Kawasaki Disease

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Key Points

• Kawasaki disease is an acute systemic vasculitis syndrome in infants and young children of unknown etiology, which mainly affects small and medium-sized arteries, particularly the coronary artery.

• Clinical features include an acute febrile illness associated with mucocutaneous involvements and lymphadenopathy.

• The coronary aneurysms develop in about 10% to 20% of patients, some of which may cause myocardial infarction or lead to ischemic heart disease.

• Combinations of high-dose gamma globulin and aspirin are the essential treatments for acute Kawasaki disease patients.

• Bypass surgery and the catheter intervention are the optional treatments for the coronary artery sequelae of Kawasaki disease.

• Some patients with coronary artery sequelae may develop into adult coronary artery disease.

Kawasaki disease (KD) is an acute vasculitis syndrome in infants and young children of unknown etiology, which mainly affects small and medium-sized arteries, particularly the coronary artery. The clinical feature is an acute febrile illness associated with mucocutaneous involvement and lymphadenopathy. Coronary aneurysms develop in about 10% to 20% of patients, some of which may cause myocardial infarction or ischemic heart disease in children and young adults. High-dose gamma globulin and aspirin are the essential treatments for acute Kawasaki disease in patients.

Background and History

Kawasaki disease (KD) or mucocutaneous lymph node syndrome (MCLS) is an acute arteritis of small and medium-sized arteries, particularly coronary arteries.¹ The cardiovascular problems in KD include coronary artery lesions that develop aneurysm formation, thrombotic occlusion, progression to coronary artery disease, and premature atherosclerosis.² These problems may cause myocardial infarction or sudden death in the young. The disease was first described by Dr. Tomisaku Kawasaki³ in Japan, and he recognized the first case in 1961. At that time, this disease was thought to be benign and the prognosis good because all acute symptoms disappeared within 2 or 3 weeks, and the patient was usually doing well. Yamamoto and Kimura⁴ reported a case complicated with myocarditis; however, the presence of coronary artery involvement was not identified. In 1970, the first nationwide survey in Japan showed that 1.7% of the patients died from acute myocardial infarction; autopsies showed coronary arteritis accompanied by aneurysms and thrombotic occlusions. At that time, most pediatricians believed that Kawasaki disease was complicated with vasculitis only in small numbers of fatal cases, because of the great contrast in prognosis between these rare fatal cases and the large number of nonfatal cases that were asymptomatic.

In 1973, Kato et al.⁵ performed the coronary angiography in 20 infants and children when their acute symptoms had remitted. Twelve of these patients showed multiple coronary aneurysms in both the right and left coronary arteries, which was the first recognition that coronary artery aneurysms are present not only in fatal cases but also in survivors, even if the patient is free from cardiac symptoms. From pathologic studies and the coronary angiographic findings, KD is now recognized to be a systemic arteritis syndrome in small and medium-sized arteries in infants and young children.

In the past, KD may have been misdiagnosed as another disease, such as scarlet fever, measles, rheumatic fever, juvenile rheumatoid arthritis, Stevens-Johnson syndrome, and infantile polyarteritis, which are now listed in the differential diagnosis of KD.⁶ Landing and Larson⁷ reported that pathologic findings are identical between fatal KD and infantile polyarteritis, which was described only by autopsy cases. It is now believed that KD and infantile polyarteritis are both a systemic arteritis syndrome in infants and young children.

Reference

¹ Kawasaki T. Mucocutaneous lymph node syndrome. Japan J Pediatr 1967;19:139-142.
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³ Kawasaki T. Aseptic necrosis of the knees in children. Jpn J Pediatr 1961;14:907-913.
⁴ Yamamoto H, Kimura T. Mucocutaneous lymph node syndrome associated with myocarditis. J Pediatr 1968;73:582-587.
⁵ Kato H, Tsuda M, et al. Coronary aneurysms in Kawasaki disease. Lancet 1973;2:772-775.
⁶ Landing GL, Larson DL. Pathologic findings in Kawasaki disease. J Pediatr 1973;82:309-312.
⁷ Kato H, Tanabe H, et al. Kawasaki disease: a clinical and coronary angiographic study of 100 cases. Pediatrics 1981;68:1027-1032.
children with a wide spectrum of clinical symptoms and disease severity.

**Epidemiology**

Epidemiology in Japan where KD is most prevalent has been well documented by the research committee organized by the Health and Welfare Department of the Japanese government. A summary of the epidemiologic picture is as follows: Kawasaki disease has increased in incidence since 1968, and the number of patients affected is now more than 190,000. Kawasaki disease affects over 6000 children each year in Japan, and the incidence is increasing by year to 150 per 100,000 children under 4 years of age. The age affected starts at 1 month of age and peaks at 1 year of age. Fifty percent of cases are under 2 years of age. Cases over 10 years of age are quite rare. Boys are affected more than girls (1.5:1). It is evident that KD is more prevalent in the Japanese and in Orientals than in Caucasians. There are no geographical differences in urban or rural areas, and there is wide prevalence throughout all regions of Japan. Seasonal variation is not distinct; however, there are small peaks in winter and spring. The recurrence rate is about 3.3%, and sibling cases are only 1% to 2%. Time-space clustering or outbreaks in communities are recognized; however, there is no evidence of person-to-person transmission. In 1979, 1982, and 1986, there were large outbreaks in Japan, but in the past 10 years, there have not been similar occurrences.

