CASE STUDY

Recognition of Kawasaki Disease

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Abstract

Kawasaki disease is one of the most common vasculidities of childhood. It is the leading cause of acquired heart disease in children in the US.[1] Although its course is typically self-limited, it is important that the clinician have a high degree of suspicion for its presence in light of its potential cardiac complications. It should be included in the differential diagnosis for any child with prolonged fever that is unresponsive to antibiotics. Diagnosis is often difficult in that the symptoms tend to present at different times. Usually a detailed medical history and multiple examinations (on different days) are needed to establish the diagnosis. Here, we present the case of a boy in whom a delayed diagnosis of Kawasaki disease was made after he had made multiple visits to pediatricians and also to the Emergency Department. In addition, the diagnostic criteria, differential diagnosis, treatment, and possible complications of Kawasaki disease are reviewed here.

Introduction

Kawasaki disease is a generalized vasculitis that affects medium-size arteries. It is characterized by systemic inflammation that manifests as persistent fever, erythema of the mucous membranes, bilateral nonexudative conjunctivitis, rash, swelling and redness of the hands and feet, and cervical lymphadenopathy. Diagnosis is made difficult by the fact that these symptoms are not usually all present at the same time; the only persistent symptom is fever. Therefore, repeated examinations usually occur before a diagnosis of Kawasaki disease is made. Ninety percent of cases involve children younger than five years, with the average age of patients being two years. The disease is relatively uncommon in children younger than six months. Boys are affected about 50% more often than girls are. The disease occurs year round, but cases tend to cluster in the winter and spring.[2] The annual incidence of Kawasaki disease in the US is 17 to 18 children per 100,000.[3] The incidence is greatest in those with Asian ancestry.

The disease tends to be self-limiting and usually resolves without treatment within about 12 days.[4] However, serious cardiac complications can occur, such as coronary artery aneurysms, decreased myocardial contractility, congestive heart failure (CHF), arrhythmias, and myocardial ischemia. Early recognition and treatment significantly reduces the incidence of these complications. Without treatment, 20% to 25% of patients develop cardiac complications;[2,4,5] with treatment, the incidence decreases to 4%.[4] Treatment should be initiated as soon as the diagnosis is made and should involve the administration of intravenous immunoglobulin (IVIG) and high-dose aspirin.

Case Study

A previously healthy boy, age 11 years, was seen in both the clinic and the Emergency Department a total of 5 times during a 13-day period for symptoms that included persistent fevers of up to 40º C [104° F], vomiting, diarrhea, headache, cough, sore throat, and rash. The rash was erythematous and initially appeared on his groin and upper thighs. It eventually spread to involve most of his torso, thighs, and upper arms; the skin in the involved areas later began to peel. The boy also developed redness and swelling on the palms of his hands and soles of his feet. His presentation differed at each examination, with the only consistent symptom being high fevers. No laboratory tests were done except for a throat culture, which produced negative findings. It was not until his fifth visit 13 days after initial presentation that Kawasaki disease was suspected. At that point, the patient reported ongoing fevers, vomiting, diarrhea, ear pain, and rash. The skin on his distal fingertips had begun to blister and peel in sheets. His lips were dry and cracked, and he had tender, right-sided cervical lymphadenopathy. It was also noted that he had lost approximately 7 kg since his initial visit 13 days earlier. Laboratory tests done at the time produced normal findings except for the following: erythrocyte sedimentation rate (ESR), 107 mm/h; C-reactive protein (CRP) level, 98 mg/L; hemoglobin level, 11.1 mg/dL;

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sodium level, 132 mEq/L; potassium level, 3.3 mEq/L; antistreptolysin O titer, >1500 Todd units/mL.

The boy was then hospitalized and treated with IVIG and high-dose aspirin. An echocardiogram produced normal findings. By the following morning, his symptoms and appearance had improved, and within two days, he was afebrile. He was then discharged from the hospital and instructed to take aspirin for six weeks. A follow-up echocardiogram done six weeks after discharge showed normal coronary arteries, and repeat ESRs gradually trended down to near normal over the two month period following discharge.

