

CHAPTER 88

Kawasaki Disease

ETIOLOGY

Kawasaki disease (KD) is a vasculitis of unknown etiology that is characterized by multisystem involvement and inflammation of small to medium-sized arteries with resulting aneurysm formation.

EPIDEMIOLOGY

KD is the second most common vasculitis of childhood. It is more common in children of Asian descent. It has been described in variable frequency in all parts of the world; the highest frequency is in Japan. KD most commonly occurs more often in males, in children younger than 5 years of age, with a peak between 2 and 3 years; it is rare in children older than 7 years. The incidence in the United States is approximately 6 per 100,000 children who are younger than 5 years of age. A seasonal variability has been described with a peak between February and May, but the disease occurs throughout the year. In the United States KD is the leading cause of acquired heart disease in children.

CLINICAL MANIFESTATIONS

The clinical course of KD can be divided into three phases, each with unique manifestations. Aneurysmal involvement of the coronary arteries is the most important manifestation of KD.

Acute Phase

The acute phase of KD, which lasts 1–2 weeks, is marked by sudden onset of a high, hectic **fever** without an apparent source. The onset of fever is followed by **conjunctival erythema**; mucosal



FIGURE 88.1 (A) Kawasaki disease. Hyperemia of the tongue with prominent lingual papillae (“red strawberry tongue”). (B) The conjunctivitis in this patient demonstrates the notable perilimbal sparing (halo of noninvolvement adjacent to the iris). (C) Nonpitting edema of the hand in a young male with Kawasaki disease. (D) Confluent, erythematous patches and plaques of the sole in a young boy with Kawasaki disease. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. 5th ed. Philadelphia, PA: Elsevier; 2016:504–505 [figs. 21-20, 21-23, 21-24, 21-26].)

changes, including dry, **cracked lips** and a **strawberry tongue**; **cervical lymphadenopathy**; and swelling of the hands and feet (Fig. 88.1). Conjunctivitis is bilateral, bulbar, and nonsuppurative. Cervical lymphadenopathy is found in 70% of children and should be greater than 1.5 cm in diameter for the purposes of diagnosis. A rash, which can vary in appearance, occurs in 80% of children with KD and may be particularly accentuated in the inguinal area and on the chest. Extreme irritability is prominent, especially in infants. Abdominal pain and hydrops of the gallbladder, cerebrospinal fluid pleocytosis, sterile pyuria, and arthritis, particularly of medium-sized to large joints, may occur. Carditis in the acute phase may be manifested by tachycardia, shortness of breath, or overt heart failure. **Giant coronary artery aneurysms**, which are rare but occur most commonly in very young children, can appear during this phase.

Subacute Phase

The subacute phase, which lasts until about week 4, is characterized by gradual resolution of fever (if untreated) and other symptoms. **Desquamation** of the skin, particularly of the fingers and toes, appears at this point. The platelet count, previously normal or slightly depressed, increases to a significant degree (often >1 million/ mm^3). This phase heralds the onset of **coronary artery aneurysms**, which may also appear in the convalescent phase and pose the highest risk of morbidity and mortality. Risk factors for development of coronary artery aneurysms include prolonged fever, prolonged elevation of inflammatory parameters such as the erythrocyte sedimentation rate (ESR), age younger than 1 year or older than 6 years, poor response to therapy, and male gender.

Convalescent Phase

The convalescent phase begins with the disappearance of clinical symptoms and continues until the ESR returns to normal, usually 6–8 weeks after the onset of illness. Linear nail creases

known as Beau lines of the fingernails may appear during this phase.

LABORATORY AND IMAGING STUDIES

It is particularly important to exclude other causes of fever, notably infection. It is appropriate to obtain blood and urine cultures and to perform a chest x-ray. In the acute phase, inflammatory parameters are elevated, including white blood cell count, C-reactive protein (CRP), and the ESR, which can be profoundly elevated (often >80 mm/hr). Platelet counts may be inappropriately low or normal. A lumbar puncture, if performed to exclude infection, may reveal pleocytosis. Tests of hepatobiliary function may be abnormal. Greatly elevated platelet counts develop during the subacute phase. The development of coronary artery aneurysms is monitored by performing two-dimensional echocardiograms, usually during the acute phase, at 1–2 weeks, and again at 4–6 weeks. More frequent echocardiograms and, potentially, coronary angiography are indicated for patients who develop coronary artery abnormalities.

DIFFERENTIAL DIAGNOSIS

The diagnosis of KD is based on the presence of fever for more than 5 days without an identifiable source and the presence of four of five other clinical criteria (Table 88.1).

