KA W ASAKI SYNDROME IN A SAUDI CHILD: A CASE REPORT AND REVIEW OF THE LITERATURE

YOUSSEFA. AL-EISSA, MB, BS, DABP, FAAP, FRCP(C)

KAWASAKI syndrome is an acute febrile illness of the young children. It was first recognized and described in Japan by Kawasaki in 1967; however, Kawasaki syndrome has now been recognized throughout the world.3-13 Since the etiology of the illness is unknown and a specific diagnostic test is not available, the diagnosis is made on clinical grounds.2,3 Prolonged fever, injection of mucosa and conjunctivae, redness, edema and desquamation of extremities, skin rashes, and cervical lymphadenopathy make up the syndrome.14 The illness is usually self-limited in most children but serious complications can occur, including coronary aneurysms which may result in thrombotic occlusion and ultimately myocardial infarction.15,16 Although rational treatment is not available at present, early reports of recent therapeutic trials using high-dose intravenous gamma globulin (IVGG) in conjunction with aspirin have been encouraging.17,18

The following report describes the first Saudi boy who developed a prolonged febrile illness that fulfilled the classical diagnostic criteria of Kawasaki syndrome which was complicated by a persistent mitral valve regurgitation.

Case Report

A 21/2-year-old Saudi boy presented to King Khalid University Hospital (KKUH), Riyadh, on 14 January 1988 with a 10-day history of sudden onset of high fever, sore throat, and a generalized but fleeting erythematous rash. He had been initially treated in a local hospital with oral penicillin and paracetamol for possible diagnosis of scarlet fever, but his symptoms persisted. A few days after the onset of his illness, he developed marked redness of the tongue and lips and swellings of the hands, feet, and the right side of the neck. He became irritable, anorexic, and unable to walk. By the end of the first week, oral penicillin was discontinued and an oral antihistamine together with calamine lotion for the skin rash was started, with a consideration of possible allergic penicillin drug reaction. Since the child did not improve over the next three days, he was referred to KKUH. Physical examination showed an extremely irritable, ill-looking, well-nourished child with an axillary temperature of 39.5 °C and a heart rate of 120 beats per minute. He was unwilling to stand, and he had limited use of his hands. He had dry red lips, normal conjunctivae, and marked congestion of the oropharynx but no exudate, ulcers, or vesicles. There was a firm, minimally tender, enlarged lymph node measuring 3 x 4 cm in the right anterior cervical region, firm indurative edema of the dorsa of the hands and feet, fusiform swelling of the digitii, pronounced deep-red discoloration of the palms and soles, and minimally pruritic discrete large erythematous macules on the trunk and extremities. He had normal cardiovascular examination and no hepatosplenomegaly or palpable abdominal masses.

Initial blood count showed a hemoglobin of 108 g/L, a white blood cell count of 19.1 x 10^9/L with 70% polymorphonuclear cells and a platelet count of 315 x 10^9/L. The erythrocyte sedimentation rate (ESR) was 82 mm/h; C-creative protein was positive; and the cerebrospinal fluid examination was normal. Bacterial cultures of the throat, blood, cerebrospinal fluid, and urine were negative. Urinalysis showed 20 white blood cells per high power field and mild proteinuria. Results of the

From the Department of Pediatrics, College of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. AlEissa: Department of Pediatrics (39), College of Medicine, King Saud University, Riyadh 11461, Saudi Arabia.
following laboratory investigations were normal or negative: sickling test, monospot test, entero-viral serology, antistreptolysin O (ASO) titer, rheumatoid factor, antinuclear antibody (ANA), serum total protein, serum immunoglobulins, serum glutamic-oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH) and creatine phosphokinase (CPK), typhoid, paratyphoid, and Brucella titer. Electrocardiography (ECG) and chest roentgenogram were normal as well as the abdominal ultrasound of the gallbladder.

The diagnosis of Kawasaki syndrome was suspected on admission and the child was started on oral aspirin, 100 mg/kg/day. The child's fever continued with a temperature ranging from 38.5 to 40 DC. On day 14 of the illness, fever, rash, and lymphadenopathy subsided but irritability, anorexia, swelling, and erythema of the hands and feet persisted over the next few days. An apical holosystolic murmur was discovered on auscultation of the heart on day 16 of the illness. Two-dimensional echo cardiogram and Doppler examination demonstrated mild dilatation of the proximal right main coronary artery and mild mitral regurgitation. On day 18 of the illness, the characteristic skin desquamation and peeling at digit tips and along the sides of the nails became apparent. Repeat complete blood counts demonstrated a gradual rise in platelet count up to 760 X 10^9/L and a fall in ESR to 52 mm/h, 2 weeks after admission. The child was discharged on aspirin 5 mg/kg/day, 21/2 weeks after admission. He developed bilateral nonpurulent conjunctivitis two weeks after discharge, although the slit lamp examination was normal. Follow-up two-dimensional echocardiograms and Doppler examinations showed normal coronary arteries, but persistent mitral regurgitation, 4 weeks after the first examination. The child remained asymptomatic during the first 12 months of close follow-up, but the mitral regurgitation persisted.

