

Case Report**Atypical Kawasaki Disease in Two Infants Younger Than 6 Months***H. Dahifar MD*, A. Ghorbani MD*****ABSTRACT**

Two infants, a boy and a girl aged 2.5 and 5 months, respectively, were admitted to Tehran's Children Hospital, for fever of unknown origin lasting for about two weeks. The boy presented with abdominal distention, diarrhea, irritability, pyuria, anemia, leukocytosis, thrombocytosis and raised titer of acute phase reactants. The girl presented with irritability, diarrhea and abdominal distention, Leukocytosis, thrombocytosis, anemia and elevated titer of acute phase reactants. All bacterial cultures and serological tests were negative. Cardiac echocardiography showed coronary artery aneurysm in both patients and confirmed the diagnosis of Kawasaki disease.

These cases showed that atypical Kawasaki disease was often a late diagnosis and therefore should be quickly suspected in febrile young infants with abnormal inflammatory laboratory results without infection. Echocardiography is an important tool for diagnosis of atypical Kawasaki disease.

Key words: Kawasaki disease, Infant, Coronary artery

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Kawasaki disease (KD) is an illness of unknown etiology which generally affects children less than 5 years of age¹. It is the leading cause of acquired heart disease among children in the United States and Japan². Since the etiology of KD is not known, the diagnosis is made by persistence of fever for at least 5 days along with 4 of the following signs: erythema and swelling of palms and soles, inflammatory changes of lips and oral cavity, cervical adenopathy, non-purulent conjunctivitis and polymorphous exanthema³. The most serious complication of KD is coronary artery involvement, which has been reported in about 20% of the patients⁴.

The term atypical KD describes the condition of children who fail to meet the strict definition for classic KD but have convincing laboratory findings and no other explanations for their illness⁵.

The prevalence of such presentation is 7-10%. KD is uncommon among infants younger than 3 months⁶⁻⁸.

In a series of KD patients in Japan, only 1.67% were younger than 3 months⁹ but in the United States, there were no cases of KD in infants younger than 2.25 months of age⁷.

We report two cases of atypical KD in infants under 6 months who suffered coronary artery involvement. Here, we try to highlight atypical presentations, associated features, confusing and deceptive laboratory findings and risk factors.

Patient 1:

An Iranian infant boy aged 2.5 months old was referred to our hospital (Tehran's Children Hospital) in August 1997, for his fever which started 15 days earlier besides diarrhea and irritability. He had already received wide spectrum antibiotics in two separate hospitals. The patient's body temperature was 39.3°C. Physical examination revealed only abdominal distention and irritability without dehydration. The weight was 5,600 grams, blood pressure, growth criteria and other organs, were normal.

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Initial laboratory findings revealed white blood cell count (WBC) of 22,500/mm³ with a differential of 58% neutrophils, 40% lymphocytes and 2% monocytes. The platelet count was 390,000/mm³, erythrocyte sedimentation rate (ESR) 104 mm/hr, hemoglobin level 8.5 g/dL and CRP++. On repeated blood tests WBC rose to 34,000/mm³ with a differential of 60% neutrophils, 35% lymphocytes, 5% monocytes, hemoglobin level of 9g/dL. The platelet count was 1,300,000 /mm³, ESR 135mm/hr, and CRP ++. Urinalysis showed 20-40 WBC per high power field with negative culture and cerebrospinal fluid (CSF) analysis and culture besides blood culture were normal. Stool smear and culture was negative, immunoelectrophoresis, Widal and Wright testes were normal, chest X-ray, barium enema and 24 urine vanilylmandelic acid (VMA) were normal. After 3 days, the patient was sent to the pediatric cardiology unit for echocardiography just on a clinical suspicion that the illness might be KD.

The echocardiography revealed a fusiform aneurysm of the left coronary artery. Aspirin was then administered as 100 mg/kg/day for two weeks and was subsequently reduced to 5mg/kg/day. The desquamation of the fingers and toes developed one week later and Aspirin was continued until disappearance of coronary artery aneurysm and normalization of platelet count. ESR and CBC became normal about 6 weeks later.

Patient 2:

A 5-month-old Iranian girl was admitted to our hospital in November 2000, for a 10-day-fever, diarrhea and irritability. She had received ceftriaxon with the diagnosis of urinary tract infection for 10 days in another hospital prior to admission, but fever and diarrhea persisted.

On admission the patient's body temperature was 39.3°C. Physical examination revealed only abdominal distention and irritability. Her weight was 5,600 grams with normal growth pattern. All other organs seemed normal. Initial laboratory findings were hemoglobin level

8.5g/dL, HCT 35%, WBC 15,400/mm³ with 65% neutrophils, 27% lymphocytes, 4% monocytes and 4% eosinophils. The platelet count was 832,000/mm³, ESR 125 mm/hr, CRP++, liver and renal function tests were normal, stool smear and culture were normal, urinalysis and culture, blood culture, wright and widal agglutination tests were normal. Chest X-ray was normal too. Echocardiography was recommended because of a clinical suspicion of KD two days after admission.

Echocardiography showed aneurysm of the right and left coronary arteries. Aspirin as 100mg/kg/day was started for 2 weeks and was reduced to 5 mg/kg/day thereafter. The fever stopped and irritability lessened after three days. Ten days later, desquamation of the fingers and toes developed. Aspirin was discontinued after normal results of echocardiography, WBC, ESR, CRP and platelet counts (about 6 weeks later) were reported.

