

# 36

## Kawasaki Disease

■ Synonyms:	Mucocutaneous lymph node syndrome
■ Etiology:	Unknown
■ Associations:	None
■ Histology:	Coronary arteritis with macrophages, plasma cells, lymphocytes, and occasionally eosinophils; skin nonspecific with dermal edema and perivascular lymphocytes
■ Evaluation:	Throat culture, serologic testing for viral infections, urinalysis, complete blood count with differential, electrocardiogram, transthoracic echocardiography in younger patients, magnetic resonance angiography in older patients
■ Treatment:	Intravenous gammaglobulin and aspirin
■ Prognosis:	Good with treatment, 1%–2% cardiac sudden death due to coronary arteritis

Kawasaki disease, or mucocutaneous lymph node syndrome, was first described in Japan in the late 1960s as an illness characterized by persistent fever, conjunctivitis, mucous membrane changes, acral erythema with desquamation, and cervical adenopathy, associated with coronary arteritis (1,2). While earlier descriptions of the disease were limited to Asia and Hawaii, the disease is now known to occur worldwide. The disease is primarily one of young children, with 85% of cases occurring in children under five years. It is uncommon in children less than 6 months. There have been some epidemiologic investigations linking Kawasaki disease to freshly cleaned carpets, humidifier use, and living near a body of water, but these associations have not been observed consistently (3).

The etiology of Kawasaki disease is unknown. There are seasonal peaks in the winter and spring months, with occasional epidemics. There are only rare cases of the disease occurring in infants less than three months, suggesting protection via passive maternal antibodies. These findings have suggested an infectious agent, yet extensive investigations have failed to detect one. There is a recently described association between Kawasaki disease and a novel coronavirus in a small series, but further study will be required to evaluate the strength of this association (4). IgA plasma cells have been found in early and subacute lesions of Kawasaki vasculitis, suggesting the

possibility of an immune response to a gastrointestinal or respiratory tract pathogen (5). Furthermore, the IgA response is oligoclonal rather than polyclonal, favoring an antigen-driven response over nonspecific B-cell activation (6). The incidence of Kawasaki disease is greater in the Asian population and in siblings and parents of those with the disease, suggesting a genetic predisposition (3).

Patients with Kawasaki disease present with persistent fever despite antibiotics, conjunctival congestion, oral dryness, redness, fissuring of the lips, strawberry tongue, and mucosal erythema (Figures 36.1 and 36.2). These findings are accompanied by acral erythema and edema, followed by desquamation in the convalescent stage (Figure 36.3). The acral erythema spreads to a truncal exanthem within three to five days (Figure 36.4). Cervical adenopathy is also a relatively constant feature. Other symptoms may include diarrhea, arthralgia or arthritis, and aseptic meningitis (2). A feature found in the majority of patients, but not emphasized in early descriptions, is perineal erythema and subsequent desquamation (Figure 36.5) (7). Small sterile pustules have also been described in some patients with Kawasaki disease, occurring symmetrically on erythematous skin on the buttocks, axillae, genitalia, and extensor surfaces (8).

Diagnostic criteria for Kawasaki disease are as follows (3):



**FIGURE 36.1.** Conjunctival injection. Courtesy of Nancy Esterly, MD.



**FIGURE 36.2.** Lip and tongue erythema and edema. Courtesy of Nancy Esterly, MD.

### Diagnostic Criteria for Kawasaki Syndrome

Presence of fever for at least 5 days, 4 of the 5 criteria below, and lack of another known disease process to cause the illness:

1. Bilateral conjunctival injection
2. Changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue
3. Polymorphous rash
4. Changes of the extremities: peripheral edema, peripheral erythema, periungual desquamation
5. Cervical adenopathy

Strict use of these criteria will miss cases of Kawasaki disease, so-called “atypical” or “incomplete” Kawasaki disease. These are patients in whom coronary arteritis is present, in association with persistent fever, and fewer than four other diagnostic criteria. Vigilance for these cases is mandated because of the potential for disastrous consequences in untreated coronary arteritis. In cases of suspected Kawasaki disease, imaging of the coronary vessels is indicated. In young children, trans-thoracic echocardiography can be used to diagnose coronary artery changes with high specificity, but in older children and in adults, visualization of the vessels is more difficult. Coronary X-ray angiography has been the



**FIGURE 36.3.** Acral edema and erythema. Courtesy of Nancy Esterly, MD.



**FIGURE 36.4.** Morbilliform exanthem. Courtesy of Nancy Esterly, MD.



**FIGURE 36.5.** Inguinal and genital accentuation of exanthem with minute pustules. Courtesy of Nancy Esterly, MD.

mainstay of evaluation. However, recently, magnetic resonance angiography has been shown to be comparable to X-ray angiography, and is likely to become the future standard for evaluation of coronary abnormalities in

older children and in adults (9). Laboratory findings may include elevated erythrocyte sedimentation rate and C-reactive protein, leukocytosis with left shift, pyuria, proteinuria, or anemia. In cases of suspected Kawasaki disease, a suggested diagnostic evaluation is given.

