Kawasaki's Disease

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Abstract

Kawasaki disease was first described in 1967 by Tomisaku Kawasaki and is now recognized as the leading cause of acquired heart disease among children. Kawasaki disease is an acute febrile illness affecting primarily infants and young children and rarely teenagers. Although the disease is self-limited, coronary artery abnormalities have been reported in approximately 20–25 % of untreated patients. The diagnostic criteria include a history of 5 or more days of fever and at least four of five principal clinical features. Although the etiology remains unknown, standard therapy consists of high dose, single infusion of intravenous immunoglobulin and oral acetylsalicylic acid. This regimen was studied in patients presenting in the first 10 days of illness and was found to reduce the risk of coronary abnormalities to 5 %. Approximately 10–15 % of IVIG-treated patients are initial IVIG nonresponders and are at increased risk of developing coronary artery abnormalities. In patients who develop coronary aneurysms, approximately 50 % of the lesions may remodel within 1–2 years after the illness. Patients with giant aneurysms are at the greatest risk to develop secondary thrombotic occlusion. Long-term follow-up studies in Kawasaki disease patients are still ongoing. However, studies have shown prolonged endothelial dysfunction even in children without any evidence of coronary abnormalities. Therefore, until further data become available, many experts recommend long-term cardiology follow-up even in patients without a history of coronary involvement.

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Introduction

In 1961, Dr. Tomisaku Kawasaki saw a 4-year-old boy with a 7-day history of high fevers, cracked lips, conjunctival injection, rash, erythema and edema of the palms and soles, and a swollen cervical lymph node. In 1967, he described 50 children with these clinical features in a Japanese journal (published in English in 1974) and referred to the disease process as mucocutaneous lymph node syndrome [1, 2]. Currently, Kawasaki disease is recognized worldwide and described in children of all races and ethnicities.

The association of Kawasaki disease with cardiac complications was first described in 1968 in Japan [3]. Although Kawasaki disease is a self-limited vasculitis of medium-sized arteries, the hallmark of this disease is the coronary artery abnormalities that develop in approximately 20–25 % of untreated patients [4–6]. In developed countries, Kawasaki disease has surpassed acute rheumatic fever as the most common cause of acquired heart disease among children [7]. In addition, Kawasaki disease is now reported as a potential risk factor for adult ischemic heart disease and sudden death in early adulthood [8]. Despite over 40 years of Kawasaki disease research, there is no specific diagnostic test for Kawasaki disease, and the diagnosis remains a clinical one.

Epidemiology

Kawasaki disease is most common in young children aged 6 months to 5 years, with a peak incidence in children at 1 year of age. It is less common in children less than 6 months of age and adolescents, but there is an increased risk of coronary artery abnormalities in children with Kawasaki disease in both of these age groups. Some adult cases have been reported, but these are extremely rare [9, 10]. Overall, 80 % of Kawasaki disease cases occur before 5 years of age.

Kawasaki disease is overrepresented among Asian populations, especially among Japanese. Children of Asian heritage, who were born in the United States, also have the same elevated risk. The highest incidence is reported among Japanese children and is estimated at 184 per 100,000 children less than 5 years of age [11]. In the United States, the incidence for African American, Hispanic, and Caucasian children is 16.9, 11.1, and 9.1 per 100,000, respectively, whereas the incidence among American-Indian and Alaskan native children is only 4.3 per 100,000 children [12].

Kawasaki disease is more common in boys, who are affected 1.5 times more often than girls. The recurrence rate has been reported to be approximately 3 % in Japan [13]. Although there is no evidence for person-to person transmission, there may be a genetic predisposition to developing Kawasaki disease. Japanese children, whose parents had Kawasaki disease, have an increased risk of developing the disease, are more likely to have a severe course, are more likely to have a recurrence, and have a higher incidence of coronary artery aneurysms [14]. Siblings of patients have a tenfold greater risk of acquiring Kawasaki disease than children in the general population [15]. In the case of twins, when one twin has Kawasaki disease, the risk of the other twin acquiring Kawasaki disease is 13 % [16]. Kawasaki disease is seen year around, but distinct seasonal variation has been reported with peak occurrence in the spring and winter months in Japan [17].

Etiology

The etiology of Kawasaki disease remains unknown. Many agents have been investigated as potential causes of Kawasaki disease and etiologies proposed include an infectious trigger, host immune response, and genetic predisposition.

Infectious Agents

Several clinical and epidemiologic observations suggest that Kawasaki disease is triggered by

an unknown infectious agent, for the following reasons. First, the winter/spring seasonality peak seems to imply a recurring infectious vector. Second, epidemic outbreaks of Kawasaki disease with geographic clustering have been reported in Japan and the United States [18, 19]. In Japan, outbreaks are described starting in one geographic area and then spreading throughout the country. Third, Kawasaki disease has a peak incidence in children younger than 5 years of age, with fewer cases seen in children less than 3 months of age, suggesting protective transplacental antibodies. Although epidemiologically Kawasaki disease seems to behave as an infectious disease, conventional bacterial and viral cultures and serologic investigations have failed to identify an etiologic agent. Historically, many infectious agents have been studied in children with Kawasaki disease including *Yersinia pseudotuberculosis*, *Rickettsiae*, *Leptospira*, *Chlamydia*, *Adenovirus, Measles virus, Parvovirus B 19, Epstein-Barr virus*, *Cytomegalovirus*, *Retroviruses*, *NL63 (New Haven Coronavirus)*, and *Mycoplasma pneumoniae*, but none have been confirmed as an etiologic agent.

Host Immune Response: Superantigens

A possible superantigen etiology has also been proposed based on some clinical and immunologic similarities of Kawasaki disease to staphylococcal toxic shock syndrome and streptococcal toxic shock syndrome. Superantigen production has been associated with both toxic shock syndromes and, like Kawasaki disease, both have clinical manifestations that include fever, conjunctival injection, oral mucosal changes, extremity changes, rash, and subsequent desquamation of the hands and feet. Immunologic evidence of a superantigen etiology includes reports of T-cell receptor V-beta skewing in Kawasaki patients [20–22]. However, other studies have not detected V-beta skewing, so this remains controversial [23, 24]. A few studies have isolated superantigen-producing *Staphylococcus aureus* from Kawasaki disease patients [25, 26]. However, these findings have not been confirmed by others [27, 28], and a prospective multicenter study with Kawasaki patients and controls showed no significant differences in isolation rates of superantigen-producing *S. aureus* in the Kawasaki patients as compared to controls [29]. Therefore, there is ongoing controversy regarding the superantigen theory as the etiology of Kawasaki disease.