Discussion

Diagnosis

The symptoms of Kawasaki disease are representative of systemic inflammation. It is important to realize that often not all of the symptoms are present at the same time, so repeated examinations may be necessary before a diagnosis can be made. Diagnosis requires the presence of persistent, unexplained fevers for at least five days. Fevers are usually high (often 40° C [104° F] or higher) and are unresponsive to antibiotics and minimally responsive to antipyretics. Four or more of the following symptoms must also be present (Table 1):

- Mucous membrane changes, including red, swollen, cracked lips and strawberry tongue, are commonly present in patients with either typical or with incomplete Kawasaki disease [discussed under the heading "Incomplete (Atypical) Kawasaki Disease"]. Pharyngeal erythema without exudate is also common. The presence of exudate makes the diagnosis of Kawasaki disease less likely.
- Bilateral, nonexudative conjunctivitis typically begins within days of the onset of fever, and is present in >90% of patients with Kawasaki disease.[4] Photophobia is common. The conjunctivitis of Kawasaki disease tends to spare the limbus. These patients may also develop anterior uveitis.
- Rash tends to be polymorphic. It often begins in the perineal region as erythema and progresses to desquamation. Later it tends to involve the trunk and extremities.
- Cervical lymphadenopathy is the least consistent feature of Kawasaki disease and is absent in as many as three-quarters of patients with the condition. It is usually unilateral and tends to involve the anterior cervical lymph nodes. One or more lymph nodes must be larger than 1.5 cm in diameter.[4]
- Extremity changes are often the last manifestation to develop. They include swelling of the hands and feet, with erythema of the palms and soles. Sheetlike desquamation of the hands and feet often occurs during the convalescent phase and tends to begin at the periungual region. This type of desquamation is characteristic of Kawasaki disease.[6]
- Of note is that younger children with Kawasaki disease tend to be more irritable than they are with other conditions.[2] Although not included in the diagnostic criteria, gastrointestinal complaints such as nausea, vomiting, and diarrhea are frequent findings in Kawasaki disease. Arthritis and arthralgia are also commonly seen.

Table 1. Diagnostic criteria for Kawasaki disease

Diagnosis requires unexplained fever for ≥5 days in addition to the presence of ≥4 of the following:
• Oral mucosa changes, including red or cracked lips, pharyngeal erythema, or strawberry tongue
• Bilateral nonexudative conjunctivitis, sparing the limbus
• Cervical lymphadenopathy, usually unilateral, with one node ≥1.5 cm in size
• Polymorphous rash
• Extremity changes (erythema of palms and soles, swelling of hands and feet, periungual desquamation in the convalescent phase)

Table 2. Laboratory findings suggestive of Kawasaki disease

• Elevated erythrocyte sedimentation rate (≥40 mm/h) or C-reactive protein level (≥3.0 mg/L)
• White blood cell count ≥15,000/μL
• Normochromic, normocytic anemia for age
• Sterile pyuria (≥10 white blood cells per high-power field)
• Serum alanine aminotransferase level >50 U/L
• Serum albumin level ≤3.0 mg
• Platelet count ≥450,000/mm^3 after seven days of illness

Laboratory Tests

The diagnosis of Kawasaki disease is clinical, and there are no confirmatory laboratory tests. However, certain laboratory findings can be used to support the diagnosis, which include those listed in Table 2 and the following:

- Thrombocytosis, which usually occurs around the second to third week of illness, with an average value of 700,000/mm^3 [1]
- Moderate elevation of transaminase levels, which occurs in 30% of patients (due to hepatic congestion)
- Abnormal serum lipid levels, including elevated triglyceride levels and low-density lipoprotein levels and decreased high-density lipoprotein levels. These can take years to return to normal if the patient is not treated with IVIG[4]
- Hyponatremia (sodium levels <135 mEq/L), is associated with an increased risk of coronary artery aneurysms.[4]

Echocardiography

An echocardiogram should be obtained at the time of diagnosis in all patients with typical or incomplete Kawasaki disease to look for cardiac complications. A repeat echocardiogram should be done six to eight weeks after disease onset to confirm the efficacy of treatment.

Disease Course

The course of Kawasaki disease tends to be self-limited, with symptoms lasting an average of 12 days without treatment. It consists of three phases:

- Acute febrile phase: This is the phase during which most symptoms occur. It tends to last 7 to 14 days[2]
- Subacute phase: This lasts from the end of the fever until approximately day 25. This is the phase during which desquamation, arthritis, and arthralgias usually occur. Elevated platelet counts are also commonly seen during this phase[2]
- Convalescent phase: This covers the period from when clinical signs disappear until the acute-phase reactants (eg, ESR) return to normal. The average duration is six to eight weeks after the onset of illness.[2]