Discussion

As the exact etiology of KD and its specific laboratory tests remain unknown, the diagnosis of KD basically depends upon the clinical presentation. The diagnostic criteria for KD are extremely useful, particularly in preventing overdiagnosis and overtreatment. Lack of such criteria may result in unrecognized atypical features of the illness such as in our two patients in whom significant coronary artery abnormalities developed after only one essential clinical criterion, Fever of Unknown Origin, was prolonged. We can prevent severe sequelae with starting appropriate therapy early in the course of the disease with Aspirin and intravenous gammaglobulin which are extremely useful in reducing the frequency of coronary artery abnormalities.

In some studies, 28% of infants with KD had atypical presentation as compared to 7%-10% in older children^{3, 5, 7, 11, 12}. The clinical presentation of KD in infants younger than 6 months was described by some authors^{13, 18}. Data of our two patients are presented in table 1.

Table 1. Presentations of Kawasaki disease in infants younger than 6 months.

Reference	N	Fever >5days	Rash	Conjunctivitis	Peripheral changes	Oral changes	Lymph- adenopathy	WBC> 15000 mm ³	ESR >75/hr	Platelets >450000 /mm ³
13	1	-	-	-	-	-	-	-	-	-
14	8	8	8	7	7	8	3	8	2	7
15	1	1	1	1	-	1	-	1	1	1
16	6	5	5	2	3	3	-	NS	NS	NS
17	1	1	1	1	-	-	1	-	-	-
18	3	3	2	2	3	-	1	3	-	3
Present study	2	2	-	-	-	-	-	2	2	2

NS= not stated

Japan's Kawasaki disease research committee reported associated features in addition to the essential criteria^{19, 20}. In our patients, diarrhea, abdominal distention and irritability were associated features. Asai described the risk factors for prediction of coronary artery involvement for the first time and formed the basis for several clinical scoring systems²¹. Koren renewed those systems²² in a way that they are now extremely useful in predicting those at increased risk of coronary artery involvement. Factors that are most strongly predictive of coronary disease include male sex, age less than one year, fever lasting more than 16 days, cardiomegaly, hemoglobine less than 10g/dL, WBC greater than 30,000/mm³, ESR higher than 101mm/hr, positive CRP lasting for more than 30 days and arrhythmias. In addition, increased platelet counts equal or higher than 900,000/mm³ indicate coronary artery aneurysms in the patient^{23, 24}. Hirose demonstrated that coronary dilatation was detected at mean of 10 days of illness and that the peak frequency of coronary dilation or aneurysms occurred within 4 weeks of the onset²⁵. Our patients had several risk factors such as male sex and WBC>30,000/mm³ in the first patient and age, fever, hemoglobin less than 10g/dL, ESR>101mm/hr, positive CRP and platelet count>900,000/mm³ in both patients.

Jacob Genizi et al, described two boys less than 6 months of age with coronary abnormali-

ties with four essential criteria of KD except lymphadenopathy in both infants and WBC>15,000/mm³, platelets> 450,000/mm³ and ESR>75/hr in one infant. The prevalence rate of the diagnostic criteria in atypical KD is variable²⁶. Hsiao et al, found a lower incidence of strawberry tongue and edema of palms and soles in patients less than 6 months of age as compared to older patients²⁷. Also, typical mucosal and lymph node changes were lacking in those less than 6 months of age²⁸. Tseng et al, described 48 patients with atypical Kawasaki disease, of these 35.4% had coronary artery dilation and a longer duration of diagnosis, higher incidence of atypical presentation, lower incidence of conjunctivitis, skin rash, extremity changes and lower C-reactive protein. The predictive value of coronary artery dilation based on combination of atypical presentation, duration of diagnosis, and C-reactive protein was 81.2%²⁹. Another study from Netherlands demonstrated atypical Kawasaki in two infants with persistent fever more than 12 days and lack of classical criteria with coronary artery dilatation. They believed that atypical Kawasaki was a late diagnosed illness³⁰. The clinical presentation of one of their patients was the same as our patients (irritability, diarrhea).

Many authors believe that diagnosis of atypical KD is restricted to 3 or 4 of the classical criteria plus coronary artery vasculitis^{31, 32}.

The term atypical or incomplete KD is currently used to describe children who fail to meet the strict definition for classical KD but have confirming laboratory findings such as high ESR, elevated CRP, high neutrophil and platelet counts and no other explanation for their illness¹³. Both of our patients had coronary artery aneurysm and convincing laboratory tests. The previous study demonstrated 85% of infants younger than 6 months of age with KD developed coronary artery aneurysm²⁶. Nakamura et al, indicated that cardiac sequelae were much higher in infants, particularly in the first 6 months, than in older children with KD (64% Vs 9%)⁴, probably owing to delay in diagnosis. Only 41% of infants younger than 6 months were treated with IVIG, of whom only 14% received the therapy during the first 10 days of their illness^{6,7,9,22,33}. This might have contributed to the development of cardiac sequelae.

The diagnosis of KD is based on clinical presentation and the exclusion of other possible causes. The differential diagnosis of KD in

young infants included viral and bacterial infection, drug reaction, and connective tissue diseases. Our patients did not meet any other diagnoses, all cultures and serologic tests were negative, there were no neurologic or articular signs or skin eruption and mucosal or conjunctival abnormalities.

These cases and other investigations illustrate the fact that atypical KD is often a late consideration, especially when the symptoms of the classical form are absent. This condition should be considered in every infant presenting with long-lasting unexplained fever with associated features, risk factors of coronary artery involvement and inflammatory tests. Because young infants with KD are at an extremely high risk of developing coronary arterial abnormalities, early diagnosis and appropriate therapy are particularly important. Physicians who evaluate prolonged fever in infants with or without classical forms of KD should have "high index of suspicion" for the possibility of KD. Echocardiography is the most helpful tool for this diagnosis of the disease.

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