Genetics

The increased incidence of Kawasaki disease among Asians raises the possibility of a genetic predisposition to Kawasaki disease [30]. A genetic influence is suspected that increases likelihood of acquiring Kawasaki disease. In addition, genetic polymorphism may increase the tendency to develop coronary artery abnormalities. Previous study has shown that certain genetic polymorphisms including CD40 ligand gene and inositol-trisphosphate 3-kinase C are associated with an increased susceptibility to Kawasaki disease and to development of coronary artery abnormalities [31, 32].

Diagnosis

There is no specific diagnostic test for Kawasaki disease; therefore, the diagnosis of classic Kawasaki disease is based on clinical criteria. Other symptoms, clinical signs, and/or laboratory findings are sometimes helpful in making the diagnosis (Table 130.1) [33]. Early diagnosis and treatment is essential, as late diagnosis of Kawasaki disease (after the tenth day of the illness) has been associated with increased risk of coronary artery aneurysm formation [34, 35]. The differential diagnosis of Kawasaki disease includes measles, rubella, scarlet fever, toxin-mediated staphylococcal diseases, staphylococcal scalded skin syndrome, Stevens Johnson syndrome, juvenile rheumatoid arthritis, leptospirosis, rickettsioses, Rocky Mountain spotted fever, and viral exanthems.

Table 130.1 Clinical and laboratory features of Kawasaki disease (Modified from guideline in American Heart Association and American Academy of Pediatrics)

Classic clinical criteria	
Fever	Persisting fever at least 5 days (in presence of ≥4 principal criteria, diagnosis can be made on day 4 of illness) Presence of at least following four principal features
Changes in extremities	Acute: Erythema of palms, soles; edema of hands, feet Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem	
Bilateral bulbar conjunctival injection without exudate	
Changes in lips and oral cavity	Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
Cervical lymphadenopathy	>1.5 cm diameter, usually unilateral Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by echocardiography or angiography
Other clinical and laboratory findings	
Cardiovascular findings	Congestive heart failure, myocarditis, pericarditis, valvular regurgitation Coronary artery abnormalities Aneurysms of medium-sized noncoronary arteries Raynaud's phenomenon Peripheral gangrene
Musculoskeletal system	Arthritis, arthralgia
Gastrointestinal tract	Diarrhea, vomiting, abdominal pain
Hepatic dysfunction	Hydrops of gallbladder
Central nervous system	Extreme irritability Aseptic meningitis Sensorineural hearing loss
Genitourinary system	Urethritis/meatitis
Other clinical findings	Erythema, induration at BCG inoculation site Anterior uveitis (mild) Desquamating rash in groin
Laboratory findings in acute phase	Leukocytosis with neutrophilia and immature forms Elevated erythrocyte sedimentation rate Elevated C-reactive protein Anemia Abnormal plasma lipids Hypoalbuminemia Hyponatremia Thrombocytosis after week 1 Sterile pyuria Elevated serum transaminases Elevated serum gamma-glutamyl transpeptidase Pleocytosis of cerebrospinal fluid Leukocytosis in synovial fluid

Principal Symptoms

The diagnosis depends on a history of 5 or more days of fever and at least four of five principal clinical features (characteristic eye changes, mucous membrane changes, extremity changes, rash, and cervical adenopathy). Fever is present in >95 % of patients during the acute phase. Classically, the fever is high and spiking, and usually persists for more than a week if not

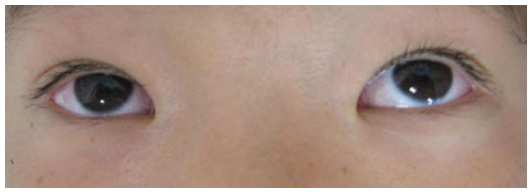

Fig. 130.1 Conjunctival injection

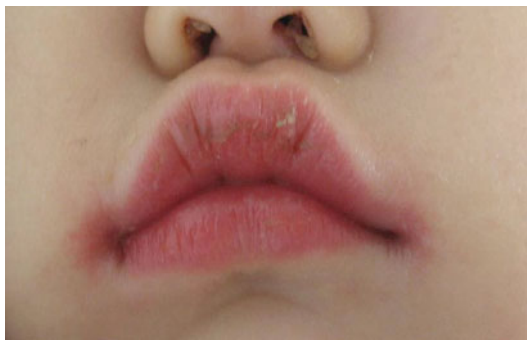

Fig. 130.2 Oropharyngeal changes (swollen, fissured, and cracked lips)

treated. Conjunctival injection is seen in 90 % of Kawasaki disease patients; it is characteristically bilateral, bulbar, and nonpurulent (Fig. 130.1). Anterior uveitis and iridocyclitis have been reported within the first week of illness [36]. Oropharyngeal changes are seen in 90 % of patients and involve the lips, tongue, or pharynx. The lips may become swollen, dry, fissured, or cracked; peeling or bleeding may be observed (Fig. 130.2). Diffuse erythema of the oropharyngeal mucosa may be seen, but pharyngeal exudates and ulcers are not associated with Kawasaki disease. A strawberry tongue (similar to scarlet fever) is described in 77 % of patients. The extremity changes include erythema of the palms and/or soles and/or swelling (indurative edema) of the hands and feet, which can be painful. Extremity changes are present during the acute phase in 75 % of patients. A polymorphous exanthem occurs in 90 % of patients. The lesions vary in appearance but are typically not vesicular or bullous. The most common presentation is a nonspecific, diffuse maculopapular eruption (Fig. 130.3) which is often most prominent on