#### Diagnostic Evaluation in Suspected Kawasaki Disease

1. Complete blood count and differential
2. Throat and nasal cultures
3. Nasopharyngeal swab for adenovirus, rapid direct fluorescent antigen test
4. Urinalysis
5. Erythrocyte sedimentation rate, C-reactive protein
6. Electrocardiogram
7. Echocardiogram or magnetic resonance angiography
8. BUN, creatinine, SGOT, SGPT

The principal differential diagnosis of Kawasaki syndrome includes scarlet fever, Staphylococcal scalded skin syndrome, toxic shock syndrome, and adenovirus infection. A summary of important features of each is given in Table 36.1.

TABLE 36.1. Differential Diagnosis of Kawasaki Disease

	Kawasaki Disease	SS	Scarlet Fever	Toxic Shock Syndrome	Adenovirus (10)
<b>Age group</b>	>3 months, <5 years	<3 months most common, but any age	2–10 years most common	Menstruating women, uncommon in children	Usually <10 years
<b>Conjunctival involvement</b>	+, injection	+, purulent	–	+/-, injection	Usually present
<b>Strawberry tongue</b>	+	–	+, white early on	+/-	rare
<b>Lip involvement</b>	+	–	–	–	–
<b>Acral</b>	+	+, but part of diffuse involvement	–	+, but part of diffuse involvement	–
<b>Perineal</b>	+	+, but part of diffuse involvement	+/-	+/-	–
<b>Bullae</b>	–	+	–	–	–
<b>Other</b>	Cervical adenopathy, may have aseptic meningitis, pyuria	May be able to culture <i>Staphylococcus aureus</i>	+throat culture, group A <i>Streptococcus</i> , truncal exanthem accentuated in skin folds, “sandpaper” texture on skin	+culture for <i>Staphylococcus aureus</i> , sometimes group A <i>Streptococcus</i> , from primary site of infection, scarlatiniform eruption, rhabdomyolysis, liver dysfunction, thrombocytopenia	May have exudative pharyngitis and conjunctivitis

The typical pathologic finding in Kawasaki disease is that of a vasculitis, occurring most commonly in the coronary arteries, but also occurring in renal, iliac, femoral, and mesenteric arteries. There are initially subendothelial cell collections of macrophages, lymphocytes, and neutrophils (11). Plasma cells and eosinophils are also constituents of the infiltrate (5,12). The inflammation eventually becomes transmural, and can extend along the adventitia as in polyarteritis nodosa. In Kawasaki disease, in contrast to polyarteritis nodosa, there are fewer neutrophils, and fibrinoid necrosis is not prominent (11). Biopsy specimens of skin in Kawasaki disease do not have specific findings, but in those with sterile pustules, the location is subcorneal (8).

The mainstay of treatment of Kawasaki disease is intravenous gammaglobulin, with aspirin. A comparison of treatment with aspirin alone versus aspirin with gammaglobulin reveals a striking reduction in the development of coronary aneurysms in the gammaglobulin group, and greater resolution of existing coronary lesions over time in the same group (13). Treatment with gammaglobulin is generally given using 2 mg/kg as a single infusion (3). High-dose aspirin is recommended early on in the disease to prevent thrombotic events, 80–100 mg/kg per day, divided in four doses, for up to 14 days, and then 3–5 mg/kg as a single daily dose for seven weeks or longer (14). Some authors advocate lower doses of aspirin (15). Aspirin does not reduce aneurysm formation (16). A recent retrospective study has called into question the benefit of aspirin therapy, but for the present, it remains part of the standard treatment (17). Eighty-nine percent of patients respond to a single dose of gammaglobulin, but the remainder will remain febrile. A second dose of gammaglobulin has been advocated in those remaining febrile for the 48 to 72 hours following the first dose. Of these, two-thirds will become afebrile with the second dose (18). Patients with persistent fever after one dose of gammaglobulin, who receive additional gammaglobulin, have a decrease in cardiac complications (19). Treatment options for those refractory to two doses of intravenous gammaglobulin include additional doses of gammaglobulin, pulse methylprednisolone, infliximab, cyclosporine, cyclophosphamide, and plasmapheresis (3,20). A small trial of pulse methylprednisolone in addition to gammaglobulin and aspirin revealed more rapid resolution of symptoms in the group treated with steroids compared to the standard treatment group (gammaglobulin and aspirin), but no differences in cardiac outcome between the two groups (21).

