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Case Report

Feverless kawasaki disease: a case report and review of the literature

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Abstract: Kawasaki disease is an acute systemic inflammatory disease with unknown etiology that affects blood vessels of the whole body during childhood, and is extremely rare. Herein, we report a case of 3-month-old female infant who presented with diarrhea and convulsions but without fever. Physical examination revealed an erythema at the Bacille Calmette-Guérin *inoculation site* on the left upper arm. Major findings from laboratory tests included increased white blood cell and platelet counts, elevated C-reactive protein concentration, increased *erythrocyte sedimentation* rate, and elevated B-type natriuretic peptide precursor levels. Cardiac ultrasound showed dilation of bilateral coronary arteries. The patient was diagnosed with atypical kawasaki disease and treated with gamma globulin and aspirin. After treatment, the diarrhea and convulsions were relieved, and all abnormal blood indexes returned to normal ranges. However, the patient still had coronary artery dilation during the 10-month follow-up period. In addition to presenting this rare case, we also review the literature related to feverless kawasaki disease.

Keywords: Kawasaki disease, bacille calmette-guérin, C-reactive protein, erythrocyte sedimentation rate, B-type natriuretic peptide

Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute systemic inflammatory disease of young childhood that involves blood vessels throughout the body [1]. KD is the most common cause of acquired heart disease, with an incidence of 150 per 100000 in Japan and 10-15 per 100000 in United States in children less than 5 years of age [2]. Based on clinical manifestations, KD has two major forms, complete and incomplete (atypical) KD [3], and children younger than 1 year of age are more frequently affected by incomplete KD [4]. Fever is included as a critical sign for both forms of KD according to the proposed diagnostic criteria [3]. However, cases of feverless KD, although extremely rare, have been reported. Given that KD may lead to severe complications including myocardial infarction, coronary artery aneurysm, and sudden death [3], an accurate diagnosis is imperative in order for early initiation of appropriate treatments to avoid the occurrence of severe complications. Here we report a case of fever-free KD in a 3-month-old female infant. The main clinical signs in this case were diarrhea and convulsions, but fever and other typical KD symptoms were absent. We also review the literature related to feverless KD.

Case report

A 3-month-old female infant was admitted to our hospital due to intermittent diarrhea lasting for 1 week and occasional convulsions lasting for 3 days. One week before admission, the baby developed diarrhea (watery stool with no pus) without any cause, with a frequency of 3-4 times/day. Three days before admission, the baby became agitated and experienced convulsions manifesting with loss of consciousness, glazed eyes, and stiff limbs. Upon presentation, she had experienced a total of 6 episodes of convulsions with the same clinical manifestations, with each lasting a few seconds to 1 minute. Her condition was fine once the convulsions stopped. She did not show any fever, any

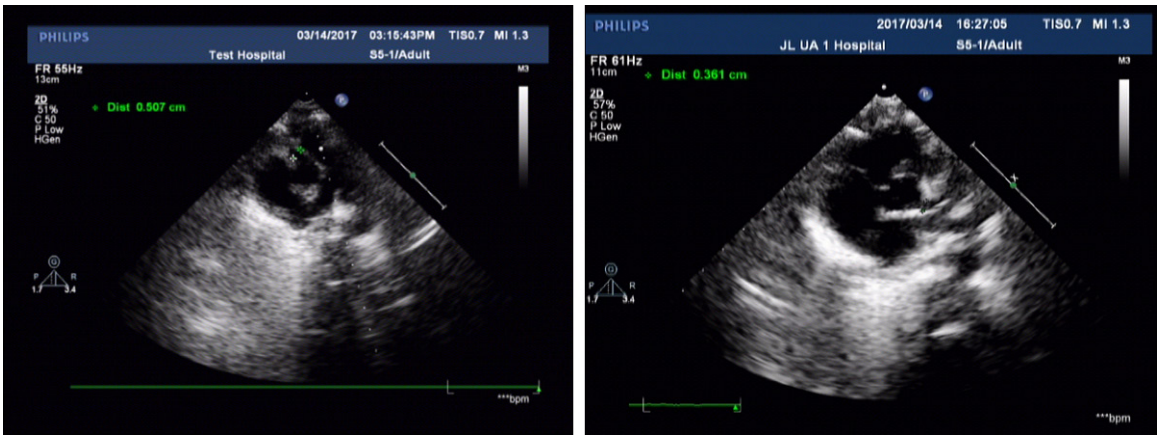

Figure 1. Representative echocardiographic image showing the left coronary artery diameter of 3.3 mm (left panel) and the right coronary artery diameter of 5.1 mm (right panel).

changes in the mucous membranes and conjunctiva, or any signs of hand and foot scaling and swelling. The patient's history included: G1P1 birth, full-term natural delivery, and no family history of convulsions. Physical examination revealed: irritability, a soft and flat anterior fontanelle, no conjunctival hyperemia, no swollen lymph nodes, no abnormalities in the heart, lung, abdomen and nervous system, and no hard swelling or scaling on the extremities, but an erythema at the Bacille Calmette-Guérin (BCG) vaccination site on the left upper arm.

