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Kawasaki Disease

Kawasaki disease (KD), formerly known as **mucocutaneous lymph node syndrome** and **infantile polyarteritis nodosa,** is an acute febrile vasculitis of childhood first described by Dr. Tomisaku Kawasaki in Japan in 1967. The disorder occurs worldwide, with Asians at highest risk. Approximately 20% of untreated patients develop coronary artery abnormalities including aneurysms, with the potential for severely affected patients to develop coronary artery thrombosis or stenosis, myocardial infarction, aneurysm rupture, and sudden death. Kawasaki disease is the leading cause of acquired heart disease in children in the United States and Japan.

ETIOLOGY.

The cause of the illness remains unknown, but epidemiologic and clinical features strongly support an infectious origin. These features include the young age group affected, epidemics with wavelike geographic spread of illness, the self-limited nature of the acute febrile illness, and the combination of clinical features of fever, rash, enanthem, conjunctival injection, and cervical lymphadenopathy. Nonetheless, it is unusual to have multiple cases present at the same time from a family or day care center. One hypothesis is that a ubiquitous childhood infectious agent causes Kawasaki disease and that symptomatic illness occurs only in genetically predisposed persons. The infrequent occurrence of the illness in infants <3 mo may be the result of maternal antibody, and the virtual absence of cases in adults may be due to widespread immunity. A KD-associated antigen may be present in cytoplasmic inclusion bodies within ciliated bronchial epithelial cells of acute fatal cases. These inclusions appear consistent with viral protein aggregates, and support the hypothesis of a respiratory portal of entry of the KD agent. Kawasaki disease has recurred in families when previously affected parents have children who develop the disease. Genetic variation of *CCR5,* which encodes a high-affinity receptor for the chemokines CCL3 and CCL3L1, suggests an influential role of gene-gene interactions for susceptibility to Kawasaki disease.

EPIDEMIOLOGY.

An estimated 3,000 cases are diagnosed annually in the United States. The incidence of Kawasaki disease in Asian children is substantially higher than in other racial groups, but the illness occurs worldwide in all ethnic groups. Most cases in the United States occur in white and black children. In Japan, almost 200,000 cases have been reported since the 1960s. Kawasaki disease is not a new illness; infantile periarteritis nodosa was an autopsy diagnosis before the 1960s . The disorder bears marked clinical similarities to measles and may have been particularly difficult to identify clinically before widespread immunization with measles vaccine. The illness occurs predominantly in young children; 80% of patients are <5 yr, and, only occasionally, are teenagers or, more rarely, adults affected. More often, affected adolescents or adults may actually meet the criteria for toxic shock syndrome, which has some similar features to Kawasaki disease.

PATHOGENESIS.

Kawasaki disease causes severe vasculitis of all blood vessels but predominantly affects the medium-sized arteries, with a striking predilection for the coronary arteries. Pathologic examination of fatal cases in the acute or subacute stages reveals edema of endothelial and smooth muscle cells with intense inflammatory infiltration of the vascular wall, initially by polymorphonuclear cells but rapidly followed by macrophages, lymphocytes (primarily CD8 T cells), and plasma cells. IgA plasma cells are particularly prominent in the inflammatory infiltrate. In the most severely affected vessels, inflammation involves all three layers of the vascular wall with destruction of the internal elastic lamina. The vessel loses its structural integrity and weakens, resulting in dilatation, or saccular or fusiform aneurysm formation. Thrombi may form in the lumen and obstruct blood flow. In the healing phase, the vascular wall can become progressively fibrotic with marked intimal proliferation, which may lead to stenotic occlusion of the vessel over time.

In acute Kawasaki disease, an inflammatory infiltrate, including IgA plasma cells, is present in certain nonvascular tissues including myocardium, upper respiratory tract, pancreas, kidney, and biliary tract, suggesting that the infectious agent may cause a host immune response in a variety of tissues. No significant sequelae appear to occur in any of these nonvascular tissues after resolution of the acute illness.

Elevated serum levels of all immunoglobulins develop during the subacute phase of illness, suggesting that a vigorous antibody response

occurs. It is unclear whether the etiologic agent, the host immune response, or both are the major causal factors leading to coronary artery disease.

CLINICAL MANIFESTATIONS.

Fever is characteristically high (104°F or higher), remittent, and unresponsive to antibiotics. The duration of fever without treatment is generally 1–2 wk, but it may persist for 3–4 wk. Prolonged fever is prognostic for the development of coronary artery disease. In addition to fever, the **five characteristic features** of Kawasaki disease are: bilateral bulbar conjunctival injection, usually without exudate; erythema of the oral and pharyngeal mucosa with strawberry tongue and dry, cracked lips, and without ulceration; edema and erythema of the hands and feet; rash of various forms (maculopapular, erythema multiforme, or scarlatiniform) with accentuation in the groin area; and nonsuppurative cervical lymphadenopathy, usually unilateral, with node size of ≥1.5 cm. Perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 1–3 wk after the onset of illness and may progress to involve the entire hand and foot.