The global epidemiology of KD was described by Nakamura and Yanagawa, and accordingly, KD is now widely recognized all over the world. However, it is primarily identified in Japan and East Asia. In the United States, the incidence has been estimated from hospital discharge data, which showed that 4248 patients with KD were hospitalized in the year 2000. The incidence is most common in Asian and Pacific Island descendants (32.5/100,000 children less than 5 years of age), in non-Hispanic African Americans (16.9), and in Hispanics (11.1), and lowest in whites (9.1).

The fatality rate was 2% in the 1970s and declined to 0.1% in the 1990s in Japan. In the U.S., the in-hospital mortality rate is 0.17% during which the peak mortality occurs 15 to 45 days after the onset of illness.

**Pathology**

Based on Hamashima’s analyses of 37 KD autopsy cases, the Japanese Kawasaki Disease Research Committee (1980) reported the following pathomorphologic findings.

Kawasaki disease is an acute inflammatory disease with systemic arteritis that is distinguishable from classic periarteritis nodosa of Kussmaul-Maier type, which is a progressive and recurrent arteritis with marked fibrinoid necrosis, but with rare pulmonary vasculitis. Kawasaki disease is an acute, self-limited inflammatory disease with rare and mild fibrinoid necrosis. Infantile polyarteritis resembles KD in many pathologic aspects, but further studies are needed. Coronary artery aneurysms are usually present at autopsy.

With KD, the arteritis is characterized by an acute inflammation lasting about 7 weeks. The course of arteritis is classified into four stages according to the duration of illness, as follows: Stage 1 (1 to 2 weeks of illness): perivascularitis and arteritis of the microvessels, small arteries, and veins; inflammation of intima, externa, and perivascular areas in the midsized and large arteries; edema and inflammation with leukocytes and lymphocytes. Stage 2 (3 to 4 weeks of illness): inflammatory changes of intima, media, externa, and perivascular areas in the midsized arteries with focal panvasculitis; aneurysms with thrombi and stenosis in the midsized arteries, especially in the coronary arteries; edema [exudative stage], infiltration with monocytes or necrosis [infiltrative stage] and cellular granulation with increase of capillaries. Stage 3 (5 to 7 weeks of illness): granulation in the midsized arteries. Stage 4 (more than 7 weeks of illness): scar formation and intimal thickening with aneurysm, thrombi, and stenosis in the midsized arteries [generally no acute inflammation in the vessels]. These findings may persist until adulthood.

Myocarditis [interstitial myocarditis with mild necrosis] involves the patient’s conduction systems. Myocardial biopsy demonstrated that 80% of the patients studied had myocarditis, with or without coronary artery lesions. At autopsy, pericarditis, endocarditis, cholecystitis, cholangitis, pancreatic ductitis, sialoadenitis, meningitis, and lymph adenitis are frequently seen.

**Pathogenesis and Etiology**

The etiology of KD remains unknown despite extensive investigations. Based on clinical features and epidemiologic data, KD is now considered to be an infectious etiology of unknown agent(s) or an infection-triggered immune disorder. A variety of possible causative agents, such as bacteria, leptospires, fungi, mycoplasma, rickettsiae, and viruses, have been proposed.

Kawasaki disease has clinical similarities to those of scarlet fever or toxic shock syndrome, both of which are caused by toxin-producing bacteria. These toxins are revealed to be superantigens capable of stimulating T cells carrying particular variable regions of the T-cell receptor β chain. A study of peripheral blood T cells in KD patients showed that T cells expressing T-cell receptor variable regions Vβ2 and Vβ8 were selectively expanded. These observations suggest that KD may be caused by a toxin [superantigen]-producing microorganism, including possibly a virus. Leung et al. suggested that the expansion of Vβ2+T cells in most patients with KD may be caused by a new clone of toxic shock syndrome toxin-secretin *Staphylococcus aureus* or SPEB [streptococcal pyogenic exotoxin-B]- or SPEC [streptococcal pyogenic exotoxin-C]-producing group A streptococci from studies on bacterial culture from patients with KD. However, other studies did not support this theory. Yoshikawa et al. reported that SPEC induces activation and polyclonal expansion of Vβ2- and Vβ6.5-positive T cells, and that SPEC-induced activation of T cells may lead to the pathogenesis of KD.

*Yersinia pseudotuberculosis* appears to be one of the etiologic agents of KD, although only a small group of KD patients can be explained by this organism. *Propionibacterium acnes* was isolated from cervical lymph nodes of the patients, which produced the cytotoxic protein–like bacterial exotoxin, but its etiologic role remains to be determined.
Epstein-Barr virus (EBV) occasionally induced clinical pictures mimicking those of KD, and three of 37 patients with chronic active EBV infection developed coronary lesions. However, epidemiologic, serologic, and virologic studies do not support that EBV is a causative agent of KD. Rowley et al. reported that immunoglobulin A (IgA) plasma cells infiltrate the vascular wall as well as other tissues, such as the myocardium, respiratory tract, kidney, and pancreas in acute KD. They suggest a mucosal portal of entry of a conventional antigen; however, no specific microbe has been proposed as the etiologic agent. Recently, a possible association between novel human Corona virus (HCoV-NH) and KD was reported; however, further studies are necessary.

