

## Atypical Kawasaki Disease in 2-Months Old Infant Presenting with Aseptic Meningitis

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### Abstract

The diagnosis of incomplete or atypical Kawasaki disease (KD) is challenging. Children presenting with febrile illnesses may have few of the classical diagnostic criteria, yet develop clinical, laboratory and echocardiographic findings compatible with the condition.

Early recognition and prompt treatment of KD is essential for better outcomes. This is particularly the case for infants who are at a greater risk of developing complications such as coronary artery aneurysms. This may be partly attributed to late diagnosis or initiation of therapy.

This report discusses the case of a febrile infant with atypical Kawasaki disease presenting with aseptic meningitis and coronary artery aneurysm.

The case highlights the importance of considering atypical Kawasaki disease in any infant with prolonged fever (more than seven days), following exclusion of infectious causes and in the absence of classical diagnostic criteria.

**Keywords:** Atypical kawasaki; 2-months old infant; Aseptic meningitis

### Abbreviations:

KD: Kawasaki Disease; CSF: Cerebral Spinal Fluid; IVIG: Intravenous Immunoglobulins; GBS: Group B Streptococcus; CAL: Coronary Arteries Lesions

### Introduction

Kawasaki disease is an acute, self-limiting systemic vasculitis. It currently represents the leading cause of acquired heart disease in children in developed countries [1,2].

The precise etiology of KD is unknown and no single pathognomonic clinical or laboratory finding exists for confirmation of diagnosis. Diagnosis is therefore based on a constellation of signs and symptoms set by both the American Heart Association [3] and Japanese Kawasaki Disease Research Committee [4].

Some children do not fulfill the diagnostic criteria for KD, but have several findings compatible with those of the condition. In these cases, the diagnosis of incomplete KD may be made. Though clinically challenging, a delay in diagnosis should be avoided at all costs due to the risk of coronary complications occurring in patients even with incomplete KD.

### Case Presentation

A two-month-old term boy was born by normal delivery to a mother with group B streptococci (GBS) in her urine during the last trimester of pregnancy. His mother was treated with antibiotics during

pregnancy and labour. The child presented to our pediatric emergency centre with a two-day history of low grade fever (38.2-38.6°C) measured rectally with no other associated symptoms such as decreased activity or feeding. Given his maternal risk factor, sepsis was suspected and therefore a full septic screen was performed. Following this, the patient was commenced on ceftriaxone 100 mg/kg/day intravenously.

Physical observations revealed the following: rectal temperature 38.2°C, blood pressure 90/60 mmHg and respiratory rate 50 breath/minute. On examination, he was alert, active and playful. Anterior fontanelle was opened and non-bulging. His lips and tongue were normal and none of the following were present: lymphadenopathy, skin rash, desquamation, hand/foot swelling, conjunctivitis or organomegaly.

Laboratory findings upon presentation were grossly normal (Table 1).

Except for high inflammatory markers and CSF cells count.

The patient was treated as aseptic meningitis. He was referred to the IV clinic where he continued receiving ceftriaxone at 100 mg/kg/day intravenously.

Four days following the start of antibiotics, he continued to spike fever up to 39.5°C rectally. Apart from the fever he was in a general good condition, physically well with no clinical signs or symptoms.

On day 11 of his fever, the patient was transferred to an inpatient setting at our hospital where re-evaluation was done. A high suspicion of atypical Kawasaki disease was raised following repeated investigations (Table 2). The decision was then made to commence intravenous immunoglobulins (IVIG) (2 g/kg) and high dose aspirin (80 mg/kg/day).

Laboratory test	Results
<b>Haematology</b>	
Leucocytes	8.3 x 10 <sup>3</sup> /ul
Neutrophils	2.6 x 10 <sup>3</sup> /ul
Lymphocytes	4.4 x 10 <sup>3</sup> /ul
Haemaglobin	11.3 g/dL
Haematocrit	32%
Platelets	306 x 10 <sup>3</sup> /ul
<b>Biochemistry</b>	
C – reactive protein	114 mg/dL
Erythrocyte Sedimentation rate	33 mm at one hour
Aspartate aminotransferase	46 U/L
Alanine aminotransferase	42 U/dL
Others	
Blood virology and cultures	Normal
Urinalysis	Normal
<b>Cerebrospinal fluid (CSF)</b>	
Leucocytes	134 u/l
Neutrophils	52/ul
Lymphocytes	40/ul
Red Blood Cells (RBC)	763/ul
Glucose	2.4 mmol/l
Protein	0.7 g/l
Virology and cultures	Negative