Discussion

Kawasaki syndrome or mucocutaneous lymph node syndrome (MCLS) is an acute febrile exanthematous illness of children which was first recognized as a clinical entity in Japan by Kawasaki in 1967 and reported in the English literature in 1974. Since that time, there has been an explosion of interest in this syndrome and a profusion of case reports in patients of all major racial groups from all continents. Local geographic and temporal clustering of cases has been reported frequently. However, Japan and Hawaii currently have the highest prevalence. To the best of our knowledge, this is the first case report of Kawasaki syndrome in a Saudi child although three cases were reported in Arab children, of whom one was an Egyptian boy living in Saudi Arabia.

Kawasaki syndrome is a syndrome of unknown etiology and pathogenesis affecting most frequently infants and young children under five years of age. The peak age incidence is approximately 12 months of age with almost equal distribution in the first 2 years of life followed by a steady decline to the age of 8 years. It is more common in boys than in girls, with an approximate male-to-female ratio of 1.5:1. Epidemiological studies suggest an infectious etiology or an immunologically mediated reaction to an infectious agent. Various bacterial, viral, rickettsial, and leptospiral microorganisms, dust mites, and environmental pollutants or toxins have been studied extensively, but to date, none of these agents has been confirmed as the causative agent. Immunoregulatory abnormalities, including the presence of circulating immune complexes or cellular and/or humoral mediated immunological injury, have been reported.

Kawasaki syndrome is typically a severe self-limited illness with a severity from that which barely meets the clinical criteria to a rapidly fatal multi-system disease. The recognition of the syndrome is based upon strict diagnostic clinical criteria set forth by the Japan Mucocutaneous Lymph Node Syndrome (MCLS) Research Committee. The criteria consist of the following six principal clinical features: (1) fever persisting for five days or more; (2) bilateral and nonexudative conjunctival congestion; (3) changes of lips and oral cavity, including redness, dryness, and fissuring of lips, strawberry tongue, and diffuse injection of oropharyngeal mucosa; (4) changes of peripheral extremities, including initial reddening and indurative edema of the hands and feet; later, there is membranous periungual desquamation; (5) polymorphous exanthem; and (6) acute nonsuppurative swelling of cervical lymph nodes of 1.5 cm or more in diameter. Five of these six principal
criteria, or more appropriately, prolonged fever and four of the remaining five criteria must be met for the diagnosis to be made. However, atypical cases that do not fulfill the diagnostic criteria but include the presence of coronary artery aneurysms have been recently reported.29-31 In addition to the six principal criteria, other associated features encountered are extreme irritability, anorexia, emotionallability, lethargy, arthralgia, arthritis, aseptic meningitis, urethritis, diarrhea, abdominal pain, hepatitis, hydrops of gallbladder, carditis, and vasculitis.2,3,14 During the evolution of the illness, our patient met all clinical criteria for Kawasaki syndrome except bilateral conjunctivitis, which he developed later during the convalescent phase. He also had some of the above mentioned associated features.

The major causes of morbidity and mortality in Kawasaki syndrome are the cardiovascular manifestations which include myocarditis, pericarditis or pericardial effusion, arrhythmia, congestive heart failure, mitral regurgitation, coronary dilatation, or aneurysm, and thrombotic occlusion with occasional myocardial infarction.15,16,20,32 Acute mitral regurgitation, as found in our patient, has been reported to be secondary to valvulitis or papillary muscle dysfunction caused by myocarditis or ischemia. 32,33 In most patients, this eventually disappears after a few months to several years. However, in others, valve fibrosis or papillary muscle dysfunction leads to persistent valve dysfunction, and in such instances valve replacement has been required. 33 Coronary artery dilation has been found in more than 50% of the patients. 32 These lesions are transient and regress within 3 to 5 weeks of illness,32 as it happened in our patient. The most important cardiovascular lesion in Kawasaki syndrome is coronary aneurysm which develops in about 20% of all patients.15,32 More than 50% of the patients will show resolution of aneurysms within 6 to 24 months after the acute illness,34 but in others there may be possible consequence of myocardial ischemia with infarction.16,34 The mechanism of aneurysm is unknown, but most likely it represents a combination of internal proliferation, thrombosis, and recanalization.34,35 In early 1970s, the mortality rate was approximately 2%.2,3; however, recent data suggest that it is now about 0.3% and usually is related to cardiac disease.32 Aneurysms in other systemic arteries, particularly axillary, iliac, or renal, have been observed in about 2% of patients. 20,32