Acute phase of KD is associated with markedly increased production of inflammatory cytokines. Tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (IF-γ) induce activation antigens and adhesion molecules, such as endothelial leukocyte adhesion molecule-1 and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, and TNF-α and IF-γ cause endothelial injury in vitro studies.

Leung and associates have proposed a hypothesis that antiendothelial antibodies cause endothelial injury in KD patients, based on the findings that circulating autoantibodies in KD were cytotoxic against human umbilical vein endothelial cells treated with TNF-α, IL-1β, or IF-γ. Coro-

Clinical Presentations

Symptoms and Diagnosis of Kawasaki Disease

The diagnosis of KD is made according to the diagnostic guidelines prepared by the Japanese Kawasaki Disease Research Committee listed in Table 41.1 because of the absence of a specific laboratory test. The principal diagnostic pictures mimicking those of KD, and three of 37 patients with chronic active EBV infection developed coronary lesions. However, epidemiologic, serologic, and virologic studies do not support that EBV is a causative agent of KD. Rowley et al. reported that immunoglobulin A (IgA) plasma cells infiltrate the vascular wall as well as other tissues, such as the myocardium, respiratory tract, kidney, and pancreas in acute KD. They suggest a mucosal portal of entry of a conventional antigen; however, no specific microbe has been proposed as the etiologic agent. Recently, a possible association between novel human Corona virus (HCoV-NH) and KD was reported; however, further studies are necessary.

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Clinical Presentations

Symptoms and Diagnosis of Kawasaki Disease

The diagnosis of KD is made according to the diagnostic guidelines prepared by the Japanese Kawasaki Disease Research Committee listed in Table 41.1 because of the absence of a specific laboratory test. The principal diagnostic
criteria of KD are persistent fever, conjunctival injection, changes in the mucosa of the oropharynx, changes in the peripheral extremities, erythematous rash, and cervical lymphadenopathy. At least five of six principal symptoms should be present for a presumptive diagnosis of KD. However, some patients do not fulfill the classic criteria (Table 41.1), and their diagnosis has been called incomplete KD. Patients with incomplete KD have fewer than four of the six principal symptoms. Fever duration may be shorter than 5 days, particularly in those treated by gamma globulin within 5 febrile days. However, patients with four of these symptoms can be diagnosed when a coronary artery abnormality is recognized by two-dimensional (2D) echocardiographic findings, or other imaging procedures, including dilatation or nonuniformity of arterial lumen and increased brightness of the arterial wall (Fig. 41.1). Incomplete KD is recognized in about 10% of all KD patients whereas they have higher incidence of coronary artery aneurysms (25%). Infants less than 6 months of age and children over 7 years of age demonstrate atypical symptoms in some instances. Incomplete KD should be considered in children with unexplained fever for more than 4 days with three or other principal symptoms. High C-reactive protein (CRP) (more than 3 mg/dL), elevated erythrocyte sedimentation rate (ESR) (more than 40 mm/h), thrombocytosis (more than 400,000/mm$^3$), white blood cell count (more than 15,000), and erythema and induration at the site of previous vaccination of bacille Calmette-Guérin (BCG) are helpful findings in diagnosing incomplete KD. In children over 7 years of age, high fever and neck lymphadenopathy are initial symptoms that occur several days after onset. Other significant symptoms and laboratory findings are listed in Table 41.1.

**Cardiovascular Spectrum**

The cardiovascular spectrum of 2180 patients with acute KD found in the past 31 years in the Kurume University Hospital in Kurume, Japan, is shown in Table 41.2. Among all patients, 14.9% were diagnosed as having coronary artery aneurysms. Beginning in 1992 we selected these patients for gamma globulin treatment, since then, the incidence of coronary artery aneurysms has declined to 8.7%. Coronary artery lesions are the most important in KD patients; however, aneurysms in other arteries, such as the auxiliary, iliac, or renal arteries, were observed in 1.0% of the patients. Valvular heart disease appeared in about 1.5% of the patients. Myocardial infarction occurred in 24 patients, 10 of whom died. It is important to know that half of the fatal cases did not demonstrate any ischemic findings before the onset of myocardial infarction.

**Myocardial Infarction and Death**

The main cause of death in KD is acute myocardial infarction (MI). A study in 104 fatal cases of KD patients in Japan
Valvular Heart Disease, Myocarditis, and Pericarditis

Valvular heart disease occurs in 1% of the patients, mostly in mitral valves and rarely in aortic valves. We found acute mitral regurgitation in 28 patients among 2180 cases (1.3%); this disappeared in half of the patients after a few months to several years. The etiology of this condition may be valvulitis or papillary muscle dysfunction caused by ischemia. Five patients presented with aortic regurgitation (0.2%). It is noteworthy that aortic regurgitation appeared after acute or subacute stages of illness and had increased to severe regurgitation over several years in some patients. Pericarditis or pericardial effusions appeared in 12.9% of the patients in the acute phase that was mostly subclinical and disappeared within 1 or 2 weeks. Massive pericardial effusion and cardiac tamponade was rare. There have been no reports on its progression to chronic or constrictive pericarditis. Relatively mild myocarditis was observed in 28% of patients in the acute phase, especially in the first and second weeks of illness, irrespective of the presence of coronary artery aneurysms. Gallop rhythms, distant heart sounds, ST-T segment changes, and decreased voltage of R waves on electrocardiogram (ECG) may suggest the presence of myocarditis. In many instances, cardiac enzyme levels, such as creatine kinase (CK), did not change significantly. Cardiomegaly and decreased ejection fractions of the left ventricle occurred, which were caused by myocarditis.

