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Node-First Kawasaki Disease Presented with Marked Pancarditis: a Case Report

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Abstract

Kawasaki disease is an acute inflammatory disorder of medium-sized arteries that predominantly affects cardiac coronary arteries and children under the age of 5 years. Cardiac involvement usually happens later than 10 days after the onset of illness. Most of cardiac complications are coronary artery abnormalities (ectasia or aneurysms) and subclinical myocarditis. Clinical myocarditis (symptomatic congestive heart failure), pericarditis, valvulitis and pericardial effusion, as well as pancarditis are rare.

This paper reports a 5-year-old boy who had heart failure (ejection fraction 48%) in the acute stage of Kawasaki disease and pericarditis. He was admitted to the hospital following 3 days of continuous fever, bilateral cervical adenopathy and dominant right side neck of torticollis. The results of physical examination after 5 days showed typical Kawasaki disease. Cardiac examination also revealed cardiac murmur and gallop rhythm. In laboratory tests, mild liver dysfunction, hypoproteinemia and hyponatremia were discovered. During hospitalization, troponin levels were positive. The patient was treated with oral high dose aspirin (100 mg/kg/d), two doses of intravenous immunoglobulin (IVIG 2 gm/kg) and three pulses of methylprednisolone. Two weeks later, cardiac evolvements were improved without further complications. The patient exhibited dramatically clinical recovery and was healthy after 8 weeks of follow-up.

This case indicates that Lymph-node-first presentation of Kawasaki disease could be examined in children with Kawasaki disease who exhibit symptoms of congestive cardiac failure, pericardial effusion and pericarditis during the acute phase of the disease.

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Introduction

Kawasaki disease (KD) is a severe systemic vasculitis that is presented by specific signs and symptoms. It usually manifests with fever, which is followed by rash, cervical adenopathy, conjunctival injection and modification of mucous membrane and extremities. When the fever persists for more than 5 days and at least 4 of 5 common clinical symptoms manifest, there is a classic (typical) case of KD.

Cervical lymphadenopathy is one of the basic diagnostic features for KD that has received scant attention. Given the lack

of a specific diagnostic test for KD, patients with KD may be erroneously diagnosed with bacterial cervical lymphadenitis, so that deferred diagnosis and treatment of KD can cause severe cardiac complications (1, 2). In some cases, KD may appear with fever and cervical adenopathy before the manifestation of other clinical symptoms, as well as node-first KD (3, 4).

Due to the lack of a specific diagnostic test for KD, the differentiation of node-first KD (NFKD) is still challenging. With age as a variable, old age, high markers of systemic and hepatobiliary inflammation and anemia contribute to the recognition of NFKD. Sometimes, NFKD is not diagnosed until the manifestation of other clinical features or observing the characteristics of coronary arteries in the echocardiogram. NFKD is not well recognized by clinicians that treat febrile children. It is difficult to differentiate NFKD from other types of cervical adenitis. NFKD should be considered in case of elevated ABC, ESR and CRP values and multiple distended solid nodes in febrile patients with cervical adenopathy to avoid the late diagnosis of KD.

Pericarditis is relatively rare (an incidence rate of 0.07 %) in KD children who present cardiac complications (5). Pericardial effusion has also been reported as a complication of KD in 6-24.5% of patients (6). Nonetheless, cardiac tamponade is extremely rare and it is often secondary to the rupture of coronary artery aneurysm (7).

In the acute phase of the disease, valvular regurgitation or valvulitis can induce mitral or aortic regurgitation, though delayed onset of regurgitation may be related to myocardial ischemia. Pericardial inflammation with effusion has also been reported (8).

This paper describes features of NFKD patients who presented only fever and cervical lymphadenopathy upon admission along with pericarditis, myocarditis and pericardial effusion.

Case report

A 4-year-old-boy (height 102 cm, weight 15 kg) was admitted because of persistent fever (up to 38.5 °C) for three days, bilateral cervical adenopathy and dominant right side submandibular (2×2.5 cm) of torticollis. At admission time, he was ill and not toxic. Early diagnosis was retropharyal abscess and lymphadenitis. We started parenteral antibiotic (cefotaxime 100 mg/kg/day and clindamycin 40 mg/kg/day) based on retropharyal abscess.

The results of primary laboratory tests were: white blood cell (WBC) 14,480/mm^3, Neut 85%, Lymph 10%, band 4%, hemoglobin (Hb) level 12.4 g/dl, Hct 35.9%, platelet 2890000/mm^3, C-reactive protein (CRP) 3 mg/dl, and erythrocyte sedimentation rate (ESR) 99 mm/h. Antistreptolysin O (ASO) titer test was normal. Furthermore, urine and blood cultures were negative.