The principal complication of Kawasaki disease is coronary artery disease. Sudden death occurs in 1%–2% of patients in the acute phase of the disease, and coronary aneurysms develop in 25% of patients with the disease; 55% eventually regress, but some are complicated by ste-

nosis or occlusion (22). Patients with giant aneurysms (those greater than 8 mm in diameter) are at considerably higher risk for complications (3). Lifelong follow-up is warranted in those with cardiac abnormalities. Recent data suggest that persistent coronary lesions tend to occur in patients with persistently elevated indices of inflammation, such as C-reactive protein, serum amyloid-A, interleukin-6, and soluble intercellular adhesion molecule-1 (23). This potential functional relationship may have implications for long-term treatment. Recurrent skin peeling has been described in patients with a history of Kawasaki disease, without any other evidence of disease reactivation. Some of these episodes have been associated with respiratory tract infections (24).

Kawasaki disease may resemble several bacterial toxin-mediated diseases, and, less likely, viral infections. Early diagnosis is important because of the ability to dramatically decrease the risk of complications with gammaglobulin treatment.

## References

1. Kawasaki T. Mucocutaneous lymph node syndrome: Clinical observation of 50 cases. *Jpn J Allerg* 1967; 16: 178–222 (in Japanese).
2. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 1974; 54: 271–276.
3. Burns JC, Glode MP. Kawasaki syndrome. *Lancet* 2004; 364: 533–544.
4. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis* 2005; 191: 499–502.
5. Rowley AH, Eckerly CA, Hans-Martin J, Shulman ST, Baker SC. IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. *J Immunol* 1997; 159: 5946–5955.
6. Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. *J Immunol* 2001; 166: 1334–1343.
7. Fritter BS, Lucky AW. The perineal eruption of Kawasaki syndrome. *Arch Dermatol* 1988; 124: 1805–1810.
8. Kimura T, Miyazawa H, Watanabe K, Moriya T. Small pustules in Kawasaki disease: A clinicopathological study of four patients. *Am J Dermatopathol* 1988; 10: 218–223.
9. Greil GF, Stuber M, Botnar RM, et al. Coronary magnetic resonance angiography in adolescents and young adults with Kawasaki disease. *Circulation* 2002; 105: 908–911.
10. Barone SR, Pontrelli LR, Krilov LR. The differentiation of classic Kawasaki disease, atypical Kawasaki disease, and acute adenoviral infection: Use of clinical features and a rapid direct fluorescent antigen test. *Arch Pediatr Adolesc Med* 2000; 154: 453–456.
11. Jennette JC. Implications for pathogenesis patterns of injury in small- and medium-sized-vessel vasculitis. *Cleveland Clin J Med* 2003; 69: SII-33–38.

12. Terai M, Yasukawa K, Honda T. Peripheral blood eosinophilia and eosinophil accumulation in coronary microvessels in acute Kawasaki disease. *Pediatr Infect Dis J* 2002; 8: 777–781.
13. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986; 315: 341–347.
14. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: The Seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126: 645S–687S.
15. Brogan PA, Bose A, Burgner D, et al. Kawasaki disease: An evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002; 86: 286–290.
16. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997; 131: 888–893.
17. Hsieh KS, Weng KP, Lin CC, Huang TC, Lee CL, Huang SM. Treatment of Kawasaki disease: Aspirin's role in the febrile stage revisited. *Pediatrics* 2004; 114: 689–693.
18. Freeman AF, Shulman ST. Refractory Kawasaki disease. *Pediatr Infect Dis J* 2004; 23: 463–464.
19. Miura M, Ohki H, Tsuchihashi T, et al. Coronary risk factors in Kawasaki disease treated with additional gammaglobulin. *Arch Dis Child* 2004; 89: 776–780.
20. Weiss JE, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as novel therapy for refractory Kawasaki disease. *J Rheumatol* 2004; 31: 808–810.
21. Sundel RP, Baker AL, Fulton DR, Newburger JW. Corticosteroids in the initial treatment of Kawasaki disease: Report of a randomized trial. *J Pediatr* 2003; 142: 611–616.
22. Kato H, Sugimura T, Akagi T, et al. Long term consequences of Kawasaki disease. *Circulation* 1996; 94: 1379–1385.
23. Mitani Y, Sawada H, Hayakawa H, et al. Elevated levels of high-sensitivity C-reactive protein and serum amyloid-A late after Kawasaki disease: Association between inflammation and late coronary sequelae in Kawasaki disease. *Circulation* 2005; 111: 38–43.
24. Michie C, Kinsler V, Tulloh R, Davidson S. Recurrent skin peeling following Kawasaki disease. *Arch Dis Child* 2000; 83: 353–355.