Case Report

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Incomplete Kawasaki Disease Clinically Diagnosed From Urgent Care: A Case-Report-Based Review

Urgent Message: The accurate and prompt diagnosis of Kawasaki disease depends on clinicians' familiarity with the diagnostic criteria and ability to recognize the waxing and waning manifestations of this pediatric condition.

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Abstract

Introduction

Kawasaki Disease (KD) is a panvasculitis condition that is the leading cause of coronary artery disease (CAD) and heart disease in childhood. It is a diagnosis that depends heavily on the clinician's ability to recognize the clinical manifestations. Lab tests and other tests can aid clinicians with the diagnosis, but they do not confirm the presence of KD. The key to efficient diagnosis is recognizing the clinical diagnostic criteria for KD and promptly initiating treatment. The diagnostic criteria involves fever for at least 5 days and at least 4 out of the 5 additional clinical findings, with symptoms not explained by another diagnosis. If only 2 or 3 criteria are met with a fever for at least 5 days, incomplete KD can be diagnosed. Although KD can be a self-limited disease, morbidity and mortality can arise if children are inadequately treated. Complications of KD associated with delays in treatment include coronary artery aneurysms. Intravenous immunoglobulins (IVIG) and high-dose aspirin are the cornerstones of KD treatment.

Clinical Presentation

A 3-year-old boy presented to a local urgent care (UC) twice within a period of several days. He had fever at both visits and associated rash, conjunctivitis, lymphadenopathy, and oral involvement. Rapid testing for Strep pharyngitis, throat culture, and influenza viral testing were negative. The fever had persisted for 6 days by the time of his second visit and was not responsive to antipyretics.

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Diagnosis, Interventions, and Outcome

Based on the clinical criteria for diagnosis, KD was confirmed at the second UC visit. The patient was referred immediately to a pediatric emergency department (ED). The hospital clinicians felt that the diagnosis of KD was appropriate, and the patient was admitted. He received IVIG and was discharged without any adverse events. At a 1 month cardiology follow-up, his echocardiogram was reassuring, and no apparent persistent cardiac consequences were evident.

Conclusion

The accurate and prompt diagnosis of KD depends heavily on clinicians' familiarity with the diagnostic criteria and ability to recognize the commonly waxing and waning manifestations of this pediatric condition. While KD can be diagnosed clinically, signs and symptoms overlap with many self-limited illnesses for which children commonly present to UC. However, vigilance and consideration for KD are critical as early diagnosis dramatically reduces the risk of cardiac complications.

Introduction

Kawasaki disease, formerly known as mucocutaneous lymph node syndrome, is a panvasculitis condition affecting children most commonly under the age of 5.[1] It was discovered by Tomikasu Kawasaki, MD, in 1967.[1] Mucocutaneous lymph node syndrome gets its name because it typically affects mucous membranes, skin, lymph nodes, and blood vessels.[2] Kawasaki disease received increased attention during the SARS-CoV-2 (COVID-19) pandemic given its relation to the multisystem inflammatory syndrome in children (MIS-C), a novel entity and uncommon, but serious complication of COVID in children. MIS-C consists of myocarditis, toxic shock syndrome, and KD.[3]

While COVID-19 can lead to MIS-C, a Kawasaki-like illness, the etiology of KD remains poorly understood. Multiple candidate theories regarding the etiology have been proposed, including autoimmunity most notably, and research on the pathogenesis continues.[2,4]

The incidence of KD in children under 5 years ranges from 3.4 to 218.6 cases per 100,000 children and varies regionally throughout the world.[5] The prevalence of KD is highest in Asia, specifically in Japan, China, and Korea. Mortality associated with KD, which typically relates to cardiovascular complications, has been declining from greater than 1% in the 1970s to approximately 0.01% today. This decline in mortality is likely driven by trends toward earlier detection and increasing recognition of incomplete and atypical versions of the condition.[5]

UC is ideally suited for detection of KD, as the diagnosis relies heavily on clinical criteria.[6] There are no laboratory findings specific to the diagnosis of KD. However, laboratory findings can offer support for the diagnosis and are required, especially in infants who less commonly have the major criteria present.

Case Presentation

A 3-year-old boy was brought in by his mother with concerns for 4 days of tactile fever, runny nose, and decreased appetite. The mother denied that the patient had any vomiting, diarrhea, cough, ear pain, rashes, recent travel, or insect bites. The patient's vaccinations were up to date.