On the 5th day of illness, physical examination exhibited bilateral conjunctival congestion, erythema of the oropharynx, strawberry tongue, rash and edema in hands and feet. Cardiac examination revealed cardiac murmur with gallop rhythm. The liver was not palpable below the right costal margin.

In laboratory tests, mild liver dysfunction were found; aspartate aminotransferase (AST) 73 IU/L, alanine aminotransferase (ALT) 112 IU/L, hyponatremia 130 mmol/L, and hypoproteinemia (total protein 4.6g/dl, albumin 2.8g/dl). Troponin levels during hospitalization were positive. (Table 1)

Table 1. The results of laboratory tests of the reported case in different days of hospitalization

Parameter \ Day	1st day	3rd day	5th day
WBC	14480	18700	23900
Hb	12.4	9.8	8.2
Plt	289000	398000	576000
Neutrophil	85	85	67
Lymphocyte	10	10	21
ESR	59	104	140
CRP	2+	2+	4+
Urea	26	18	15
Na	139		130
K	4.3		3.5
ALT			112
AST			73
ASO		negative	negative
Alb			3
Troponin		Negative	positive

Chest X-ray and echocardiography ruled out cardiomegaly. Abdominal sonography was performed on the account of abdominal pain, with the results revealing trivial fluid in pelvic and multiple focus echogenic and sludge in the gall bladder.

The antibiotic therapy was discontinued after KD diagnosis and with the confirmation of KD diagnosis, aspirin (100 mg/kg/day) and IVIG (2g/kg for 24h) were started on the 5th day of the illness.

Echocardiography revealed normal coronary arteries and normal left ventricular (LV) wall motion, though there was mild mitral regurgitation and moderate tricuspid regurgitation.

Given the persistence of fever after 24h, the second dose of IVIG was modified. The patient had tachycardia, tachypnea and abdominal pain. The second echocardiography reveled moderate MR and mild AI along with decreased ejection fraction (EF= 40%) and clinical myocarditis so appropriated treatment was initiated with captopril and frusemide.

With the persistence of high fever, the ESR level spiked (149 mg/dl) and the EF dropped so that three doses of methylprednisolone were prescribed.

Pulse methylprednisolone therapy (30 mg/kg/day IV for 3 days) was started. Progressive clinical improvement was observed within 72h. Fever subsided and acute phase reactants declined rapidly. In the absence of cardiac tamponade, pericardiocentesis was not preformed.

During the hospitalization, hypotension and oliguria were not observed. Aspirin was also sustained despite liver dysfunction.

The fever subsided and cardiac failure improved without coronary aneurysm or abnormal LV motion on the 15th day,

and the EF improved on the 18th day. Also, improvement in aorta, mitral and tricuspid regurgitation was observed. Aspirin was continued for two months, and then tapered off. Three and five months after the admission, transthoracic echocardiography showed normal function and without any valvar involvement.

Discussion

Acute bilateral cervical lymphadenitis with fever is prevalent among children. Symptoms are usually resolved with empiric antibiotics, making diagnostic tests unnecessary. KD often appears with fever followed by rash, conjunctival injection, cervical adenopathy, and changes in mucous membrane and extremities. The main diagnostic indicator, cervical adenopathy, is relatively rare. These presentations may be erroneously diagnosed as bacterial cervical lymphadenitis (BCL), which delays the conclusive treatment of KD and leads to serious cardiac sequelae. In the absence of specific diagnostic tests, NFKD diagnosis would be inconclusive until other clinical features discovered in the echocardiogram reveal characteristic coronary artery changes.

In previous studies, NFKD has been defined as typical KD combined with myocarditis. Moreover, patients with NFKD have been shown to face severe complications compared to those with typical KD and it has been shown that variables such as old age, high markers of systemic and hepatobiliary inflammation, and anemia contribute to the diagnosis of NFKD (1-3). Most of these factors were present in our case. Our subject was older than typical KD patients and had anemia, elevated ALT and AST or progressive ESR.

In the patients with NFKD, WBC, ANC and aspartate aminotransferase levels were high, and they lacked the relative anemia and thrombocytopenia (1-3). while anemia was observed in our case.

In a previous study, a 4-item scoring system to distinguish NFKD from BCL (age >5.0 years, ANC >10×109 cells/L, CRP >7.0 mg/dL, aspartate aminotransferase level >30 IU/L) has been presented (3). However, due to the lack of some parameters, it could not be used in our study.

Absolute band count (ABC) and CRP are the most robust variables that can differentiate NFKD from bacterial cervical lymphadenitis (BCL). In our case, these indices were not sufficiently clear for diagnosis.