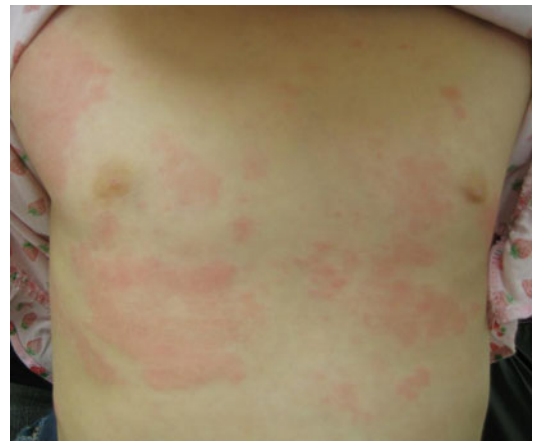

Fig. 130.3 Maculopapular rash

the trunk. Cervical lymphadenopathy is the least commonly observed of the principal clinical features (70 %); the observed lymph node (1.5 cm or larger in diameter) is typically nonsuppurative, tender, is usually unilateral, and is more commonly seen in older children. Clinically, the adenopathy usually appears to be a solitary node; however, ultrasound evaluation has shown there may be a cluster of nodes. In some patients, there is marked erythema of the skin overlying the node, appearing like bacterial adenitis. Although not part of the diagnostic clinical criteria, many patients with Kawasaki disease may be toxic and irritable during acute phase. Infants less than 6 months of age, who are at the highest risk for development of coronary lesions, may display subtle clinical signs and are more likely to have incomplete Kawasaki disease. In the subacute phase (10–15 days after the onset of the illness), desquamation and peeling of the skin usually begin in the periungual region and may extend to include the palms and soles in about 70 % of patients (Fig. 130.4).

Other Significant Symptoms or Findings

Noncardiac Symptoms and Findings

A unique manifestation of Kawasaki disease is induration and erythema which may develop at

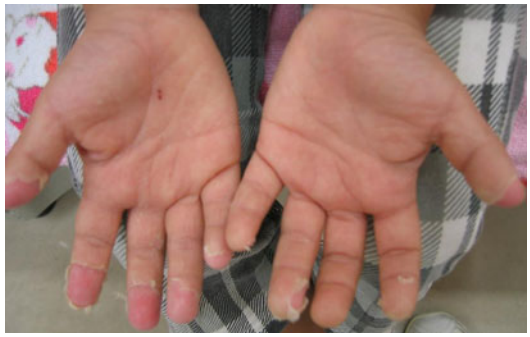

Fig. 130.4 Desquamation of hands seen in the subacute phase

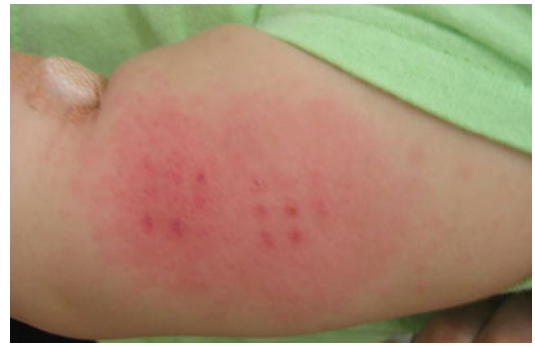

Fig. 130.5 Erythema at the site of BCG inoculation

the site of a previous Bacille Calmette-Guérin (BCG) inoculation (Fig. 130.5). This is seen most commonly in infants who develop Kawasaki disease within 1 year after the inoculation [37]. The gastrointestinal features of Kawasaki disease include diarrhea, vomiting, abdominal pain, and paralytic ileus. Hydrops of the gallbladder diagnosed by ultrasound is well described. Large or small joint arthritis and arthralgia are noted in 30 % of patients [38]. Large joint arthralgia and arthritis (especially of knees and ankles) occur within 2–3 weeks of the start of the illness. In contrast, small joint arthritis usually occurs early in the illness. Transient unilateral peripheral facial nerve palsy has been reported rarely [39].

Cardiac Symptoms and Findings

Cardiovascular manifestations are the leading cause of long-term morbidity and mortality. The cardiovascular abnormalities consist of tachycardia, cardiac murmurs, gallop rhythm, electrocardiogram changes (including PR-QT prolongation), abnormal Q waves, low voltage, ST-T changes, and arrhythmias. Rarely, a systolic murmur may indicate mitral regurgitation is present. Resting tachycardia out of proportion to fever is commonly seen in Kawasaki disease and likely reflects underlying myocarditis. Myocarditis is also suggested by a gallop rhythm on cardiac auscultation and confirmed by depressed myocardial contractility on echocardiography. The electrocardiogram (EKG) is usually normal with the exception of tachycardia, but abnormalities may suggest cardiac complications. Nonspecific ST-T changes and low-voltage QRS complexes may be seen in pericarditis. EKG changes indicative of ischemia or arrhythmias on a rhythm strip may be observed. Echocardiographic findings seen in Kawasaki disease may include pericardial effusion, mitral or aortic regurgitation, dilation of the coronary arteries, and/or coronary artery aneurysms. Echocardiographic findings are not part of the formal diagnosis of Kawasaki disease.

Laboratory Findings

Laboratory findings are nonspecific since there is no specific diagnostic test for Kawasaki disease. During the first week there is typically leukocytosis with a left shift, mild anemia (normocytic, normochromic), high erythrocyte sedimentation rate, and/or high C-reactive protein. In addition, hypoalbuminemia and mild to moderate increase in serum transaminases are common. Sterile pyuria may be present during the acute phase, which may sometimes be associated with clinical urethritis. Pleocytosis of mononuclear cells in the cerebrospinal fluid is common [40]. The platelet count is usually elevated by the second or third week of the illness. These laboratory findings typically improve after therapy with intravenous immunoglobulin.