Diagnostic Techniques

The evaluation of the coronary artery lesions in KD in the acute stage of illness is important, even essential, and is usually done by 2D echocardiography (2D echo) and coronary angiography (CAG).

Echocardiography

Serial 2D echo studies are the most important and essential method to evaluate coronary artery aneurysms. The approach for 2D echo in KD is well described in the Japan KD Research Committee’s standardization of diagnostic criteria and reporting of coronary artery lesions and the committee report of the American Heart Association (AHA). Some reports suggest that this approach may underestimate the true incidence of coronary artery dilatation. If a patient has abnormal findings on serial 2D echo studies, coronary angiography is indicated.

Systemic Artery Involvement

Coronary artery lesions are the most important lesions in KD patients; however, aneurysms in other arteries were observed in 1.0% of the patients. Our angiographic study in 22 patients with systemic artery aneurysms demonstrated that systemic artery aneurysms were seen in axillary arteries in 18 cases, common iliac arteries in 16, internal iliac arteries in 12, renal arteries in six, mesenteric arteries in two, and internal thoracic arteries in two, respectively. One patient had large common iliac artery aneurysms associated with dilatation of aorta. Although prognosis of systemic artery aneurysms is generally favorable, renovascular hypertension may develop in a patient having a renal artery lesion, and intrathoracic arterial lesions may present problems at the time of coronary bypass surgery. There are some reports on digital gangrenous changes.

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The evaluation of the coronary artery morphology is particularly important in KD patients. The method for evaluation by echocardiography is well described in the AHA scientific statement on KD published in 2004. The precordial short-axis segment is the standard approach for evaluation of the left main coronary artery, left anterior descending artery, and right coronary artery. The posterior descending artery can be evaluated by the apical four-chamber view. The middle segment of the right coronary artery is seen by the apical four-chamber view. In our experience using 2D echo, it is possible to correctly diagnose left main coronary artery aneurysms with 98% sensitivity and 95% specificity compared to angiography. The echocardiographic evaluation for right coronary artery lesions was less sensitive. False-negative diagnoses were due mainly to the presence of isolated small peripheral coronary artery aneurysms, which were rare. From echocardiographic studies, it is evident that coronary artery dilatation appears at around 10 days of illness; approximately 40% of patients show coronary artery dilatation in this period. However, two thirds of these patients demonstrate a transient dilatation and regression within 3 to 5 weeks from the onset of illness (Fig. 41.2). This means that Kawasaki arteritis may cause the various degrees of coronary artery dilatation from mild transient dilatation, small or moderate-sized aneurysms, to giant aneurysms in more than half of the patients in the acute phase of the disease. Aneurysms are classified as saccular if the axial and lateral diameters are nearly equal or as fusiform if symmetric dilatation with gradual proximal and distal tapering is seen. If the coronary artery diameter looks larger than normal without segmental dilatation, the coronary artery is considered ectatic. The follow-up echocardiography is essential to evaluate such findings to assess whether these are ectatic changes or normal variations. We performed 2D echocardiography at the time of diagnosis, at 8 to 10 days after the onset of illness when coronary dilatation may appear, and at 2 and 8 weeks after the onset. The sizes of coronary artery aneurysms are classified as small (<5 mm internal diameter), medium (5 to 8 mm) and giant or large (>8 mm).

FIGURE 41.2. Regression of coronary aneurysms. This patient was diagnosed with Kawasaki disease at age 11 months and developed aneurysms in both the right and left coronary arteries (A). One year and 2 months later, the follow-up coronary angiography demonstrated the disappearance of coronary aneurysms and no stenosis or irregular arterial lumen in the whole coronary artery (B-1, B-2). The follow-up coronary angiography 12 years later demonstrated no aneurysms, no stenosis, and no irregular arterial wall in both the left and right coronary arteries (C-1,C-2).
Acute coronary thrombosis is diagnosed by serial 2D echo. At that time, thrombolytic treatment using urokinase or tissue-type plasminogen activator (t-PA) is indicated. The evaluation of stenotic lesions of the coronary artery by 2D echo is sometimes difficult; however, by using a high-frequency transducer and performing a careful examination, it may be possible. One looks for loss of uniformity of the lumen of arteries, irregular arterial walls, and dense echoes in the coronary arterial wall.

Other Noninvasive Techniques
Magnetic resonance imaging (MRI) may evaluate aneurysms in the proximal coronary artery and coronary flow profile. Ultrafast computed tomography (CT) is also available to evaluate coronary artery aneurysms; however, further studies on larger patient groups will be necessary.

Coronary Angiography and Heart Catheterization
Selective coronary angiography (CAG) is the most accurate method to define the presence and severity of coronary arterial abnormalities in KD patients. We have used specially designed catheters (three types) for selective CAG for infants, toddlers, and children that enable the CAG to be performed safely and successfully. The indications for CAG include the presence of abnormal 2D echo findings, the presence of symptoms or signs of ischemia, valvular regurgitation, evidence of cardiac dysfunction, and the use of intracoronary thrombolytic treatment. If the patient has severe coronary artery lesions, other systemic vascular involvement such as the auxiliary, iliac, renal, or intrathoracic arteries aneurysms should also be evaluated. Because the regression of coronary artery aneurysms and progression to stenotic lesions occur within 2 years from the onset of illness, follow-up CAG are essential, especially in patients having coronary aneurysms. The regression of coronary artery aneurysms is indicated when a follow-up CAG demonstrates normal findings in a patient who previously had coronary aneurysms. Aneurysms may disappear without any residual abnormality. This condition can be diagnosed by CAG; however, 2D echo may miss some mild abnormal findings, which subsequently progress to coronary artery disease. Coronary angiography is most important and essential for the evaluation of stenotic or obstructive lesions of coronary arteries and for evaluation of collateral circulation.