Other features include **extreme irritability** that is especially prominent in infants, aseptic meningitis, diarrhea, mild hepatitis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, otitis media, and arthritis. Arthritis may occur early in the illness or may develop in the 2nd–3rd week, generally affecting hands, knees, ankles, or hips. It is self-limited but may persist for several weeks.

Cardiac involvement is the most important manifestation of Kawasaki disease. Myocarditis, manifested as tachycardia out of proportion to fever occurs in at least 50% of patients; decreased ventricular function occurs in a smaller number of patients. Pericarditis with a small pericardial effusion is common during the acute illness. Coronary artery aneurysms develop in up to 25% of untreated patients in the 2nd–3rd wk of illness and are best detected by two-dimensional echocardiography. **Giant coronary artery aneurysms** (≥8 mm internal diameter) pose the greatest risk for rupture, thrombosis or stenosis, and m yocardial infarction. Significant valvular regurgitation and systemic artery aneurysms may occur but are uncommon. Axillary, popliteal, or other arteries may also be involved and manifest as a localized pulsating mass.

Kawasaki disease is generally divided into three clinical phases.

- **acute febrile phase,** which usually lasts 1–2 wk, is characterized by fever and the other acute signs of illness. The dominant cardiac manifestation is myocarditis. In addition, a macrophage activation syndrome may rarely be evident.
- **subacute phase** begins when fever and other acute signs have abated, but irritability, anorexia, and conjunctival injection may persist. The subacute phase is associated with desquamation, thrombocytosis, the development of coronary aneurysms, and the highest risk of sudden death in those who have developed aneurysms. This phase generally lasts until about the 4th wk.
- **convalescent phase** begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) return to normal, ≈6–8 wk after the onset of illness.

Certain clinical and laboratory findings may predict a more severe outcome. These include male gender, age <1 yr, prolonged fever, recrudescence of fever after an afebrile period, and the following laboratory values at presentation: low hemoglobin or platelet levels, high neutrophil and band counts, hyponatremia, and low albumin and age-adjusted serum IgG levels.

DIAGNOSIS.

The diagnosis of Kawasaki disease is based on the presence of characteristic clinical signs. For **classic Kawasaki disease,** the diagnostic criteria require the presence of fever for at least 5 days and at least four of five of the other characteristic clinical features of illness.

In **atypical or incomplete Kawasaki disease,** the patient has persistent fever but with fewer than four other features of the illness. Accurate identification of incomplete cases is a major clinical challenge. Incomplete cases are most frequent in infants, who, unfortunately, also have the highest likelihood of developing coronary artery disease.

Recognition depends on a high index of suspicion and knowledge of the characteristic clinical features. Unfortunately, if the diagnosis is not established and treatment is not instituted, rare patients may suffer sudden death secondary to myocardial infarction or coronary aneurysm rupture, or may develop serious asymptomatic coronary disease that is

unrecognized until symptoms of myocardial ischemia develop later in life.

DIFFERENTIAL DIAGNOSIS.

The differential diagnosis of Kawasaki disease includes

- scarlet fever.
- toxic shock syndrome.
- Measles.
- adenovirus infection.
- drug hypersensitivity reactions including Stevens-Johnson syndrome.
- juvenile rheumatoid arthritis
- Rocky Mountain spotted fever and leptospirosis.

LABORATORY FINDINGS.

There is no diagnostic test for Kawasaki disease, but certain laboratory findings are characteristic.

- The leukocyte count is normal to elevated with a predominance of neutrophils and immature forms.
- Elevated ESR, CRP, and other acute phase reactants are almost universally present in the acute phase of illness and may persist for 4–6 wk.
- Normocytic, normochromic anemia is common.
- The platelet count is generally normal in the 1st week of illness and rapidly increases by the 2nd–3rd wk of illness, sometimes exceeding 1,000,000/mm^3.
- Tests for antinuclear antibody and rheumatoid factor are negative.
- Sterile pyuria, mild elevations of the hepatic transaminases, and cerebrospinal fluid pleocytosis may be present.
- Two-dimensional echocardiography, which should be performed by a pediatric cardiologist, is the most useful test to monitor potential development of coronary artery abnormalities. Echocardiography should be performed at diagnosis and again after 2–3 wk of illness. If both are normal, a repeat study should be performed 6–8 wk after onset of illness. If coronary abnormalities are not detected by 6–8 wk after onset of illness, and after the ESR has normalized, additional follow-up studies are optional. Some centers routinely perform echocardiography again 6 or 12 mo after onset of illness.