Vital signs at the initial visit included:

- Temperature: 39.7°C
- Heart Rate: 154 beats per minute
- Blood Pressure: 90/60 mm/Hg
- Respiratory Rate: 24 breaths per minute, unlabored
- Oxygen Saturation: 99% (on room air)

Physical exam revealed the patient to be alert and in no distress. The patient's eyes appeared watery, and there was mild conjunctival injection without purulent discharge. Bilateral tympanic membranes appeared normal. He had a strawberry-appearing tongue, erythema to the lips, and was drooling. There was mild bilateral, non-tender, anterior cervical lymphadenopathy (>1 cm). The patient's cardiopulmonary and abdominal exams were unremarkable. There was a vague blanching maculopapular rash noted throughout the patient's trunk and on the bilateral arms and legs, which spared the palms and soles.

During the visit, the patient had rapid swabs for Group A Streptococcus (GAS) and influenza, which were both negative, and a throat culture for Group A Streptococcus was sent to the lab, given consideration for scarlet fever. The patient was presumptively diagnosed with a viral infection.

The initial UC clinician recommended supportive treatment, prescribed saline nasal spray for congestion, and acetaminophen and ibuprofen as needed for fever. The mother was given strict return precautions including fever lasting more than an additional 2 or more days, or refractory to antipyretics, vomiting, difficulty breathing, rapid spreading of the rash, or other concerning changes.

Two days later, the throat culture results returned negative. The clinician following up on tests called the patient's mother to inform her of the results; at that

Table 1: Comparison of Kawasaki Disease to MIS-C[3]

Kawasaki Disease	Multisystem Inflammatory Syndrome in Children
• Median age of 6 months to 5 years old • Lymphopenia is rare – Thrombocytopenia, although less common, is a sign of disseminated intravascular coagulation and is directly related to increased risk of coronary artery aneurysms	• Median age of 6 to 11 years old • Lymphopenia is present • Lower platelet count compared to KD • Lower absolute lymphocyte count compared to KD • Higher levels of C-reactive protein, N-terminal pro-B-type natriuretic peptide, troponin and ferritin compared to KD • Coagulation abnormalities including elevated D-dimer and fibrinogen
• No known evidence of SARS-CoV-2 virus exposure or detection	• SARS-CoV-2 virus detected weeks before symptom onset
• High incidence of: – Conjunctival injection – Oral mucous membrane changes • Low incidence of shock	• High incidence of: – Gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea) – Myocarditis – Coagulopathy – Shock • Higher morbidity compared to KD

time, she stated that she was actually already on her way returning to the UC center because the fever had continued despite antipyretics. At this point, the patient had been febrile for a total of 6 days.

Vital signs at the second visit included:

- Temperature: 39.5°C
- Heart Rate: 150 beats per minute
- Blood Pressure: 92/60 mm/Hg
- Respiratory Rate: 24 breaths per minute, unlabored
- Oxygen Saturation: 98% (on room air)
- Weight: 28 pounds (12.73 kilograms)

On physical exam, the patient seemed more fatigued than his initial visit but was non-toxic appearing. He was alert, but fussy, and had normal skin turgor. The patient had more pronounced conjunctival injection. It was noted that the erythematous rash on his trunk and extremities had increased since his first visit and now also involved the face. The mild, bilateral cervical lymphadenopathy was present and unchanged. The patient had moist mucous membranes and the strawberry tongue persisted and was now accompanied by pharyngeal erythema.

Differential Diagnosis and Medical Decision Making

KD is an important consideration to keep in mind whenever evaluating children with fever, however, certainly this is only one condition in a necessarily broad differential. Strep throat and other Group A Streptococcal infections (eg, scarlet fever) and influenza are common causes of pediatric fever. Thankfully, most UC centers have point-of-care (POC) testing available to evaluate for these conditions.

Adenovirus can mimic signs and symptoms of KD, especially when conjunctivitis and pharyngitis are present. However, adenovirus typically presents with exudative conjunctivitis, exudative pharyngitis, and fever, and typically does not present with other signs and symptoms of KD including erythema and swelling of the hands and feet, strawberry tongue, and rash.[7] Some UC centers have access to respiratory viral panel (RVP) nucleic acid testing which may be considered in situations with an ambiguous etiology. However, clinicians should exercise caution in interpreting these tests as up to 70% of children presenting with fever may test positive for one or more viral pathogen, yet testing positive for a respiratory virus does not confirm this is the source of present fever.[8]

POC urinalysis can be considered if urinary tract infections is suspected or when children present with fever and no localizing symptoms. In unvaccinated children, less common infections, such as measles, may be responsible. Depending on the geography and travel history, conditions ranging from leptospirosis to Rocky Mountain spotted fever (RMSF) might be considered. Finally, non-infectious causes such as Stevens-Johnson syndrome, hematologic malignancies, and autoimmune conditions, such as juvenile idiopathic arthritis, might be considered.[9]

Kawasaki disease can mimic atypical pneumonia, with the possibility of interstitial and/or peribronchial infiltrates seen on chest radiography.[7] In the presence of what seems like atypical pneumonia in children aged 3 and older, KD is a consideration when there is no response to antibiotics or the patient is failing to improve

or defervesce as expected.