Complications

As already mentioned, cardiac complications can occur in 20% to 25% of untreated patients and in 4% of treated patients.[2,4,5] The most common cardiac complication seen in Kawasaki disease is coronary artery aneurysm; however, other cardiac sequelae can occur, including decreased myocardial contractility, congestive heart failure, arrhythmias, pancarditis, pericardial effusion, and myocardial ischemia. It has surpassed rheumatic fever as the most common cause of acquired heart disease in children.[1] Mortality from cardiovascular complications in Kawasaki disease is approximately 0.1% to 2%.[1]

Coronary artery aneurysms usually become apparent 1 to 3 weeks after the onset of fever; appearance more than 5 weeks after fever onset is uncommon.[2] They tend to resolve in 50% of patients within 5 to 18 months.[4] Expeditious diagnosis is important because treatment with IVIG within the first 10 days of illness produces a fivefold reduction in the incidence of coronary artery aneurysms.[4]

Certain patient characteristics appear to be related to an increased risk of developing coronary artery aneurysms:[4]

- Age <1 year or >6 years (because of delayed diagnosis)
- Male sex
- Fever for >14 days
- Serum sodium level <135 mEq/L
- Hematocrit <35%
- White blood cell count >12,000/μL.

Cardiovascular complications can be prominent in the acute phase and are the leading cause of morbidity and mortality in Kawasaki disease. Decreased contractility can occur in the acute phase, and it occasionally progresses to CHF. However, normal contractility is usually restored after treatment with IVIG.[4,7] Patients are unlikely to develop clinically significant cardiac dysfunction after the fevers have resolved.

Myocardial infarction (MI) can occur during the acute phase but is more likely to occur one year or even several years later, especially in patients with giant aneurysms (ie, those >8 mm in diameter).[7] Symptoms of MI in children include inconsolable crying, vomiting, stomach upset, and shock. The majority of these infarcts occur during sleep or rest.[2]

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Patients younger than one year appear to be at the greatest risk of developing cardiovascular complications, possibly because of delayed diagnosis.[4] Therefore it is important to have a high degree of suspicion for the disease regarding children of all ages who appear with prolonged, unexplained fevers.

Incomplete (Atypical) Kawasaki Disease

Patients may be found to have incomplete Kawasaki disease if they exhibit fever and some of the classic symptoms but not enough to meet the diagnostic criteria (ie, fewer than four of the five principal clinical findings). Ten percent of children who develop coronary artery aneurysms fall into this category.[4] Infants, especially those younger than six months, are especially likely to have an incomplete presentation. The finding most consistently absent in incomplete Kawasaki disease is cervical lymphadenopathy (present in only 10%). Rash is absent in 50%, and extremity changes are absent in 40%. Mucous membrane changes are the most consistent finding.

Laboratory evaluation is recommended for the following:[8]

- Patients younger than six months with unexplained fever for ≥7 days, even if they exhibit none of the classic symptoms of Kawasaki disease
- Patients of any age with unexplained fever for ≥5 days who exhibit three or fewer of the classic symptoms
- Laboratory evaluation should include: complete blood cell count, ESR, CRP level, urinalysis, alanine aminotransferase level, and albumin level.

Differential Diagnosis

Kawasaki disease can closely mimic other syndromes and infections (Table 3). It is commonly misdiagnosed as a viral exanthem. Symptoms that point to a diagnosis other than Kawasaki disease include exudative conjunctivitis, exudative pharyngitis, generalized (rather than cervical) lymphadenopathy, discrete intraoral lesions, and a bullous or vesicular rash.

Toxin-mediated illnesses, such as group A streptococcus infections (eg, toxic shock syndrome and scarlet fever) can also present with fever, rash, mucous membrane changes, and abnormal extremity findings.[4,6] Desquamation in Kawasaki disease tends to affect the hands and feet, as it does in toxic shock syndrome; however, in Kawasaki disease, it usually begins in the periungual region. In scarlet fever, the desquamation tends to be diffuse and flaking, whereas in Kawasaki disease it tends to be sheetlike.[6] Toxin-mediated illnesses generally lack the articular involvement.

Measles, echovirus, adenovirus, and Epstein-Barr viral infections can also mimic Kawasaki disease; however, these conditions usually lack the signs of systemic inflammation as well as the extremity changes seen in Kawasaki disease.[4] Another condition that can be mistaken for Kawasaki syndrome is acrodynia (mercury hypersensitivity reaction). This also presents with fever, rash, swelling of the hands and feet, desquamation, and photophobia. However, this is relatively rare and is a much less likely diagnosis unless there is a convincing history of mercury exposure.