The diagnosis of **incomplete (atypical) KD**, which occurs more commonly in infants, is made when fever is present for at least 5 days, even if only two or three clinical criteria are present, particularly in the presence of coronary artery aneurysms. The diagnosis of KD should be considered in infants younger than 6 months of age with fever for at least 7 days even if no other criteria are present. Because many of the manifestations of KD are found in other illnesses, many diagnoses must be considered and excluded before the diagnosis of KD can be established (Table 88.2).

TABLE 88.1 Criteria for Diagnosis of Kawasaki Disease

Fever of >5-day duration associated with at least four* of the following five changes:
Bilateral nonsuppurative conjunctivitis
One or more changes of the mucous membranes of the upper respiratory tract, including pharyngeal injection, dry fissured lips, injected lips, and “strawberry” tongue
One or more changes of the extremities, including peripheral erythema, peripheral edema, periungual desquamation, and generalized desquamation
Polymorphous rash, primarily truncal
Posterior cervical lymphadenopathy >1.5 cm in diameter
Disease cannot be explained by some other known disease process

*A diagnosis of Kawasaki disease can be made if fever and only three changes are present in conjunction with coronary artery disease documented by two-dimensional echocardiography or coronary angiography.

TABLE 88.2 Differential Diagnosis of Kawasaki Disease

INFECTIOUS
Scarlet fever
Epstein-Barr virus
Adenovirus
Meningococcemia
Measles
Rubella
Roseola infantum
Staphylococcal toxic shock syndrome
Scalded skin syndrome
Toxoplasmosis
Leptospirosis
Rocky Mountain spotted fever
Multisystem inflammatory syndrome in children (SARS-CoV-2)
INFLAMMATORY
Juvenile idiopathic arthritis (systemic)
Polyarteritis nodosa
Behçet syndrome
HYPERSENSITIVITY
Drug reaction
Stevens-Johnson syndrome

Multisystem inflammatory disease–children (MIS-C) is a complication of COVID-19 characterized by fever, rash, non-purulent conjunctivitis, gastrointestinal symptoms, cardiac involvement (myocarditis, coronary artery lesions), shock, marked inflammation (elevated CRP, fibrinogen, ESR, ferritin, procalcitonin), and a positive serologic test for SARS-CoV-2

(often with a negative polymerase chain reaction [PCR] for the virus). In the absence of a positive serologic test, it is often difficult to distinguish from KD.

TREATMENT

Intravenous immunoglobulin (IVIG) is the mainstay of therapy for KD, although the mechanism of action is unknown. A single dose of IVIG (2 g/kg over 12 hours) usually results in rapid defervescence and resolution of clinical illness in most patients and, more important, reduces the incidence of coronary artery aneurysms. Aspirin is initially given in **antiinflammatory doses** (60–80 mg/kg/day divided every 6 hours) in the acute phase. Once the fever resolves, aspirin is reduced to **antithrombotic doses** (3–5 mg/kg/day as a single dose) and given through the subacute and convalescent phases, usually for 4–6 weeks, until follow-up echocardiography documents the absence or resolution of coronary artery aneurysms.

Up to 10% of children with KD initially fail to respond satisfactorily to IVIG therapy. Most of these patients respond to retreatment with IVIG, but an alternative preparation of IVIG may be required. Corticosteroids or infliximab are used less frequently in KD, as opposed to other vasculitides, but may have a role during the acute phase if active carditis is apparent or for children with persistent fever after two doses of IVIG.

COMPLICATIONS

Most cases resolve without sequelae. Myocardial infarction has been documented, most likely caused by stenosis of a coronary artery at the site of an aneurysm. Coronary artery aneurysms found on autopsy in older children following sudden cardiac death may have been due to past KD. Other complications are listed in Table 88.3.

TABLE 88.3 Complications of Kawasaki Disease

Coronary artery thrombosis
Peripheral artery aneurysm
Coronary artery aneurysms
Myocardial infarction
Myopericarditis
Heart failure
Kawasaki shock syndrome
Hydrops of gallbladder
Aseptic meningitis
Irritability
Arthritis
Sterile pyuria (urethritis)
Thrombocytosis (late)
Diarrhea
Pancreatitis
Peripheral gangrene

PROGNOSIS

IVIG reduces the prevalence of coronary artery disease from 20–25% in children treated with aspirin alone to less than 5% in children treated with IVIG and aspirin. Prolonged inflammation (>10 days) puts the patient at greater risk for developing coronary artery aneurysms. Other than the risk of persistent coronary artery aneurysms, KD has an excellent prognosis.

PEARLS FOR PRACTITIONERS

See *Rheumatic Diseases of Childhood: Pearls for Practitioners* at the end of this section.