Incomplete (Atypical) Kawasaki Disease

About 10 % of patients do not fulfill the criteria for the diagnosis of complete Kawasaki disease [41]. These patients are classified as having

"incomplete" Kawasaki disease (formerly called "atypical" Kawasaki disease). Patients with incomplete Kawasaki disease have the same or a higher risk of coronary artery abnormalities (as patients with complete Kawasaki disease), therefore making it important to diagnose these patients. Incomplete Kawasaki disease is diagnosed more commonly in patients less than 6 months of age; these patients are at the highest risk for development of coronary abnormalities. Children in this age group may have subtle or transient signs, making the diagnosis difficult. Incomplete Kawasaki disease should be considered in patients with persistent fever, even if the clinical presentation does not fulfill classic Kawasaki disease criteria. In such cases, laboratory and echocardiographic evaluations, as well as exclusion of other possibilities in the differential diagnosis, can be helpful to assess the patient.

Figure 130.6 shows an algorithm developed by the American Heart Association for evaluation of suspected incomplete Kawasaki disease [33]. This algorithm incorporates use of supplemental laboratory tests and echocardiography to assist in making the diagnosis. According to the guideline, infants $\leq$6 months old with $\geq$7 days of fever without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, an echocardiogram, even if the infants have no clinical criteria. If the echocardiogram is positive, treatment should be given to children within 10 days of fever onset and those beyond day 10 with clinical and laboratory signs of ongoing inflammation.

Cardiovascular Complications

Cardiac complications include coronary abnormalities (Figs. 130.7–130.10), systemic arterial aneurysms, myocarditis, congestive heart failure, pericarditis with pericardial effusion, mitral or aortic valve insufficiency, arrhythmia, and myocardial infarction. Coronary artery aneurysms, thrombosis, or myocardial insufficiency are the leading causes of morbidity and mortality in Kawasaki disease.

Coronary Artery Abnormalities

Coronary artery abnormalities include dilatation (ectasia), stenosis, and aneurysms. Coronary artery abnormalities appear in 20–25 % of untreated patients with Kawasaki disease [4–6]. Randomized, placebo-controlled studies found that if treated during the first 10 days of the illness (with intravenous immunoglobulin and aspirin), the risk of coronary artery abnormalities decreased to 3–5 % [42]. Several studies have identified risk factors for coronary artery abnormalities in Kawasaki disease including male sex, age less than 1 year, high C-reactive protein, high erythrocyte sedimentation rate, high white blood count, low albumin, low hemoglobin concentration, and low platelet count [43, 44]. The original echocardiographic criteria established by the Japanese Ministry of Health defined abnormal coronary arteries as having intraluminal diameters greater than 3 mm in children younger than 5 years, greater than 4 mm in those older than 5 years, lumen diameter greater or equal to 1.5 times the size of an adjacent segment, or if the coronary lumen is clearly irregular. However, coronary artery size in normal children correlates linearly with increasing body surface area. Therefore, body surface area adjusted coronary dimensions, termed z-scores, are thought to be better for the evaluation of coronary artery abnormalities [45]. The z-score system is used only for the left main coronary artery, proximal left anterior descending coronary artery, and proximal right coronary artery. Coronary artery dilatation or aneurysms are usually classified as follows: mild dilatation is characterized by a coronary artery intraluminal diameter of up to 5 mm (small aneurysms); moderate dilatation is characterized by diameters of $>$5 mm and up to 8 mm; and giant aneurysms are characterized by intraluminal diameters that exceed 8 mm [33, 45].

Giant aneurysms occur in about 1 % of patients and can cause serious morbidity or mortality in the acute, convalescent, and remote phases. Thrombosis is the most common complication associated with giant aneurysms in the acute phase, although rupture has been reported rarely. Later, stenotic lesions may develop as a consequence leading to