Although the patient described in the case study was somewhat atypical regarding age, his symptoms were highly suggestive of Kawasaki disease. Swelling of the palms and soles as well as periungual desquamation are very typical for Kawasaki disease. The elevated ESR and CRP levels also support the diagnosis, as does the rapid improvement in symptoms after the initiation of treatment.

Etiology

The cause of Kawasaki disease is unknown. Data support the idea of an infectious etiology; however, no one particular virus or bacteria has been implicated. There are circumstantial data supporting the role of

Table 3. Differential diagnosis of Kawasaki disease[5]

Indications	Kawasaki disease	Stevens-Johnson syndrome	Streptococcal scarlet fever	Toxic shock syndrome	Systemic juvenile rheumatoid arthritis
Age (years)	Usually <5	Any age	Usually 2–8	Usually >10	2–5
Fever	Persistent	Prolonged	Variable, usually <10 d	Usually <10 d	Prolonged
Eyes	Nonexudative conjunctivitis, limbal sparing	Exudative conjunctivitis, keratitis	Normal	Conjunctivitis	Normal
Oral mucosa	Diffuse erythema, strawberry tongue	Erythema, ulceration, pseudomembrane formation	Pharyngitis, strawberry tongue	Erythematous	Normal
Extremities	Erythema of palms and soles, indurative edema, periungual desquamation (tends to be sheetlike)	Normal	Flaky desquamation	Swelling of hands and feet	Arthritis
Rash	Erythematous, polymorphous; targetoid or purpuric	Target lesions	Sandpaper rash, Pastia sign, circumoral pallor	Erythroderma	Transient, salmon pink
Cervical lymphadenopathy	At least one lymph node ≥1.5 cm	Normal	Painful swelling	Normal	Diffuse adenopathy
Characteristic lab results	Systemic inflammation, anemia, transaminitis, thrombocytosis after day 7	Associated herpes virus infection	Positive throat culture	Thrombocytopenia	Systemic inflammation, anemia
Other	Arthritis	Arthralgia, associated herpes virus infection (30%–75%)	Throat culture positive for group A streptococcus	Mental status changes, coagulopathy, shock	Pericarditis

Adapted from Yanagihara R, Todd JK. Acute febrile mucocutaneous lymph node syndrome. Am J Dis Child 1980 Jun;134(6):603–14, with permission of the American Medical Association.

some bacterial toxins (eg, staphylococcal toxic shock toxin, streptococcal erythrogenic toxin) and viruses (Epstein-Barr virus, parvovirus, HIV-2); however, these data have not been substantiated.[2,4,6,9,10] Evidence in support of an infectious etiology includes seasonal distribution, age of affected persons, and the fact that the disease often occurs in epidemics. As the condition is more frequently found in those with Asian ancestry, it is likely that genetic factors play a role as well.

Treatment

Treatment should begin with IVIG and high-dose aspirin as soon as the diagnosis is made. The recommended dose of IVIG is 2 g/kg given as a one-time infusion during an 8- to 12-hour period. It is recommended that this be given within the first 10 days of illness, the point before which aneurysms typically develop.[2,4] The exact mechanism of action of IVIG is unknown, but it appears to have generalized anti-inflammatory properties. In addition to prevention of coronary artery aneurysms, it also appears to help normalize lipid profiles and improve cardiac contractility.

The patient should also be given aspirin for its anti-inflammatory and antiplatelet activity. This should be given as 80 to 100 mg/kg per day, divided into 4 doses. This dosage should be continued until the child has been afebrile for 48 hours. The dose should then be decreased to 3 to 5 mg/kg per day. This lower dose should be continued until laboratory markers (eg, ESR, platelet counts) return to normal, unless coronary artery aneurysms are present.

Prognosis

The overall prognosis for patients with Kawasaki disease is dependent on the severity of coronary artery involvement as a risk factor for myocardial ischemia. Patients with aneurysms larger than 8 mm are at highest risk for MI. Aneurysms that are 8 mm or smaller tend to regress over time, and those that are 6 mm or smaller tend to resolve completely.[7] Patients without any cardiovascular abnormalities tend to do well and are generally asymptomatic at their long-term follow-up examination.

Conclusion

Kawasaki disease is a common vasculitis of childhood that presents with unexplained fevers for more than five days, rash, oral mucous membrane changes, conjunctivitis, cervical lymphadenopathy, and peripheral extremity changes. Because all of the symptoms are rarely present together at the same time, the diagnosis can be difficult to make, and the clinician must have a high degree of suspicion for the disease. Kawasaki disease should be included in the differential diagnosis for any child with a prolonged unexplained fever, and the appropriate medical history questions should be asked. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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