Routine blood tests revealed the following: leukocyte count of 28.81×10^9/L, neutrophil percentage of 37%, lymphocyte percentage of 53%, hemoglobin level of 73 g/L, hematocrit level of 0.274 L/L, mean corpuscular volume of 80.6 fL, platelet count of 1276×10^9/L, serum sodium level of 134 mmmol/L, C-reactive protein (CRP) concentration of 96.7 mg/L, and procalcitonin (PCT) concentration of 0.23 ng/ml. There was negativity for Epstein-Barr virus, unilateral urticaria, rubella, cytomegalovirus and toxoplasma antibodies, mycoplasma antibody, and anti-streptolysin O (ASO). Liver function tests showed: liver aspartate aminotransferase level of 122.7 U/L, alanine aminotransferase level of 121.3 U/L, and albumin level of 34 g/L. In addition, the erythrocyte sedimentation rate (ESR) was 120 mm/h, and the level of B-type natriuretic peptide precursor was 469 pg/ml. Routine biochemical examination of cerebrospinal fluid showed no abnormalities. Blood cultures were negative. Abdominal color Doppler ultrasonography, head magnetic resonance imaging, and 6-hour video electroencephalography all showed no abnormalities. On echocardiography, the diameters of the left and right coronary artery were 3.3 and 5.1 mm, respectively (**Figure 1**).

Based on the clinical symptoms and laboratory test results, this female infant was diagnosed with feverless incomplete KD. She was then treated with gamma globulin at a dose of 2 g/kg and oral aspirin, standard treatments for KD. Three days after initiation of treatment, routine blood tests revealed a leukocyte count of 15.67×10^9/L, a platelet count of 984×10^9/L, and a CRP concentration of 38.8 mg/L. After 7 days of treatment, the erythema at the BCG inoculation site had disappeared. After 10 days of treatment, the white blood cell and platelet counts had dropped to within normal ranges, and the hemoglobin level was 77 g/L. Oral aspirin treatment was continued after discharge. Two months of follow-up revealed no diarrhea and normal blood components. Tests for liver function, ESR, and CRP concentration were normal. The patient did not experience convulsions during 10 months of follow-up. However, the coronary artery dilatation was not resolved.

Discussion

KD is an acute inflammatory disease involving blood vessels of the whole body that most commonly occurs in young children and has become the most common acquired heart disease in Western countries [2]. While the exact cause of

Table 1. Summary of 10 fever-free KD cases reported worldwide

Reference	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[14]	[15]	[15]
Age	3 M	2 Y	5 Y	17 M	3 M	7 M	7 M	13 M	1 Y	1 Y
Gender	Male	Male	Female	Male	Male	Male	Female	Male	Male	Female
Rash			Yes		Yes		Yes		Yes	Yes
Conjunctival hyperemia		Yes	Yes	Yes	Yes		Yes	Yes	Yes	
Lips and tongue			Strawberry tongue	Erythematous and chapped lips	Erythematous lips and tongue			Erythematous lips	Erythematous and chapped lips	Strawberry tongue
Swollen lymph nodes			Yes		Yes					
Extremities			Erythema	Hand edema, desquamation	Hand edema	Desquamation			Edema, desquamation	Edema
Other symptoms		Arthritis	Bilateral Beau's lines in all fingers	Hand pain	Irritability Poor feeding	Erythema around the BCG inoculation site	Diarrhea Erythema around the BCG inoculation site	Erythema around the BCG inoculation site	Diarrhea Erythema around the BCG inoculation site	Erythema around the BCG inoculation site
CRP (mg/L)	16.79	41	102	54	158		94.3	7.5	0.3	7.1
ESR (mm/h)		quicker		75	40		125		22	
Coronary artery involvement	LCA Z score of + 6.2	Coronary arterial ectasia in segments 1, 5, 6	Normal	Normal	Aneurysms of the proximal right (7.0 mm)	LCA Z-score of 2.8	RCA and LCA Z scores of 7.4 and 8.0	RCA and LCA Z scores of 5.8 and 7.2	Normal	Normal
Treatment	Aspirin + IVIG	Aspirin	Untreated	Aspirin + IVIG	Aspirin + IVIG	IVIG	Aspirin + IVIG	Aspirin + cyclosporin	IVIG + acetylsalicylic acid	Aspirin + IVIG
Prognosis	In 6 weeks, coronary artery dilatation recovered, platelet and white blood cell and CRP returned to normal	In 45 days, CRP returned to the normal, coronary dilatation lessened, and full recovery was achieved after 1 year	In 2 months, platelet counts returned to normal	In 10 days, the blood test results and clinical symptoms were ameliorated	Clinical symptoms and the left coronary artery returned to normal, and the right coronary artery dilatation gradually lessened	In 17 days, BCG site redness disappeared,left coronary dilation recovered	In 5 months, clinical symptoms disappeared, laboratory tests returned to normal, and coronary artery dilatation fully recovered	In 8 months, clinical symptoms disappeared, laboratory tests returned tonormal, and coronary artery dilatation fully recovered	Symptoms resolved	N/A