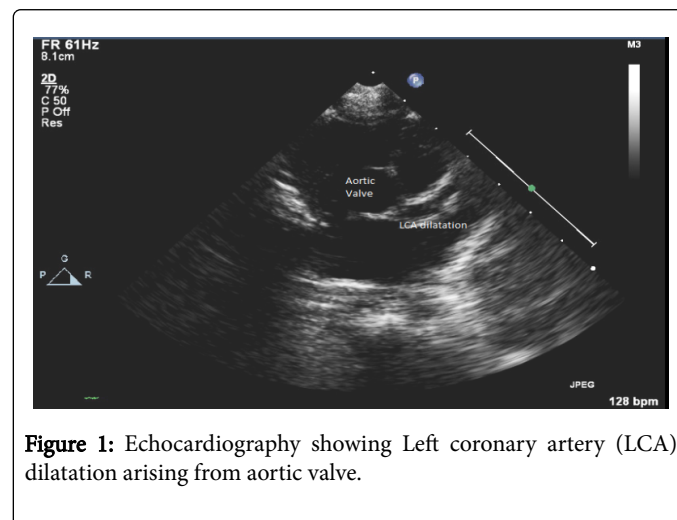
**Table 1:** Blood and CSF results for patient.

Laboratory test	Results
<b>Haematology</b>	
Leucocytes	23 x 10 <sup>3</sup> /ul
Neutrophils	12.2 x 10 <sup>3</sup> /ul
Lymphocytes	8.4 x 10 <sup>3</sup> /ul
Haemaglobin	10.2 g/dL
Platelets	702 x 10 <sup>3</sup> /ul
<b>Biochemistry</b>	
C-reactive protein	144 mg/dL
Erythrocyte Sedimentation rate	40 mm at one hour

**Table 2:** Blood results for patient in the second week of illness.

Suspicion for atypical KD was raised based on prolonged fever course more than 7 days duration without an obvious cause or source of infection, not responding to antibiotics and abnormal lab results that started to appear during the second week of illness supported by negative CSF and blood cultures as well as virology.

24 hours following the start IVIG and aspirin, echocardiography was performed and showed a significantly dilated left main coronary artery (LMCA) and left anterior descending artery (LAD). In addition, multiple aneurysmal dilations were also demonstrated in the right coronary artery (Figure 1).



**Figure 1:** Echocardiography showing Left coronary artery (LCA) dilatation arising from aortic valve.

After receiving IVIG and aspirin, the patient remained stable and afebrile for the whole 72 hours of his hospital admission with no mucocutaneous manifestations. He appeared to develop coryzal symptoms with associated rapid breathing. This was thought to be an isolated respiratory syncytial virus (RSV) infection. He did not require any respiratory support and eventually aspirin dose was reduced to 5 mg/kg/day. The patient was subsequently discharged with planned follow up in both the general pediatric and cardiology clinics.

## Discussion

Kawasaki disease, also known as mucocutaneous lymph node syndrome, is an acute, self-limiting systemic type of vasculitis, affecting small and medium-sized arteries, and occurs predominantly in young children [5].

It was first described in Japan in 1967 [5]. Till this day, the aetiology remains unknown, yet KD is the leading cause of acquired heart disease in children in developed countries.

Untreated Kawasaki disease may lead to the formation of coronary artery aneurysms and sudden cardiac death in children.

Due to the non-specific nature of symptoms (vomiting, joint pain, cough, decreased oral intake, rhinorrhea, and abdominal pain), KD can be difficult to diagnose, especially in children who present with an incomplete form of the condition.

To establish a diagnosis, we mainly rely on the diagnostic criteria, described by the American Heart Association (AHA), (Table 3) [3] or the Japanese Kawasaki Disease Research Committee (Table 4) [4].

However, pediatricians sometimes encounter febrile children who do not fulfill the diagnostic criteria but have several findings

compatible with those of KD. In these cases, the diagnosis of incomplete KD is a clinical challenge. Any delays in diagnosis should be avoided due to the risk of coronary complications pertaining even to the incomplete presentation of the disease [6,7].