This patient's illness occurred before the COVID-19 pandemic. If he had been seen during the era of COVID, MIS-C secondary to COVID-19 certainly would have been important to include in the differential for this presentation. While almost half of the patients with MIS-C meet the criteria for KD, there are key differences between the two illnesses worth noting as detailed in **Table 1**.[3]

Final Diagnosis and Disposition

Given that this patient's fever had lasted for 6 days and there were no alternate explanations for his symptoms, the clinician astutely had a high suspicion for KD. Although the patient did not meet all the major criteria for diagnosis, the UC clinician recommended that the patient be referred to the pediatric ED.

The pediatric clinicians caring for the patient diagnosed the patient with incomplete KD, and he was admitted and started on IVIG. He was hospitalized for nearly a week until the fevers had resolved and his echocardiogram was verified to be stable and normal. He subsequently followed up as an outpatient 1 month later in the pediatric cardiology clinic. A repeat echocardiogram did not show any coronary artery aneurysms, and the patient had fully recovered.

Discussion

KD is the leading cause of acquired coronary artery disease and heart disease in childhood.[10] Treatment of KD with IVIG within 10 days of fever onset reduces the risk of these complications.[11] Fortunately for the patient and his family, the clinician suspected KD on the sixth day of fever and referred him to the ED where the diagnosis was confirmed.

Laboratory tests that help in confirming the diagnosis of KD include elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine aminotransferase, anemia, leukocytosis, hypoalbuminemia, and pyuria. Thrombocytosis commonly develops somewhat later in the disease course. Although these laboratory findings are not specific to KD, the diagnosis can be excluded if the platelet count, ESR, and CRP are normal after the seventh day of illness.[12]

The diagnosis of KD relies on presence of clinical manifestations. The American Heart Association (AHA) first published the KD criteria for diagnosis in 2004,[13] and these updated most recently in 2017.[7] A high fever (at least 38.5-39C) must be present for 5 days or more and accompanied by 4 out of 5 of the major diagnostic criteria as seen in **Table 2**.[7] If 4 or more of the major diagnostic criteria are met, and there is redness and swelling of the hands and feet, the diagnosis of KD can be made after only 4 days of fever instead of 5.[7] Other diagnoses with similar symptoms importantly must be excluded to confirm KD, such as viral exanthems (eg, measles), other viral infections (eg, adenovirus and enterovirus), Stevens-Johnson syndrome, vector-borne illnesses (eg, RMSF), and GAS and Staphylococcal toxin-mediated diseases (eg, scarlet fever and toxic shock syndrome).[10,14] It is important to note that not all criteria necessary to diagnose KD need be simultaneously present to make the diagnosis. To that end, when considering KD, it is worthwhile to inquire about the presence of symptoms that may have resolved prior to UC evaluation.

In addition to the major clinical findings, other signs and symptoms that may be present but are not diagnostic of KD are enumerated in **Table 2**.

KD tends to present with less overt symptomatology in infants. Diagnostic clues to KD in infants include the presence of prolonged fever and irritability, especially in those less than 6 months of age, or aseptic meningitis, culture-negative shock, cervical lymphadenitis unresponsive to antibiotics, and persistent pharyngeal inflammation unresponsive to antibiotics.[7]

If only 2 or 3 of the major clinical findings are met in addition to fever for at least 5 days, atypical, otherwise known as incomplete, KD may be diagnosed.[14] Incomplete KD comprises between 15% and 35% of cases with the likelihood of incomplete, or atypical, KD being highest in children less than 12 months or over 5 years.[4] Those with incomplete KD are roughly 3 times more likely to experience a delay in diagnosis.[15]

The patient in this case report had incomplete KD as he only had 3 of the 5 major criteria present for diagnosis. Specifically, the major criteria present were: fever (>39C) for 6 days accompanied by a polymorphous rash, oral mucosal changes (ie, strawberry tongue and erythematous lips), and conjunctival injection. The patient had mild bilateral cervical lymphadenopathy, but it did not meet the specific criterion as they were not >1.5cm or unilateral.

The primary goal in the diagnosis of KD surrounds early identification, as this offers the best opportunity to prevent cardiac complications. IVIG and high-dose aspirin are the mainstays of treatment. The incidence of coronary artery aneurysms (CAA) is 15–25% in untreated patients, and less than 5% in patients who receive IVIG.[4] CAA occur mostly in children less than 12 months and those older than 5 years, and in those for whom IVIG is initiated late in the disease process. Nearly 65% of children with KD under the age of 6 months will develop CAA, even if promptly treated with IVIG.