There are no diagnostic laboratory tests for Kawasaki syndrome. The laboratory abnormalities which are nonspecific but are consistently found in patients with this disease include: a high leukocyte count with leftward shift; elevated levels of acute-phase reactants as measured by ESR; C-reactive protein and serum alpha2-globulin; mild anemia; thrombocytosis peaking at levels of 600 to 1900 X 109/L during the second phase; mild proteinuria; and pyuria.14,20 Similar laboratory findings were seen in our patient. In addition, slightly elevated levels of serum transaminases, bilirubin, and mild cerebrospinal fluid pleocytosis of mononuclear cells are occasionally observed.14,20 Minor transient electrocardiographic abnormalities consisting of prolonged P-R and QTc intervals, abnormal Q wave, ST segment and T wave changes, and arrhythmias have been reported.14,20,32,34 Angiography, an invasive procedure, is the most reliable method for the visualization of the entire coronary system and the evaluation of left ventricular function.34,36 With the widespread availability of two-dimensional echocardiography, it has become the most useful noninvasive technique to detect and follow coronary artery lesions, pericardial effusion, and left ventricular dysfunction.32 Although the proximal portions of the coronary arteries are better imaged than the distal portions, aneurysms most often arise proximally. 20,32 In the experienced hands, echocardiography can accurately demonstrate more than 90% of coronary aneurysms detected by angiography. 34,37 Evolution of cardiac lesions is then followed serially through the acute and convalescent phases.

The clinical manifestations evolve over a period of time; thus, all of the clinical symptoms and signs are not apparent simultaneously. The course of the disease was best described by Melish20 as a triphasic illness. The initial or acute febrile phase starts with a fever followed within a few days by most of the principal diagnostic criteria: mouth changes, rash, swelling and erythema of the hands and feet, conjunctival injection, and lymphadenopathy. The fever is generally spiking and unresponsive to antibiotic therapy. The child usually appears toxic and may show the associated
features of the syndrome. By the end of the acute phase, which lasts 7 to 14 days, the fever, rash, and lymphadenopathy have resolved. The second or subacute phase usually occurs between the 10th and 25th day of the illness. Anorexia, irritability, and conjunctival injection persist with slow improvement in the child's status and attitude. Desquamation of the skin on hands and feet, especially on the tips of the fingers and toes, becomes prominent. It is during this phase that the diagnosis of Kawasaki disease is most commonly made. Arthralgia or arthritis, cardiac abnormalities, and thrombocytosis occur during this phase. The third or convalescent phase lasts, from the time of disappearance of all signs of illness until the sedimentation rate has returned to normal, usually 6 to 8 weeks from onset. Our patient had typically followed this stereotyped and predictable clinical course.

Other diseases that might mimic Kawasaki syndrome and must be excluded are scarlet fever, Steven-Johnson syndrome, measles, roseola, enteroviral infections, leptospirosis, infectious mononucleosis, juvenile rheumatoid arthritis, and adverse drug reactions.2,3

Due to the absence of a definite etiology and pathogenesis of the syndrome, there is no rational treatment available at present. However, current therapeutic regimens are aimed at reducing the vascular inflammation during the acute phase and preventing thrombosis during the subacute and convalescent phases. Although aspirin administration is the most frequently used supportive therapy, there is no unanimity on the optimal dosage schedule. During the acute phase, an aspirin dosage of 30 mg/kg/day is recommended in Japan32,36; in contrast, a higher dosage of 80 to 100 mg/kg/day is frequently used in the United States.20 The dosage of aspirin is then decreased to 3 to 5 mg/kg/day and continued for 2 months or as long as coronary aneurysm persists, in order to inhibit platelet aggregation and thrombus formation.32 In children with giant aneurysms or with clinical evidence of myocardial infarction, a single antithrombotic drug may be insufficient; and combinations of aspirin with other drugs such as dipyridamole are warranted because of the poor outcome.32 Steroid therapy should be avoided since the results of Japanese studies have indicated that such therapy increases the probability of aneurysm formation.36 Recent studies in Japan and the United States demonstrate that high-dose IVGG therapy (400 mg/kg/day for 4 to 5 consecutive days), when administered in conjunction with aspirin early in the course of Kawasaki syndrome, is effective in reducing the prevalence of coronary artery abnormalities.17,18 Children treated with IVGG plus aspirin were one third as likely to develop coronary abnormalities as those treated with aspirin alone. If IVGG therapy is to be instituted, it should be given early, probably between the sixth and tenth day of the illness. Furthermore, IVGG has been reported to provide an anti-inflammatory effect, suggested by the significant reduction of fever and laboratory-measured levels of acute-phase reactants.18 The mechanism by which IVGG ameliorated the vasculitis of Kawasaki syndrome is not clear. A number of possibilities were suggested, including blockade of the immunological activation of the inflammatory response directed to vascular surfaces, saturation of Fc receptors on platelets or reticuloendothelial cells, or provision of a specific antibody to neutralize an unidentified etiologic agent of Kawasaki syndrome.17,18 Because of the high cost of IVGG therapy, this form of therapy should be selectively given to patients at high risk of developing coronary lesions. A number of risk factors were found to be associated with increased likelihood of coronary aneurysms; these include a male infant younger than 1 year of age; prolonged fever lasting more than 2 weeks; elevated platelet count; elevated acute-phase reactants; and palpable axillary arterial aneurysms.38-40

This case is instructive in two ways. Firstly, it reveals the difficulty in reaching a diagnosis of Kawasaki syndrome in a country where it is unknown. Secondly, Kawasaki syndrome should be entertained as a diagnostic possibility in a young child with persistent fever beyond the usual short duration expected for most viral illnesses.

References

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