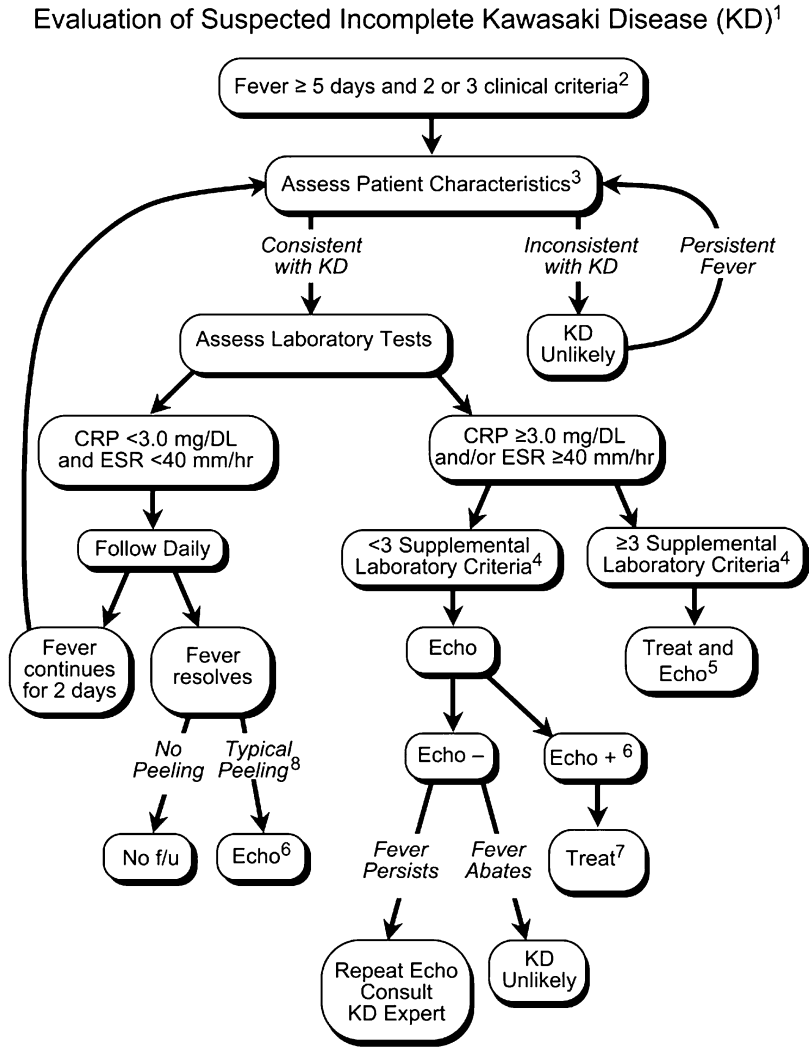

Fig. 130.6 Diagnostic algorithm for incomplete Kawasaki disease (from guideline in American Heart Association and American Academy of Pediatrics). [1]Bilateral nonprulent conjunctivitis. [3]Nonspecific exanthema. [4]Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after 7 days of illness ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine with ≥10 white blood cells per high-power field. [5]Uncommon in schoolchild. [6]Echocardiogram is considered positive if any of three conditions are met: *z*-score of left descending coronary artery or right coronary artery ≥2.5, coronary arteries meet Japanese Ministry of Health criteria for aneurysms, or ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or *z*-scores in left descending coronary artery or right coronary artery of 2–2.5. [7]CAA; echocardiography (LAD). [8]Typical peeling begins under nail bed of fingers and then toes. [9]CAA; angiography (LAD). [10]CAA; 3D CT (RCA and LAD). *Abbreviations*: *CRP* C-reactive protein, *Echo* echocardiography, *ESR* erythrocyte sedimentation rate, *KD* Kawasaki disease

myocardial ischemia or myocardial infarction in either the convalescent phase or many years later (remote phase).

The in-hospital mortality rate for children with acute Kawasaki disease is 0.17 % in the United States [46]. The peak mortality occurs 15–45 illness days when both coronary vasculitis and hypercoagulability (due to marked elevation of the platelet count) may occur [47]. Physicians should recognize that patients with coronary

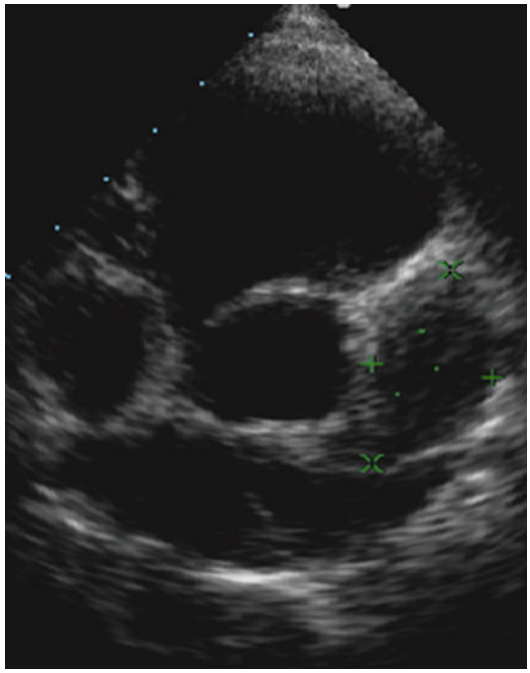

Fig. 130.7 CAA; echocardiography (LAD)

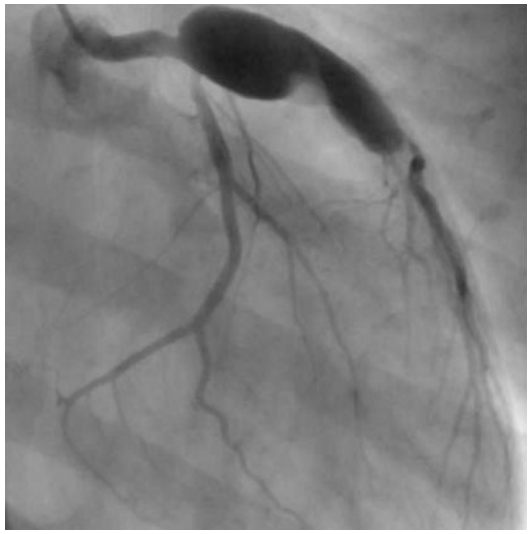

Fig. 130.8 CAA; angiography (RCA)

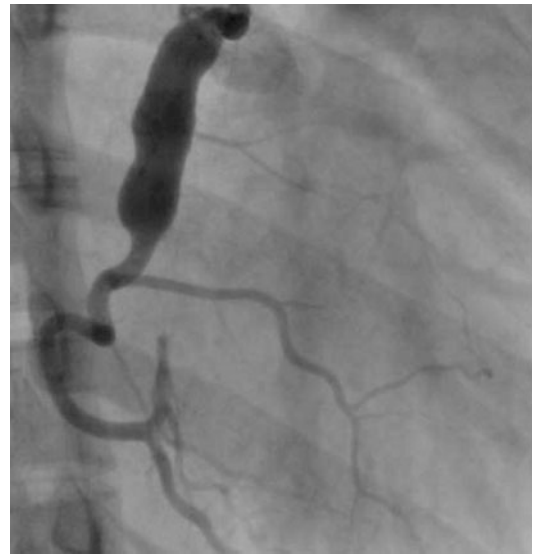

Fig. 130.9 CAA; angiography (LAD)

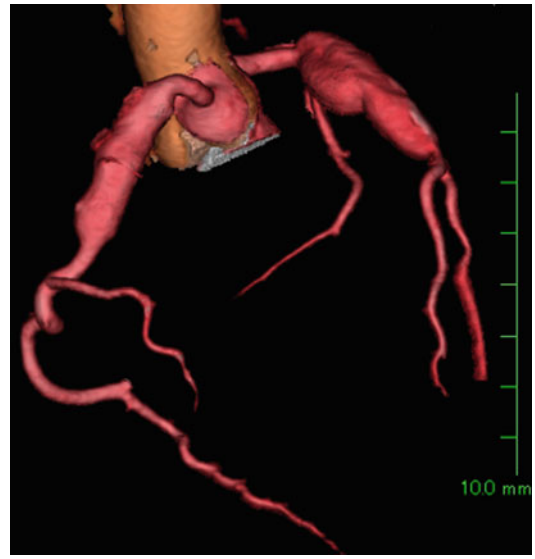

Fig. 130.10 CAA; 3D CT (RCA and LAD)

artery aneurysms also remain at increased risk for myocardial infarction or cardiac sudden death in adulthood.