The clinical feasibility of intravascular ultrasound imaging for coronary arteries has been reported in patients who had KD to assess long-term pathology in vivo. At the site of regressed aneurysms, it has been shown that there is marked thickening of the intima. The portion of the coronary artery with normal angiographic findings shows normal findings except in the region near the regressed aneurysm where mild intimal thickening exists. Positive remodeling (or compensatory remodeling) may contribute to maintain the normal lumen with mild intimal thickening.

Evaluation for Myocardial Ischemia
Because the morbidity and mortality of this disease primarily depend on the extent of associated coronary artery disease, it is particularly important to assess accurately the presence of myocardial ischemia during follow-up. The conventional methods have some limitations. Two-dimensional echocardiography can detect coronary aneurysm; however, its evaluation of stenotic lesions is not satisfactory. Similarly, electrocardiographic sensitivity for detection of myocardial ischemia is insufficient. Coronary angiography is an accurate method to assess coronary artery involvement; however, repeated evaluation is often difficult because it is an invasive technique. Although exercise stress tests can detect myocardial ischemia, and this noninvasive technique is easy to repeat, its sensitivity is not sufficient, even in patients with significant coronary stenosis, and it is difficult to perform in young children. In this regard, myocardial single photon emission computed tomography (SPECT) using pharmacologic stress (dipyridamole infusion) is considered to be the most accurate diagnostic method for identifying myocardial ischemia, especially in children in whom an exercise test cannot be performed. Because pharmacologic stress SPECT studies provide quantitative analysis, changes in the severity of myocardial ischemia can be detected when consecutive studies were performed. Kamiya reported that the sensitivity of detecting myocardial ischemia in patients having significant coronary artery stenoses was >75%. The most sensitive method was dipyridamole stress SPECT (85% sensitivity); the sensitivity of treadmill exercise tests was <50%. Other stress tests reported in children with KD include nuclear perfusion scans with exercise, exercise echocardiography, stress echocardiography using dobutamine, and contrast echocardiography with dipyridamole stress.

Evidence-Based Treatment and Management
Recommendations of treatment and management are described in an evidence-based grading scale of the American Medical Association. The levels of evidence are classified as follows: level A, randomized controlled trial (large scale); level B, randomized controlled trial (small sample); level C, prospective trial or large case series; level D, retrospective analysis; level E, expert opinion or consensus; level M, meta-analysis; level X, no evidence.

Treatment of Acute Kawasaki Disease
The combination of aspirin and high-dose gamma globulin is a major therapeutic strategy in acute KD at the present time [level A evidence]. In 1984, high-dose gamma globulin treatment was reported to be effective by Furusho et al. in Japan [level A evidence]. The treatment was confirmed by a U.S. multicenter randomized trial [level A]. Both studies found that 400 mg/kg of gamma globulin may prevent coronary artery aneurysm formation. Gamma globulin is presently the most effective treatment; however, the optimal dose and indications for this treatment are still controversial. Some reports demonstrate a dose-dependent effect with higher doses in single infusions being more effective [level M evidence]. A large single dose of 2 g/kg has been reported to be more effective [level A evidence]. This treatment should be started...
within 10 days of illness, and if possible, within 7 days. It is uncertain whether very early treatment, that is, within 4 days of illness, is more effective [level C evidence].

As mentioned before, coronary artery aneurysms develop in less than 20% of KD patients. If we can predict which patients may have coronary aneurysms and can select them for gamma globulin treatment, it might be more effective and reduce medical expenses. Harada's scoring system may be useful in selecting high-risk patients for gamma globulin treatment. Harada suggests the following criteria: (1) white blood cell count >12,000/mm³; (2) platelet count <350,000/mm³; (3) CRP level >3 mg/dL; (4) hematocrit level <35%; (5) serum albumin level <3.5 mg/dL; (6) age <12 months; and (7) male gender. The presence of at least four of the seven criteria is an indication for gamma globulin treatment.

The mechanisms of benefit from gamma globulin are uncertain; however, possible Fc-mediated mechanisms include downregulation of inflammatory cytokines; modulation of T/B-cell functions through binding to lymphocyte Fc receptors; and inhibition of activated complement to targets, such as vascular endothelium. As Fab-mediated mechanisms entail the neutralization of microbial toxins, antibodies against cytokines and anti-idiotypic reaction against autoantibodies are possible.

Another problem with gamma globulin treatment in KD is that coronary artery aneurysms may develop in some patients [about 13% of gamma globulin treated patients] even using high-dose gamma globulin treatment. These patients may have a higher incidence of coronary aneurysms. Repeat gamma globulin treatment of 2 g/kg or pulse therapy by high-dose methylprednisolone (30 mg/kg for 3 days) may be indicated [level D evidence].