Table 2. Diagnosis of Kawasaki Disease (adapted from AHA 2017 update)[7]

Kawasaki disease can be diagnosed with a fever (generally ›38.5C) for ≥ 5 days with 4 out of the 5 of the major clinical findings listed below.

Kawasaki disease can be diagnosed after only 4 days of fever instead of 5 in the following scenarios:
- Must meet 4 or more of the major diagnostic criteria listed below
- Edema and erythema of the hands and feet must be present

Incomplete KD can be diagnosed with a fever for ≥ 5 days, less than 4 of the major clinical findings, and compatible laboratory or echocardiographic findings.

Transient clinical findings should be included in the diagnostic criteria, even if not present during evaluation.

Major Clinical Findings Considered Diagnostic Criteria For KD	
1. Extremity changes	**Acute** • Edema of hands and feet • Erythematous rash of palms and soles **Subacute (weeks 2-3)** • Desquamation of palms and soles • Periungual desquamation of fingers and toes
2. Polymorphous rash	• Diffuse maculopapular • Urticarial • Erythema multiforme-like
3. Conjunctival injection	• Bilateral non-exudative conjunctival injection
4. Oral mucosal changes	• Erythema of lips • Lips cracking • Strawberry tongue • Diffuse injection of oral and pharyngeal mucosa
5. Cervical lymphadenopathy	• Unilateral and measuring › 1.5 cm diameter
Other Clinical Findings Not Included In The Diagnostic Criteria For KD That May Present	
Cardiovascular	• Myocarditis or pericarditis • Coronary artery abnormalities • Medium-sized non-coronary artery aneurysms • Peripheral gangrene • Aortic root enlargement • Shock – Patients with shock are at higher risk of complications including coronary artery aneurysms and IVIG resistance
Respiratory	• Infiltrates on chest X-ray • Pulmonary nodules
Musculoskeletal	• Arthritis
Gastrointestinal	• Vomiting and diarrhea • Abdominal pain • Jaundice • Gallbladder hydrops • Hepatitis • Pancreatitis
Nervous system	• Aseptic meningitis • Irritability • Facial nerve palsy • Sensorineural hearing loss • Seizures
Genitourinary	• Urethritis • Hydrocele
Other	• Desquamating rash to the groin • Anterior uveitis • Retropharyngeal phlegmon • Erythema and induration of Bacillus Calmette-Guérin (BCG) injection site

It appears that the size of CAA is positively correlated with the duration of fever.[16] If the fever lasts more than 10 days, it also increases the risk of IVIG resistance.[17] Because of this, children with KD should start IVIG treatment within 10 days of fever onset to minimize cardiovascular morbidity and IVIG resistance.

Children with incomplete KD are at higher risk of developing CAA, which is largely felt to be attributed to delays in diagnosis.[18] UC clinicians should consider this when discharging pediatric patients with suspected viral illnesses and ensure that parents seek repeat evaluation in the case of persistent fevers. It is also important to appreciate that KD can co-exist even in presence of infections if patients meet the diagnostic criteria for KD.[7]

Thankfully, the patient outlined had a favorable outcome, as do most children when KD is diagnosed early and appropriate treatment is initiated. Unfortunately, patients who are not diagnosed with KD in a timely fashion, as is often the case with incomplete KD, may not respond to standard therapies and are at higher risk of serious cardiac complications.

Take Home Points

Kawasaki disease is a clinical diagnosis. Lab tests can be helpful but do not confirm the diagnosis of KD.

- To diagnose KD, a high fever (>38.5°C) must be present for at least 5 days and accompanied by a minimum of 4 out of the 5 the major criteria which are:
  - Extremity changes, including erythematous rash and swelling of palms and soles
  - Polymorphous rash
  - Conjunctival injection
  - Oral mucosal changes
  - Unilateral cervical lymphadenopathy
- If there are 4 or more of the major diagnostic criteria met, and there is redness and swelling of the hands and feet, the diagnosis of KD can be made after only 4 days of fever.
- If only 2 or 3 of the major diagnostic criteria are met with at least 5 days of fever, incomplete KD may be diagnosed.
- The symptoms of KD do not have to be present at the same time to make the diagnosis. It is important to ask parents about the presence of symptoms that may have been resolved before the urgent care visit.
- The primary goal is to diagnose KD as early in the disease process as possible to avoid the complications associated with it, including coronary artery aneurysms, or coronary artery dilatation, and IVIG resistance.
- IVIG is the mainstay of treatment, along with high-dose aspirin for anti-inflammation.
- Strict return precautions are important to convey to parents, especially when there is suspicion for KD.

Ethics Statement and Patient Perspective

The patient and his family were lost to follow-up and were therefore unable to give consent. Patient demographics were changed to protect patient anonymity and confidentiality. ■

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