Echocardiography is a noninvasive imaging method that is recommended and widely available for the routine assessment of cardiac complications due to Kawasaki disease. Angiography may be utilized for evaluation of suspected thrombosis or stenosis. Two-dimensional echocardiographic evaluation should focus on left ventricular wall motion, regurgitation of mitral and aortic valve, pericardial effusion, and coronary artery morphology (including the left main coronary artery, left

anterior descending coronary artery, proximal left circumflex coronary artery, and proximal right coronary artery). Increased echogenicity or brightness of the coronary arteries has been described. Echocardiography is recommended at the time of diagnosis, at 1–2 weeks after diagnosis, and at 6–8 weeks after diagnosis. In Japan, clinical assessment is also performed at 6 months after the diagnosis (in the United States, imaging is not routinely performed at 6 months). More frequent echocardiographic evaluation may be needed in children at higher risk for coronary artery abnormalities or those with poor cardiac function during acute phase. After discharge, follow-up echocardiography can identify the progression or regression of coronary abnormalities.

Recently, multidetector computed tomography (MDCT) scans and magnetic resonance angiography (MRA) have been useful in the diagnosis of coronary aneurysms, occlusions, and stenoses [48, 49]. Three-dimensional CT can visualize the aneurysm at distal coronary artery. The advantage of 64-slice MDCT is to detect coronary stenosis with high sensitivity and specificity, but the presence of calcifications and the high-radiation dose are problems. Likewise, MRA also can detect distal coronary stenosis, but it requires anesthesia in children.

Myocardial infarction is the main cause of death in patients with Kawasaki disease. Thromboembolic occlusion of coronary aneurysm or stenotic lesion leads to myocardial infarction and sudden cardiac death in children and/or young adults. Around 2–4 % of patients with giant coronary aneurysms develop myocardial infarction within first year after the diagnosis [50, 51]. The diagnosis of myocardial infarction is suggested from the patient's symptoms and confirmed by electrocardiography, echocardiography, and biochemical data (e.g., troponin). Rarely, patients with giant coronary aneurysms may be asymptomatic despite ischemia. The obstruction in two or three vessels including the left main coronary artery is high risk of sudden death. To mitigate or prevent thrombosis, most patients with giant coronary aneurysm receive anticoagulant and/or thrombolytic medications.

Other Cardiac Complications

Myocarditis using scintigraphy has been demonstrated to occur in 50–70 % of patients [52]. Autopsy and biopsy studies in patients with acute Kawasaki disease also report myocarditis as a common finding [53]. Myocarditis is often detected by auscultation of a gallop rhythm; rarely patients develop signs or symptoms of congestive heart failure. Myocardial function rapidly improves after treatment with high-dose immunoglobulin therapy, suggesting that improvement of myocardial function may be associated with resolution of the systemic inflammation. In most patients, myocardial dysfunction, which resolves promptly with immunoglobulin treatment, has no long-term sequelae. The severity of the myocarditis does not appear to be related to the presence or absence of coronary artery aneurysms [54].

Pericarditis is often observed in Kawasaki disease, with a small pericardial effusion detected by echocardiography in almost 30 % of patients within the second week of illness [4]. Inflammation of the endocardium involves the pericardium, which may lead to a pericardial effusion. Rarely, the pericardial effusion requires an emergency pericardiocentesis due to cardiac tamponade, but usually it resolves during the acute phase without specific interventions.

Mitral regurgitation may result from transient papillary muscle ischemia, myocardial infarction, or valvulitis. The prevalence of mitral regurgitation is about 1 % in patients with acute or subacute Kawasaki disease [55]. Mitral regurgitation is usually mild and may resolve, but rarely can lead to congestive heart failure. Aortic regurgitation also occurs due to valvulitis in the acute or subacute phase [56].

Pathology

The vasculitis of Kawasaki disease has been studied. In the acute stage, there is immune activation of the endothelium, with increased proinflammatory cytokines leading to panvasculitis predominantly of small- to medium-sized arteries. Aneurysms can develop in any artery

including coronary, celiac, mesenteric, femoral, iliac, renal, subclavian, axillary, and brachial arteries [57].

Treatments

First-Line Treatment

The main goals of pharmacological therapy in Kawasaki disease are suppression of the underlying inflammatory response and inhibition of platelet aggregation to prevent coronary thrombosis. In the United States, the United Kingdom, Europe, and Japan, standard therapy in Kawasaki disease consists of intravenous immunoglobulin (IVIG) at 2 g/kg given in a single infusion over 10–12 h together with oral acetylsalicylic acid at 80–100 mg/kg daily in four divided doses. At least two-thirds of the patients will be afebrile by 24 h after the IVIG infusion ends, and approximately 85 % of the patients will be afebrile by 36 h. IVIG treatment should be initiated as soon after diagnosis as possible. Although IVIG infusion within 10 days of the onset of illness has been shown to reduce the risk of coronary artery abnormalities, IVIG should still be given in patients diagnosed after 10 days of illness. Rare exceptions to this would include the patient who is now afebrile, without signs or symptoms of inflammation (and without current clinical manifestations of Kawasaki disease), who has no laboratory evidence of inflammation (normal CRP and ESR), and who has a normal echocardiogram. The mechanism of action of IVIG in Kawasaki disease remains unknown. Possible mechanisms of IVIG include decreasing cytokine production, neutralization of antigens, blockade of the Fc receptors, and suppression of activated monocytes and macrophages [58]. The adverse effects of IVIG include fever, chills, aseptic meningitis, renal insufficiency (usually reversible), anaphylaxis, and hypotension [59]. Like other blood products, IVIG undergoes tests for HIV blood-borne pathogens, but transmission of a currently unknown pathogen (i.e., currently not tested for) is theoretically possible. Live vaccines should be deferred for 11 months after receipt of high-dose IVIG.