Aspirin is also important and provides antipyretic, anti-inflammatory, and antiplatelet effects; however, optimal doses are still controversial [level C evidence]. The AHA recommends high-dose aspirin [80 to 100 mg/kg] and reducing the dose to 3 to 5 mg/kg/day after the child has been afebrile for 48 to 72 hours. High-dose aspirin and intravenous immunoglobulin [IVIG] appear to provide additive anti-inflammatory effects. In Japan, lower doses of aspirin are prescribed, such as 30 mg/kg per day in two doses [middle dose] for 2 weeks and then reducing the dose to 5 mg/kg [level A evidence]. Regarding the effects of aspirin on platelet aggregation in KD, a lower dose [30 mg/kg] can successfully reduce the platelet aggregation that usually increases in the second or third week of illness. However, a higher dose of aspirin such as that used in collagen vascular disease, 100 mg/kg or more, did not have significant effects on platelet aggregation. Biosynthesis of thromboxane B₂ was completely blocked in both groups; however, plasma 6-keto prostaglandin F₃α, a metabolite of prostacyclin that has potent antiaggregatory effects on platelets, was also blocked in the high-dose group. These findings suggest that high-dose aspirin may be disadvantageous for prevention of thrombosis in some of these patients. Liver dysfunction was seen more frequently in the high-dose group. In such cases, we discontinued aspirin and began flurbiprofen. It has been reported that the absorption of aspirin in the gastrointestinal tract is impaired and clearance may increase in the acute stages of KD. The middle dose of aspirin may reduce aspirin intoxication, liver dysfunction, and gastrointestinal irritation, and have a lower risk for Reye's syndrome. For these reasons, we recommend 30 mg/kg in the acute stage and reduction to 5 mg/kg in convalescent stage [level C evidence]. However, the optimal dose of aspirin is still controversial.

Is steroid therapy beneficial? In the 1970s, steroids [2 mg/kg prednisone for 2 weeks] were frequently used for KD patients as a treatment for arteritis; however, there appeared to be a higher incidence of coronary artery aneurysms in patients receiving steroids, and also the regression of coronary aneurysms was less frequent. Furthermore, rupture of coronary aneurysm was frequently recognized in patients treated by steroids. Recently, studies reported that steroid pulse therapy for shorter periods with gamma globulin results in shorter fever periods [level B evidence].Steroid pulse therapy may effectively shorten the fever period and reduce acute inflammation; however, the longer use of steroids, such as the use of prednisone for 2 weeks, may have adverse effects on vascular remodeling, coronary aneurysm development, and Kawasaki arteritis. Frequent evaluation by echocardiography and long-term follow-up are necessary.

Other treatments that are available for acute KD patients are as follows: pentoxifylline [specific inhibitor of TNF-α messenger RNA transcription]; Ulinastatin [inhibitor of neutrophil elastase]; plasma exchange for IVIG-refractory cases; infliximab [monoclonal antibody against TNF-α]; and cytotoxic agents such as cyclophosphamide or cyclosporine. As an antiplatelet agent, abciximab [platelet glycoprotein IIb/IIIa receptor inhibitor] may have efficacy for regression of coronary aneurysms. All these drugs may have some efficacy for treatment of KD patients; however, the control data are lacking, and small numbers of patients are reported [level E evidence].

**Long-Term Management**

Long-term management of patients with KD depends on the degree of coronary arterial involvement. Low-dose aspirin [3 to 5 mg/kg/day single dose] is the basic treatment in the convalescent phase, and it continues up to 6 to 8 weeks in patients without coronary artery abnormalities. If coronary arterial abnormalities are present, low-dose aspirin should be continued until they are resolved. Coronary angiography is recommended in children in whom cardiovascular abnormalities have been found by 2D echo. Since the risk of progression to ischemic heart disease is high, particularly in those with giant aneurysms, patients should be managed by pediatric cardiologists. We recommend the combination of aspirin and warfarin for patients with giant coronary aneurysms with controlled international normalized ratios (INRs) of 1.5 to 2.5 [level D evidence]. Beta-blockade is indicated for patients with ischemic symptoms. Table 41.3 lists the recommendations for long-term management of patients with this disease.

When symptoms of acute MI are noted, the patient should be immediately hospitalized, given oxygen, and made to rest. Vital signs and electrocardiograms must be examined, and central venous pressure monitored. Since the main cause of
Acute MI in KD patients is acute thrombotic occlusion in stenotic coronary aneurysms, thrombolytic treatment and anticoagulation therapy are important treatment for acute MI, and they include intravenous t-PA, intracoronary infusion of urokinase, and heparin (Fig. 41.3). Intracoronary infusion of urokinase within 6 hours after the onset of MI is an effective treatment (level D evidence)\(^42\); however, t-PA can be used by intravenous infusion. Therefore, when acute MI occurs, t-PA should be used immediately intravenously and the patient referred to a cardiac center.

Interventional catheterization to treat coronary artery disease in KD patients has been performed in limited cases, so the long-term results are unknown. Balloon angioplasty is effective in some patients within 6 to 8 years from onset; however, with adult atherosclerotic coronary lesions, it was not so effective because of the elastic recoil and stiffness of the coronary artery.\(^72\) Recently, we have successfully performed coronary rotational ablation for long-term severe stenosis of the coronary artery in some patients that is frequently associated with severe calcification (level E evidence).\(^73\) Stent implantation may be useful in some patients. The guidelines for catheter intervention in KD patients are published by the Japanese KD Research Committee (level C evidence).\(^74\) Catheter intervention may postpone or substitute for bypass surgery\(^75–77\) (Fig. 41.4).