Kawasaki disease is an acute vasculitis; there is no convincing evidence of long-term cardiovascular sequelae in children who do not develop coronary abnormalities within 2 mo after the onset of illness.

For patients who develop coronary artery abnormalities, more frequent echocardiographic studies and, potentially, angiography may be indicated.

TREATMENT.

Patients with acute Kawasaki disease should be treated with intravenous immunoglobulin (IVIG) and high-dose aspirin as soon as possible after diagnosis and, ideally, within 10 days of disease onset .

The mechanism of action of IVIG in Kawasaki disease is unknown, but treatment should result in rapid defervescence and resolution of clinical signs of illness in 85–90% of patients. With therapy, the CRP normalizes much more quickly than the ESR, which will often increase immediately after IVIG therapy. IVIG reduces the prevalence of coronary disease from 20–25% in children treated with aspirin alone to 2–4% in those treated with IVIG and aspirin within the 1st 10 days of illness. Consideration should even be given to treatment of patients diagnosed after the 10th illness day if fever has persisted, because the anti-inflammatory effect may be helpful, although the effect of such therapy on the risk of developing coronary aneurysms is unknown. The dose of aspirin is decreased from anti-inflammatory to antithrombotic doses (3–5 mg/kg/day as a single dose) on the 14th illness day or after the patient has been afebrile for at least 3–4 days. Aspirin is continued for its antithrombotic effect until 6–8 wk after onset, when the ESR has normalized in patients that have not developed abnormalities detected by echocardiography.

Treatment of Kawasaki Disease

ACUTE STAGE
Intravenous immunoglobulin 2 g/kg over 10–12 hr *with* aspirin 80–100 mg/kg/day divided every 6 hr orally until 14th illness day
CONVALESCENT STAGE
Aspirin 3–5 mg/kg once daily orally until 6–8 wk after illness onset
LONG-TERM THERAPY FOR THOSE WITH CORONARY ABNORMALITIES

Aspirin 3–5 mg/kg once daily orally ± clopidogrel 1 mg/kg/day (max 75 mg/day) (most experts add warfarin for those patients at particularly high risk of thrombosis)
ACUTE CORONARY THROMBOSIS
Prompt fibrinolytic therapy with tissue plasminogen activator, streptokinase, or urokinase under supervision of a pediatric cardiologist

Occasional patients have **refractory Kawasaki disease** that does not respond to an initial IVIG infusion, or exhibits only a partial or transient response. Strong consideration should be given to retreatment of these patients with an additional infusion of IVIG (2 g/kg). Optimal therapy for patients who do not respond to two infusions of IVIG is uncertain.

If there is a poor response to the second dose of IVIG, some patients have responded to IV methylprednisolone at a dose of 30 mg/kg/day for 3 days. The value of infliximab (which binds TNF-α), other immunomodulators (cyclophosphamide, methotrexate), and plasmapheresis in Kawasaki disease is yet to be determined.

Acute thrombosis may occasionally occur in an aneurysmal or stenotic coronary artery. Thrombolytic therapy may be lifesaving in this circumstance .Abciximab, a glycoprotein IIb/IIIa inhibitor, has been used in some patients with Kawasaki disease who develop giant coronary aneurysms with possible thrombosis.. Long-term follow-up of patients with coronary artery aneurysms should include periodic echocardiography with stress testing, and possibly angiography for those with larger aneurysms. Catheter intervention with percutaneous transluminal coronary rotational ablation, directional coronary atherectomy, and stent implantation have all been used for the management of coronary stenosis caused by Kawasaki disease, with some patients requiring coronary artery bypass grafting.

Patients receiving long-term aspirin therapy are candidates for annual influenza vaccination to reduce the risk of Reye syndrome. Varicella vaccination should be strongly considered, since the risk of Reye syndrome in children who take salicylates and who receive varicella vaccine is likely to be lower than with wild-type varicella.

Patients treated with 2 g/kg IVIG should have measles-mumps-rubella and varicella vaccinations delayed for 11 mo because the specific antiviral antibody in IVIG may interfere with the immune response to live-virus vaccines. Other vaccinations do not need to be delayed.

COMPLICATIONS AND PROGNOSIS.

Recovery is complete and without apparent long-term effects for patients who do not develop coronary disease. Recurrent acute illness occurs in only 1–3% of cases. The prognosis for patients with coronary abnormalities depends on the severity of coronary disease. In Japan, fatality rates are very low, about 0.01%. Overall, 50% of coronary artery aneurysms resolve as assessed by echocardiogram 1–2 yr after the illness.