High-dose acetylsalicylic acid (80–100 mg/kg daily) is used together with IVIG, due to the anti-inflammatory effect. In Japan, lower salicylate doses are utilized (30–50 mg/kg daily). Generally, the acetylsalicylic acid can be reduced to a low-dose regimen of 3–5 mg/kg daily (given as a once-daily oral dose), once the child is afebrile for at least 48 h after IVIG treatment. Low-dose acetylsalicylic acid acts as an inhibitor of platelet function (antithrombotic effect), which should be continued for 6–8 weeks if no coronary artery abnormalities are present (patients with coronary artery abnormalities should be on prolonged acetylsalicylic acid). The risks of acetylsalicylic acid include elevation of transaminases, transient hearing loss, and, rarely, Reye syndrome. Although Reye syndrome is rarely experienced in the current era, the association with acetylsalicylic acid has been reported in Kawasaki disease patients [60]. Therefore, acetylsalicylic acid should be withheld if patients have any symptoms of influenza or varicella virus infection. Cardiologists often substitute other antiplatelet agents temporarily in this situation. Immunizing patients and family members with influenza vaccine is an important way to decrease the risk of patients contracting influenza. Patients with Kawasaki disease should receive only the injectable (killed) influenza vaccine (live, attenuated influenza vaccine is contraindicated in patients taking acetylsalicylic acid).

Second- and Third-Line Treatment

Approximately 10–15 % of patients may have persistent or recurrent fever $\geq$36 h after the initial IVIG administration. Persistent fever generally represents ongoing inflammation. These patients, as initial IVIG nonresponders, are at risk of developing coronary artery abnormalities. There are no randomized studies indicating the best second-line therapy for IVIG nonresponders. Many experts use a second dose of 2 g/kg IVIG [61]. Other experts use steroids, infliximab, or rarely cyclosporine. A small subset of patients (2 % or 3 %) will remain febrile despite second-line therapy. There are no guidelines for the

management of these children who have ongoing inflammation and a high risk of coronary involvement. Referral to a center with expertise in Kawasaki disease management is recommended for children who do not respond to a first dose of IVIG.

Corticosteroid therapy has been used as second- or third-line therapy for patients with ongoing fever and inflammation after IVIG, but steroid use has been controversial. An early Japanese study, published in 1979, suggested that corticosteroids were associated with increased risk of coronary aneurysms and may be potentially harmful to patients with Kawasaki disease [62]. After this report, the use of corticosteroids in Kawasaki disease decreased dramatically. However, this study was based on a small number of patients and was not stratified according to risk factors for the development of aneurysms; thus, these data are difficult to interpret. Since this report, several studies have reported more positive experiences with steroids. A Japanese retrospective study revealed that steroid pulse therapy was beneficial in the prevention of coronary artery abnormalities [63]. Pulsed steroid therapy is usually initiated using intravenous methylprednisolone 30 mg/kg over 2 h once daily for 1–3 days. The risks associated with steroid therapy include leukocytosis, hyperglycemia, and rarely hypertension. Intravenous heparin or low molecular weight heparin may be given along with methylprednisolone, especially in patients with coronary artery abnormalities because steroids may increase thrombogenicity. A meta-analysis involving 862 Kawasaki disease patients demonstrated significant reduction in the incidence of coronary artery aneurysms in the patients receiving corticosteroids [64]. However, a US randomized trial reported that IVIG plus steroid pulse therapy had equal efficacy, but found no significant difference in the prevalence of coronary artery abnormalities, adverse events, and illness days spent in hospital compared with standard IVIG therapy [65]. As a result of conflicting studies, steroids (pulse steroids or oral steroids with taper) continue to be controversial in Kawasaki disease but are used by many experts as second- or third-line therapy [66].

A recent, prospective, multicenter, randomized, open-label, blinded-endpoints trial (*RAISE study*) investigated the use of steroids plus IVIG versus IVIG + acetylsalicylic acid in 125 patients with Kawasaki disease at increased risk for coronary artery aneurysms [67]. In this study, patients at high risk for severe Kawasaki disease (as defined by a risk score) [66] were randomized to one of two treatment arms: IVIG (2 g/kg given over 24 h and acetylsalicylic acid 30 mg/kg per day) versus IVIG (2 g/kg given over 24 h) plus prednisolone (2 mg/kg per day given until the CRP <5 mg/dL; once the CRP was <5 mg/dL, the predinsolone was tapered over the next 15 days, then stopped). The incidence of coronary artery abnormalities was significantly lower in the IVIG plus prednisolone group than in IVIG plus acetylsalicylic acid group. This study has not been repeated in the US population to date. Additionally, the standard therapy in Japan (used in one of the study arms) is different from that used in the United States. Specifically, the dose of acetylsalicylic acid used in Japan (30 mg/kg/day) is lower than the 80–100 mg/kg/day dose used in the United States as "high-dose" therapy for the first few days after diagnosis. Second, IVIG is infused over 24 h in Japan, as opposed to 10–12 h in the United States. Whether either of these factors or whether the same results would be seen in a more genetically diverse population is unknown. However, this study is an interesting addition and will likely prompt further research in this area. Other therapies that are reported in the literature for refractory Kawasaki disease include infliximab [68], abciximab [69], cyclosporine [70], cyclophosphamide [71], methotrexate [72], and plasma exchange [73]. Infliximab is a humanized mouse monoclonal antibody to tumor necrosis factor-α. Tumor necrosis factor-α is a pro-inflammatory cytokine and plays a pivotal role in rheumatoid arthritis and other vasculitides. Tumor necrosis factor-α levels are elevated in patients with acute Kawasaki disease, and the highest serum levels were observed in patients with coronary artery abnormalities [74]. Recently, the experience of infliximab use in IVIG nonresponders in an

open-label study has been published [68]. However, there are no large studies addressing the clinical efficacy of infliximab therapy. Although several reports have described potential benefits of other therapies in Kawasaki disease, no large studies on the efficacy of these agents exist.

Follow-Up Management

Prevention of Coronary Artery Thrombosis

Once a coronary artery aneurysm has been identified, it is critical to prevent thrombosis and occlusion in the aneurysm. There are no prospective or controlled data in children with coronary artery aneurysms; thus, recommendations are derived from the experience in adults with coronary disease. The prevention regimens, including antiplatelet therapy and/or anticoagulant therapy, depend on the severity of coronary involvements.