**Convalescence phase**

Aspirin
3 to 5 mg/kg/day single dose for patient with coronary aneurysm
Optional combination with dipyridamole 2 to 5 mg/kg, ticlopidine 5 to 7 mg/kg
Warfarin [0.05–0.12 mg/kg/day; INR 1.5–2.5] in combination with aspirin for patient with giant coronary aneurysm

Coronary bypass surgery may be indicated for patients with extreme coronary artery lesions, and the result is generally favorable (level C evidence).\(^78,79\) Bypass grafting using an intrathoracic artery is recommended for left coronary artery bypass, because the long-term patency is more favorable (3
years, 77.1%) compared to saphenous vein grafts (3 years, 52.8%) [level D]. The gastroepiploic artery is suitable for right coronary artery bypass grafting because it is usually large enough, even in young children. Surgical indications at the present time are as follows: [1] three-vessel obstruction; [2] severe stenosis of the left main coronary artery; and [3] severe stenoses in both left anterior descending artery and right coronary arteries. Even if patients are asymptomatic but demonstrate significant ischemic findings by exercise stress testing or myocardial scintigraphy, surgery may be indicated. A native, intrathoracic arterial graft is preferable, which can grow with age. Infants and children under 3 years of age present technical difficulties for bypass surgery. The viability of the myocardium should be evaluated by myocardial scintigraphy. Cardiac transplantation has been performed in several cases in the United States and the United Kingdom. It may be indicated in very rare instances in patients having severe diffuse myocardial fibrosis due to ischemia or previous multivessel bypass surgery with difficult revascularization.

**FIGURE 41.3.** Myocardial infarction caused by acute thrombotic occlusion. This 3-year-old boy was diagnosed with Kawasaki disease and developed giant aneurysms in both the right and left coronary arteries as shown by two-dimensional echocardiography (A). Coronary angiography demonstrated a large aneurysm in the left main coronary artery and circumflex artery (LCX) and the stenosis in the anterior descending artery (B). No ischemic findings were recognized at that time. Three months later, he complained of frequent chest pain and vomiting. Echocardiogram during the acute myocardial infarction demonstrated complete occlusion in the left main coronary artery and the anterior descending artery (C). The follow-up coronary angiography just after myocardial infarction demonstrated complete obstruction of the anterior descending artery (D).
**Prognosis and Long-Term Issues**

**Long-Term Consequences of Coronary Aneurysms**

The natural history or fate of coronary aneurysms is an important issue in KD patients [Fig. 41.5]. We evaluated 594 consecutive patients with acute KD between 1973 and 1983, and this cohort was followed for 10 to 21 years. In all patients, we evaluated the coronary lesions by coronary angiography after the acute stage. One hundred forty-six patients (24.6%) were diagnosed as having coronary artery aneurysms. A second angiography was performed 1 to 2 years later in all 146 patients who had previous coronary aneurysms, which demonstrated that 72 (49.3%) had regression in the coronary artery aneurysms. It suggests that coronary artery aneurysms in KD patients show a strong tendency of regression. None of the patients with regression of coronary aneurysms had cardiac symptoms in the long-term follow-up periods, and results of their ECGs, exercise stress tests, and left ventricular function were all within normal limits. In contrast, by 10 to 21 years after the onset of the illness, stenoses in the coronary aneurysms had developed in 28 patients. Myocardial infarctions occurred in 11 patients, five of whom died. From this study, it is estimated that about 4% of patients with KD may develop ischemic heart disease.

When does this condition occur? We studied the time and the incidence of regression or progression to obstructive lesions from the onset of KD using the Kaplan-Meier life table method. Regression of coronary aneurysms mostly occurred within 2 years from the onset of illness, whereas the obstructive lesions developed in 2 years and gradually increased over several years.

We investigated various factors that could affect the prognosis of coronary aneurysms. The risk factors for coronary aneurysms to develop into ischemic heart disease are as follows: (1) aneurysm diameter more than 8 mm; (2) large
diffuse or saccular-type aneurysms, prolonged fever for >21 days, and age at onset >2 years. In the 26 patients with giant coronary aneurysms, stenotic lesions developed in 12, and no regression occurred in our follow-up study. Thus, giant coronary aneurysms often progress to ischemic heart disease. The incidence of giant coronary aneurysms was 17.8% in the patients with coronary aneurysms and 4.4% among all KD patients in our series.

The biologic mechanism of regression of aneurysms is marked proliferation of intima without massive thrombus formation, and the intima consists of rich, smooth muscle cells and well-regenerated endothelium. Hemodynamic forces may regulate such arteries to maintain adequate lumen. It is uncertain whether intimal thickening eventually develops into obstructive lesions. However, in our 10- to 21-year follow-up study, none of the patients who had regressed aneurysms developed ischemic heart disease. Our experience indicates that stenotic lesions do not develop, at least within one or two decades, in patients with complete regression of coronary artery aneurysms.

Impact of Kawasaki Disease on Overall and Cardiovascular Mortality

Chronologic changes in mortality and fatality rates from KD patients were studied by Hayakawa et al. by analyzing 679 death cases in Japan between 1972 and 1998. The male-to-female ratio of the number of deaths was 2.07. The age-specific mortality rate was highest in infants under 1 year of age. The case fatality rate has decreased annually, declining from 2.23% in 1973 to as low as 0.02% in 2002, which may be due mostly to the improvement of cardiac evaluation and treatment, particularly by gamma globulin and aspirin.