Diagnosis	Clinical criteria
Persisting Fever	≥ 5 days
Presence of ≥ principal features	Changes in extremities
	Polymorphous exanthema
	Bilateral bulbar conjunctival injection without exudates
	Changes in lips and oral cavity
Cervical lymphadenopathy	>1.5 cm diameter
Exclusion of other diseases	With similar findings

**Table 3:** Classical diagnostic clinical criteria of Kawasaki disease prepared by the American Heart Association.

Diagnosis	Clinical criteria
Persisting Fever	≥ 5 days
Presence of principal features	Bilateral conjunctival congestion
	Changes of lips and oral cavity
	Polymorphous exanthema
	Changes of peripheral extremities
	Acute non-purulent cervical lymphadenopathy

**Table 4:** Six principal symptoms in the diagnostic guidelines for Kawasaki disease prepared by the Japanese Kawasaki Disease Research Committee.

Incomplete KD accounts for 15% to 20% of KD diagnoses and is more common in children aged less than six months and in children aged greater than five years [7].

According to studies comparing typical and atypical KD, infants differed substantially from older children in several aspects. Infants had fewer of the accepted criteria, including less mucositis, conjunctivitis, cervical adenopathy, and pharyngitis [8]. In addition, infants had a higher incidence of atypical KD [8] (45% versus 12%,  $P=0.007$ ) and of coronary artery complications.

In infants with atypical KD, the same findings applied, with an even higher rate of coronary artery complications (100%) and the only death in the study [8].

Other reports have also shown infants to have a high incidence of other manifestations proposed as important in early diagnosis. Burns and colleagues [9] report the cases of infants having pyuria (75%), aseptic meningitis (43%), respiratory signs (75%), and desquamation (75%), with increased erythrocyte sedimentation rates, thrombocytosis, leukocytosis, and anemia. They conclude that these infants have an increased risk of coronary artery aneurysm and an atypical evolution of the disease [9].

In a review of atypical KD, the authors comment on irritability (64%), diarrhoea (29%), pyuria (44%), respiratory symptoms (47%), aseptic meningitis (75%), elevated aminotransferase levels (18%), and electrocardiographic changes (53%) [10].

However the definition of atypical KD may have created a bias for patients with atypical KD to have a high incidence of coronary artery complications.

Infants younger than six months of age are at high risk of developing coronary artery lesions (CALs), yet often have few clinical features to facilitate the diagnosis.

For these reasons, it is recommended that infants younger than six months of age who have had more than seven days of fever of unknown aetiology and elevated inflammatory markers, to undergo echocardiography [11].

Various clinical scoring systems exist to identify patients at high risk of poor coronary outcomes. Factors involved in the scoring systems include: male sex, refractory KD and fever for more than ten days.

Neurologic complications in KD have been shown to affect 1.1% of children in a Japanese cohort of 450 children with KD [12]. Aseptic meningitis is the most common, accounting for 5% of all neurologic complications [13]. Other neurologic associations and complications of KD have been described and include extreme irritability, meningoencephalitis, subdural collection, ataxia and sensorineural hearing loss [14].

Dengler et al. [15] conducted a study in 46 patients having KD. In the first ten days of the disease (prior to IVIG therapy) they performed lumbar puncture to evaluate CSF. They found that 39.1% of the patients had pleocytosis in CSF, 2.2% had low CSF glucose levels (<45 mg/dL) and 17.4% had high CSF protein levels.

Aseptic meningitis in children with KD is thought to be caused by vasculitis of the small arteries, arterioles and venules [16,17].

In our 2 month old infant having persistent fever for more than one week, shown to have no focus of infection, negative blood culture and aseptic meningitis with negative bacterial and viral study and high acute phase reactant directed us for possibility of Kawasaki disease, which was thereafter confirmed by echocardiography.

In summary, establishing a diagnosis of atypical KD in the uncommon age of infants less than six months of age remains difficult. This group have a greater risk of developing CALs highlighting the need to avoid delayed or misdiagnosis. As such, echocardiography should be performed as soon as possible to excluded cardiac involvement, however this should not delay treatment. Despite advancements in echocardiography, it is not used to routine diagnose KD due to reduce sensitivity and inability to identify early KD. Therefore, a normal initial echocardiogram should not be used to exclude the diagnosis of KD, especially if physical examination findings and laboratory tests are consistent with the diagnosis after other febrile illnesses are excluded.

### Author Disclosure

Doctors have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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