Antiplatelet Therapy

Platelet activation persists throughout the convalescent phase in Kawasaki disease. After the acute phase, there is a hypercoagulable state when marked elevation of the platelet count occurs, predisposing to coronary artery thrombosis. Therefore, antiplatelet therapy plays a pivotal role in the management of patients with or without coronary artery abnormalities. Agents used in antiplatelet therapy include acetylsalicylic acid, dipyridamole, or clopidogrel. Low-dose acetylsalicylic acid therapy at 3–5 mg/kg per day as a single dose is recommended and utilized for patients without coronary artery aneurysm or with mild coronary ectasia. In patients with more severe coronary abnormalities, dipyridamole or clopidogrel may be given in addition to acetylsalicylic acid therapy because the combination therapy may suppress platelet activation by different mechanisms.

Anticoagulant Therapy

Patients with moderate to large coronary aneurysms may have a greater risk of thrombosis compared to those with small aneurysm or transient dilation. Furthermore, patients with giant or multiple aneurysms have the highest risk of thrombosis. For these patients, anticoagulant therapy is usually used together with antiplatelet therapy, which is warfarin plus acetylsalicylic acid. The warfarin therapy should be maintained at therapeutic levels with international normalized ratio of 2.0–2.5 in children.

Thrombolytic Therapy

Myocardial infarction may occur despite aggressive anticoagulant therapy, especially in patients with giant aneurysms. When serial echocardiograms show a coronary artery thrombosis, intravenous or direct intracoronary infusion (by catheterization) of thrombolytic therapy may be indicated to restore patency of the coronary artery. Tissue plasminogen activator, streptokinase, and urokinase with systemic heparin infusion have been reported used in case series [75–77]. Thrombolytic therapy is most effective within 6 h of onset of symptoms. Generally, administration of thrombolytic agents is recommended soon after the thrombosis occurs, to try to reduce mortality in patients with myocardial ischemia. Although the ideal thrombolytic regimen and technique of catheter intervention have not been established in the pediatric population, immediate thrombolytic therapy is suggested in patients with evidence of ischemic events.

Catheter and Surgical Interventions

Use of percutaneous transluminal coronary angioplasty (PTCA) has been reported in children with stenotic lesion of coronary arteries [78]. Unfortunately, it is often difficult to reestablish the patency of the coronary arteries due to marked calcifications in stenotic lesions. Therefore, PTCA is particularly useful in Kawasaki disease patients without severe calcification and

within a relatively short time period after the onset of the illness. Percutaneous coronary rotational ablation is another strategy for patients with severe calcified coronary stenosis [78].

Long-term outcomes after coronary artery bypass grafting (CABG) in childhood are still unknown. CABG is sometimes recommended for patients with long-segment stenosis, ostial stenosis, multiple stenoses, severe occlusion of the left main coronary artery or the left anterior descending coronary artery, severe occlusion of greater than one major coronary artery, collateral coronary arteries in jeopardy, recurrent myocardial infarction, or severe left ventricular dysfunction.

Long-Term Follow-Up

The outcomes resulting from coronary aneurysms vary from complete resolution of the aneurysm to fatal myocardial infarction. The long-term prognosis for patients with coronary abnormalities depends on the size of the coronary aneurysm or other cardiovascular involvement. Recently the American Heart Association Guidelines devised a stratification system to categorize patients by their risk level as follows [33].

American Heart Association Guideline Risk Level I and II

Risk Level I is characterized by no coronary artery changes on echocardiography, and Risk Level II includes those patients with transient coronary artery ectasia or dilatation resolving by 8 weeks after disease onset. In both groups, antiplatelet therapy such as acetylsalicylic acid is recommended only through 6–8 weeks after disease onset, and no activity restrictions are recommended. Periodic reassessment, counseling regarding cardiovascular risk factors, and adherence to a heart-healthy diet and lifestyle are recommended. For Risk Level I, periodic reassessment is recommended for every 5 years, whereas follow-up is recommended every 3–5 years for patients that are classified as Risk Level II.

Risk Level III

This group includes patients with isolated small to medium (3–6 mm, z-score 3–7) coronary artery aneurysms. Low-dose aspirin is recommended to be continued at least until the aneurysms regress. Echocardiographic and electrocardiographic evaluations are recommended annually. Counseling regarding cardiovascular risk factors and adherence to a heart-healthy diet and lifestyle are recommended. Although physical activity does not need to be limited, a cardiac stress test should be performed every 2 years. If abnormalities are noted on the stress test, angiographic evaluation is recommended.

Risk Level IV and V

This group includes the patients with at least one large coronary artery aneurysm (>6 mm), including giant aneurysms and the patients with multiple or complex aneurysms without obstruction. All of these patients require long-term antiplatelet therapy. Warfarin therapy is also required when patients have giant aneurysms. Echocardiographic and electrocardiographic evaluations are recommended every 6 months. In addition, cardiac catheterization should be performed between 6 and 12 months after the acute illness. A cardiac stress test is recommended to help delineate the degree of physical activity that should be allowed. Collision and high-impact or contact sports should be avoided due to risk of bleeding with anticoagulant therapy. The Risk Level V group includes patients with coronary artery obstruction evidenced by angiography. Recommendations are similar to those of Risk Level IV, but these patients often also require beta-adrenergic blocking agents. Like all other patients with a history of Kawasaki disease, counseling regarding other cardiovascular risk factors and adherence to a heart-healthy diet and lifestyle (with modified physical activity if indicated) is recommended.

Future Studies

Approximately 50–70 % of coronary aneurysms will regress within the first year or 2 years after diagnosis [79]. The likelihood of coronary aneurysm regression over time appears to be related to the aneurysm size. Other factors influencing aneurysm resolution include age at presentation, proximal versus distal location, and morphology of the aneurysm [79]. As aneurysms regress, fibrous intimal thickening and endothelial dysfunction may occur in patients with Kawasaki disease [80]. Some follow-up studies have shown prolonged endothelial dysfunction even in children without any evidence of coronary abnormalities [81]. Definitive long-term follow-up studies on children with Kawasaki disease are ongoing.

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