Nakamura et al. followed a cohort of 6576 patients for 12.6 years to determine whether patients with KD have a higher death rate than an age-matched healthy population. In this cohort, 27 (19 males, 8 females) died, and 12 died from myocardial infarction or mitral regurgitation from KD. Eight of 12 died within 2 months of illness. The other causes of death were as follows: four died of congenital heart failure, four died of neoplasms, three died of other diseases, and five died of injuries or accidents. In contrast to the high mortality rate during the acute KD, the mortality rate was not elevated for those without cardiac sequelae after the acute phase. On the other hand, high but not significant mortality was observed for male patients with cardiac sequelae after the acute phase of the disease. This study has only a 12-year follow-up, so a longer follow-up observation in the adult may be necessary [Fig. 41.6].
Kawasaki Arteritis May Be an Atherosclerotic Risk Factor

The pathology of coronary arteritis in KD patients several years after onset demonstrates marked intimal proliferation and, in some patients, calcific deposits of protein-like material and hyalinized degeneration in the thickened intima. Intravascular ultrasound studies of the coronary arteries after KD demonstrated marked thickening of intima and calcification in the coronary aneurysms. These findings are similar to arteriosclerotic lesions. Suzuki et al. reported that the active expression of various growth factors was observed in the coronary arteries in the late phases of KD, suggesting that active vascular remodeling continues several years after the onset of the disease. However, the important issue is whether these coronary artery lesions develop into atherosclerotic coronary artery disease in adulthood.

We studied the distensibility of the coronary arterial wall by using intracoronary infusion of isosorbide dinitrate and endothelial function by intracoronary infusion of acetylcholine. Mitani and Dhillon's group reported that endothelial dysfunction was observed even in the normal artery in KD patients. Pathology of the coronary arteries in adults after KD demonstrated premature atherosclerotic changes. Mitani et al. suggested that high-sensitivity CRP was elevated in the late coronary sequela in KD. These results suggest that the coronary arteries in the late KD patients may have a potential coronary risk factor.

Adult Coronary Artery Disease Due to Childhood Kawasaki Disease

It has now been more than 35 years since the first description of KD as a new clinical entity, and the early KD children are now adults. We surveyed these adults to investigate any coronary sequelae that might be due to their earlier KD and reported 21 such cases and their cardiac conditions. Most of these 21 patients were diagnosed as having fever of unknown origin, sepsis, or pneumonia because they suffered from suspected Kawasaki disease before Dr. Kawasaki’s first description in 1968. Most of the patients had ischemic symptoms or signs, including acute or old myocardial infarction or angina pectoris, two or three decades after the onset of suspected KD. Some of the patients demonstrated mitral regurgitation or arrhythmias. Almost all patients had multiple coronary artery aneurysms with obstruction or stenosis and with severe calcification of the arteries. Coronary aneurysms of unknown etiology were also reported in 109 patients who had no history of KD. These patients were mostly free from the ischemic symptoms, but had abnormal Q waves on their ECGs or calcification of the coronary arteries on chest x-ray. We suspect that these findings in large or small part may be caused by childhood KD.

Our study suggests that some patients with coronary artery sequelae of KD have progressed into young adulthood with ischemic heart disease. The suspected findings for recognizing this condition are important. A past history in infancy or childhood is important. Abnormal Q waves or mitral regurgitation of unknown origin in the younger adults is also important. Coronary angiographic findings are essential for recognition as these are multiple aneurysms frequently associated with calcification. Familial hypercholesterolemia or collagen vascular disease should be excluded. After our report, many case reports on adult coronary artery disease attributed to childhood KD have appeared that were reviewed by Burns. The coronary artery sequelae of KD may be an important cause of ischemic heart disease in young adults, particularly those under 40 years of age. Cardiologists should recognize this condition and include the sequelae of KD in the differential diagnosis of early-onset coronary artery disease in adults.
Guidelines

The following is a list of available KD guidelines in the literature:

1. Research Committee on Kawasaki Disease.\(^5\)
2. Guideline for treatment and management of cardiovascular sequelae in Kawasaki disease.\(^6\)
3. American Heart Association guidelines for diagnosis and treatment of Kawasaki disease.\(^10\)
4. Guidelines for long-term management of patients with Kawasaki disease.\(^6\)
5. Guidelines for catheter intervention in coronary artery lesion in Kawasaki disease.\(^74\)
6. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease.\(^101\)
7. American Heart Association's diagnosis, treatment, and long-term management of Kawasaki disease.\(^40\)

Summary

Kawasaki disease is a relatively common acute febrile illness with mucocutaneous involvement that affects infants and young children in Japan and the Orient. It is an arteritis syndrome mostly affecting small and medium-sized arteries, particularly coronary arteries. Coronary artery aneurysms occur in 10% to 20% of patients and may cause myocardial infarction, sudden death, and coronary artery disease. In Japan, North America, and Western Europe, Kawasaki disease has replaced rheumatic fever as the leading cause of acquired heart disease in children. Furthermore, it may develop into coronary artery disease in adults. Long-term follow-up studies are important to clarify the long-term prognosis in pediatric through adult patients.

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