcal scalded skin syndrome, meningococcemia or other septicemias, Rocky Mountain spotted fever, typhus, toxoplasmosis, rubeola, rubella, roseola infantum, enteroviral infection, mononucleosis, acrodynia, Stevens-Johnson syndrome, juvenile rheumatoid arthritis, Reiter's syndrome, and toxic shock syndrome.

The prognosis of Kawasaki disease is directly related to the cardiac involvement. Clinical cardiac disease occurs in at least 20 percent of patients. The spectrum ranges from sinus tachycardia to congestive heart failure, pericardial effusion, serious arrhythmias, mitral insufficiency, and myocardial infarction.[3,14] It is likely that all patients with this illness have some degree of endothelial damage to coronary arteries, but only 14 to 20 percent develop coronary artery aneurysms.[3,15] While cardiac catheterization is a very sensitive method for detecting aneurysms, it is invasive and has the potential for significant morbidity. Two-dimensional echocardiography, while less sensitive, may be adequate to detect and follow aneurysms in many settings.[3] Deaths may be more common in boys (3:1) and children under two years of age,[3] and in one outbreak cardiac disease was more common in children with serum albumin under 3.3 g/100 mL.[8] Though complete angiographic regression of aneurysms by one or two years has been shown in about 50 percent of patients with aneurysms,[15] even these individuals may be at risk for premature coronary atherosclerosis.[3,15]

Current therapy consists of supportive measures, monitoring for complications, and aspirin for anti-inflammatory effects and inhibition of platelet aggregation. In the acute phase, doses of 80 to 100 mg/kg/d are used to best benefit from anti-inflammatory properties. When fever subsides,

the dose should be decreased to 10 to 30 mg/kg/d and continued indefinitely in patients with aneurysms. In the absence of aneurysms, the optimal duration of aspirin therapy is unknown, but aspirin should probably be continued at least until the sedimentation rate is normal. Steroids should be avoided, as some data suggest they may cause progression of coronary lesions.[16]

The patient in this case has had a course typical of this fascinating illness. Though she is doing very well at present, her long-term prognosis is uncertain. Her parents understand this and are able to discuss their fears with the primary physicians. They were aware of the controversy over cardiac catheterization and were involved in many discussions about the procedure. The primary care physicians felt that decisions regarding catheterization should be a natural outcome of the patient's condition, family input, and a risk-benefit analysis both from the literature and from discussions with experts. Areas considered included the risks of catheterization, the risk of the disease in this patient, the information to be gained by catheterization (given that adequate echocardiographic studies had been done), and ways in which patient management might change based on any findings that could logically be expected from catheterization. Because the patient was clinically stable, the major therapeutic decision centered on the optimal duration of aspirin therapy. Early in the course, when the echocardiogram revealed no aneurysms, the patient was receiving aspirin for anti-inflammatory and antiplatelet effects. Later in the course, aneurysms were detected by echocardiography, so that duration of aspirin therapy would not be influenced by angiographic definition of the aneurysms. Because the patient was doing well clinically, no other potential management benefit from catheterization could be anticipated, and the small risk of catheterization was felt to exceed the benefit of "defining the anatomy." It was decided that the course of the aneurysms would be followed by sequential echocardiograms. The primary care physicians studied pertinent literature and discussed the case among themselves, with the family, and with local, national, and even international experts. Through this process, they were better able to provide high-quality care with sensitivity and understanding and to most appropriately benefit from their hospital consultants. This child's illness and her management represent an excellent example of appropriate interaction between primary physicians and consultants. The utilization of expert consultation along with continuance of direct responsibility for the patient's care resulted in helping the patient and her family to cope with a difficult problem.

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