IVIG: Intravenous immunoglobulin.

KD remains unknown, it is widely believed that an infectious agent, probably a virus, is responsible for its development [5]. Diagnostic criteria for typical KD were proposed [6] and by the American Heart Association (AHA) [2]; however, these KD diagnostic criteria exhibit low sensitivity and specificity. For example, some KD patients do not have a complete presentation of clinical symptoms and such cases are considered "incomplete or atypical KD" [7]. Also, in both KD and incomplete KD, fever is proposed as a critical diagnostic criterion. However, it remains debatable whether fever always occurs in KD. A PubMed search for the key words "asymptomatic AND kawasaki disease", "without fever AND kawasaki disease" and "afebrile kawasaki disease afebrile" yielded a total of 10 cases of children with fever-free KD reported worldwide (**Table 1**) [8-15]. These findings point to the possibility that fever is not necessary for KD diagnosis, although the incidence of fever-free KD appears to be extremely low.

The clinical manifestations, treatment, and prognosis of the 10 identified cases of fever-free KD are summarized as follows: 1. The age at disease onset was young; 60% of children with fever-free KD were younger than 1 year old; 2. Atypical KD symptoms appeared more often. Nine out of 10 KD patients had more atypical symptoms such as erythema and induration at the BCG vaccination site. Therefore, erythema or crust formation at the BCG inoculation site should be a valuable sign for KD diagnosis among children aged 3-20 months; 3. Coronary artery involvement. The most severe complication of KD is the involvement of the coronary arteries, and if detected by echocardiography, this observation should support the KD diagnosis. Indeed, 60% of the cases of fever-free KD had coronary artery involvement at the time of diagnosis, and 2 had a huge coronary artery tumor; 4. Importance of the abnormal laboratory tests in making an accurate diagnosis. Although KD does not present specific changes in laboratory indexes, laboratory test results still provide an important reference for KD diagnosis. In particular, elevations in systemic inflammatory markers such as CRP and ESR are significant indicators for KD diagnosis. Also, BNP is usually elevated in the acute phase of KD and exhibits a certain degree of specificity, which may help with the diagnosis of incomplete KD [16, 17].

In this case, the affected female infant presented mainly with diarrhea and convulsions, and cardiac ultrasonography revealed coronary artery dilatation. Although a number of other diseases including Takayasu disease and juvenile polyarteritis nodosa (J-PAN) may also present with coronary artery dilatation [13], this infant was diagnosed as having fever-free KD based on: 1) the presence of an erythema at the BCG vaccination site, 2) increased CRP and BNP levels as well as an increased ESR but decreased circulating levels of albumin and sodium, and 3) coronary artery involvement. To the best of our knowledge, this represents the first report of atypical fever-free KD in an infant as young as 3 months old, making this an extremely rare case. Our diagnosis was further supported by the effective treatment: recommended by the guidelines, i.e., a single dose of gamma globulin (2 g/kg) combined with aspirin. The patient was followed up for 10 months and did not show any clinical symptoms during this period. The patient continued oral intake of 3-5 mg/kg aspirin daily. Echocardiographic re-examination suggested that coronary artery dilatation was not completely resolved. Long-term follow-up is therefore still needed to determine the patient's prognosis.

Disclosure of conflict of interest

None.

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