The radiologic findings include limited inflammation in the perinodal region, multiple discrete nodes and retropharyngeal edema, which were not clear in our case.

The patients with NFKD who required repeated administration of IVIG, had an increased risk of coronary artery lesions (1). Our patient was IVIG resistant and had cardiac complications.

The troponin-I level of the reported patient was normal. In a study, patients with elevated N-terminal pro-brain natriuretic peptide (NT-pro BNP) had significantly lower shortening fraction in the acute phase, which was normalized on the follow-up (9). On the contrary, in another study, no significant elevation of troponin-I level was observed in patients with KD and there was no correlation between troponin values and myocarditis or CA aneurysms (10).

Myocarditis represents a common cardiovascular complication in KD patients. In all patients with KD, the evidence of myocarditis can be found on histologic investigation of specimens, but only a small group of patients demonstrates clinical symptoms.

Myocarditis in KD patients is distinguished by inflammatory cells infiltrating from the coronary arteries to the interstitial myocardium, and frequent myocardial necrosis, which might account for prompt clinical improvement of the KD (11).

Myocarditis in KD is also associated with acute vasculitis, so that meticulous observation of cardiac function might be essential in patients with KD when a patient presents persistent fever. Myocarditis manifests in at least 50% of patients with KD so that mild LVD is not uncommon (12).

Following treatment with IVIG, shortening fraction of patients rose significantly within 24h. This indicates the existence of clinical or subclinical left ventricular dysfunction (LVD) during the acute phase of KD, which can be improved by IVIG treatment. The therapeutic effects of IVIG in normalization of acute-phase reactant in KD patients and low prevalence of coronary disease are well known. In addition, IVIG can improve myocardial function in patients with acute KD.

In our case, the cardiac function, valvar involvement and LV wall motion improved promptly after administering an appropriated dosage of IVIG and ASA coupled with ACEi and diuretic. Echocardiography ruled out coronary artery abnormality during convalescence.

Clinicians who are responsible for the treatment of febrile children with cervical adenopathy should consider NFKD in the differential diagnosis, so that they can counsel with a pediatric rheumatologist and cardiologist for the diagnosis and evaluation of cardiac complications, especially if laboratory results are indicative of KD.

Nomura et al exhibited that patients with NFKD often required IVIG administration and had an increased risk of coronary artery lesion (1).

Sonçaği *et al.* reported a 5.5-year-old child with KD who had aneurysm of the left anterior descendant coronary artery and spectated pericardial effusion. The pericardial effusion vanished rapidly with intravenous immunoglobulin (IVIG) therapy (5). In our case, pericardial effusion was completely treated without any complication.

Susan *et al.* have reported a case of KD presenting with hemorrhagic pericarditis. The patient demonstrated rapid clinical improvement and pleural effusion was resolved with high-dose IVIG immunoglobulin (15). We did not observe any sign or symptom of cardiac tamponade in our patient, so pericardiocanteis was not undertaken.

Okada *et al.* observed that serum levels of sTNFR1 in the PE group were higher than that in the non-PE group. Also, sTNFR1 levels were positively correlated with C-reactive protein (CRP) or total bilirubin levels. They propounded that acute PE in KD patients reveals the severity of TNF-mediated vascular inflammation and associated CALs. Based on the progression rate, these patients may require further targeted anti-inflammation therapy for enhanced coronary outcomes (14).

Dale *et al.* reported a child with apparent KD in whom cardiac tamponade had developed 14 days after response to IVIG and aspirin. The patient had responded well to three daily doses of intravenous methylprednisolone (15).

It is important to point out that the complications and clinical characteristics of patients were different in reports from other countries. Also, the incidence of typical and atypical KD was different in other regions and these differences might be

seen in difference regions of a country. Ghandi *et al.* have studied the demographic and clinical characteristics of patients in other countries. For example, in atypical KD among children, gender predilection, prevalence of coronary artery anomalies or other cardiac disorders were lower (16). Therefore, the NFKD and other complications should be considered in future studies.

Conclusion

We reported a case of NFKD accompanied with symptomatic myocarditis and pericardial effusion in the acute phase of the illness. In our case, myocarditis and pericardial effusion improved quickly after the treatment with two dosages of IVIG and three pulses of methylprednisolone. In NFKD cases with normal cardiac analysis, meticulous observation of cardiac function is essential, especially in older children, when inflammation is worsened and fever persists after the administration of the first IVIG dose. It should be pointed that pericardial effusion and pericarditis in NFKD cases do not need any therapy other than IVIG and pulse methylprednisolone.

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