CASE REPORT

Atypical Kawasaki Disease Complicated by Kawasaki Disease Shock Syndrome in a 5-year-old Boy: A Case Report

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ABSTRACT

Diagnosing Kawasaki disease (KD) has always been challenging for physicians worldwide that might be related to the ill-defined etiology along with unknown exact pathophysiology. It's an acute inflammatory process that strikingly affects small to medium vessels. It is known to mainly affect children younger than 5 years of age. Older children can also be affected, but the presentation seems to be more atypical with the older age groups. Kawasaki disease shock syndrome (KDSS) is one of the severe forms of KD that is often confused with toxic shock syndrome. This report discusses the case of a febrile child with atypical KD complicated by KDSS. Our aim is to delineate the challenges in diagnosis such severe atypical form of KD and its complication.

Key words: Atypical Kawasaki disease, intravenous immunoglobulin, Kawasaki disease, Kawasaki disease shock syndrome

BACKGROUND

Kawasaki disease (KD) is an acute febrile multisystem vasculitic syndrome of childhood, characterized by prolonged fever for more than 5 days along with other major criteria.[1] The syndrome derives its name from case reports presented by physician Kawasaki in 1967.[1] It is the most common vasculitic syndromes of unknown etiology, and it has been reported almost in all ethnic groups. In Japan, KD has 10 times higher incidences than other parts of the world, with the highest reported incidence of 243.1 cases per 100,000 populations <5 years of age occurred in 2011 and 264.8 per 100 000 in 2012. This incidence was higher than United States incidence (20.8 cases/100,000 population) yearly for the same age group.[2-4] Moreover, KD has a higher tendency to occur in males compared to females.KD has emerged as a major cause of acquired heart disease among children throughout the developed world. If KD is left untreated, it can lead to significant coronary artery disease in 15–25% of cases. As a consequence, it may lead to myocardial infarction, and eventually sudden death.[3,5,6] Complete KD features include high-grade fever (temperature higher than 39°C or 102.2F) that persists for 5 days or more, with 4 of the clinical signs that are demonstrated in Table 1. In incomplete KD, patients lack sufficient clinical signs; therefore, the diagnosis will depend more on laboratory findings and/or cardiac echo findings to support the diagnosis.[7-11] Kawasaki disease shock syndrome (KDSS) is a new entity that was first described, in 2009, by Kanegaye *et al.* who defined it as "sustained" decrease in systolic blood pressure for age from baseline of ≥20% or clinical signs of poor perfusion in addition to KD features.[12,13] The exact mechanism is still unknown; however, previous reports illustrated that it might be due to capillary leakage as a result of vasculitis, myocardial

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dysfunction, and/or cytokines dysregulation.[14] It has been reported recently that patients with KDSS have higher inflammatory marker levels and they seem to be at a much higher risk of coronary artery aneurysm.[5,14] The mainstay of treatment in KD is intravenous immunoglobulin (IVIG), although some may display resistance to IVIG treatment and may require additional therapeutic measures. IVIG resistance is defined as persistent or recrudescent fever ≥36 h after completion of the IVIG infusion.[2,14] We are reporting an Emirati child who was diagnosed with incomplete KD and later on fulfilled the criteria of KDSS. We are highlighting his clinical presentation, risk factors, and the final outcome.

CASE REPORT

A 5-year-old boy, previously healthy, presented with high-grade fever of 5 days duration. On the 2nd day of illness, he started to have a rash. The rash spread all over the body including palms and soles. The child also had bilateral red conjunctiva with watery discharges. In addition, he had deeply red tongue, sore throat, and generalized non-radiating abdominal pain. On admission, examination showed an alert boy; temperature was 40c, heart rate of 145 bpm, respiratory rate of 28 breaths/min, and blood pressure of 93/45mmhg. He had a bilateral non-suppurative conjunctival injection, strawberry tongue and maculopapular rash over trunk and distal extremities, with no palpable lymph nodes [Table 1a]. Remainder of his clinical examination was unremarkable. Initial investigations showed a normal white blood cell count, mild hypochromic microcytic anemia, and mild thrombocytopenia. There was the mild elevation of aminotransferases with indirect hyperbilirubinemia, low albumin level, and normal coagulation profile. He had a normal urinalysis and renal function test. C-reactive protein and erythrocyte sedimentation rate were markedly elevated [Table 1b]. Microbiological workup was non-contributory except for the detection of influenza B antigen in the nasopharyngeal aspirate. The history, clinical, and laboratory findings were supportive of the diagnosis of incomplete KD; therefore, intravenous immunoglobulin and high dose aspirin (100 mg/kg/24 h) were started. On the 2nd day of admission, the patient's temperature decreased to 36.6c for 6 h, and he re-spiked fever again (38.9c) after 14 h of completing the IVIG infusion. He continued to have sinus tachycardia (Heart rate ranged between 124 and 147 bpm) with normal

Table 1: Clinical diagnosis criteria as determined by the American Heart Association and laboratory criteria that may be used to help establish the diagnosis of KD

Classical KD[17,24]:
- Fever persisting>5 days, plus at least four out of five of the following principal criteria:
  - i. Changes in extremities, including indurative angioedema and desquamation
  - ii. Polymorphous exanthema
  - iii. Bilateral bulbar conjunctival injection without exudate
  - iv. Changes to the lips and oral cavity, including pharyngeal injection, dry fissured lips, and/or strawberry tongue
  - v. Acute nonpurulent cervical lymphadenopathy (>1.5 cm diameter)

Atypical KD:
- Fever of>5 days associated with<4 principle criteria, with the following three or more criteria:
  - i. Albumin<3 g/dL
  - ii. C-reactive protein>3 mg
  - iii. Erythrocyte sedimentation rate>40 mm/h
  - iv. Elevated alanine aminotransferase
  - v. Leukocytosis: White cell count>15,000/mm
  - vi. Normochromic, normocytic anemia for age
  - vii. Sterile pyuria: >10 white blood cell/mm^3
  - Or
  - Positive echocardiogram

KD: Kawasaki disease

Table 1a: Patient's clinical features that fit with incomplete KD

Classical KD:
- Fever persisting > 5 days+
  - i. Polymorphous exanthema
  - ii. Bilateral bulbar conjunctival injection without exudate
  - iii. Changes to the lips and oral cavity

Atypical KD:
- Fever of > 5 days associated with < 4 principle criteria, with the following 4 more criteria:
  - i. C-reactive protein > 3 mg
  - ii. Erythrocyte sedimentation rate > 40 mm/h
  - iii. Elevated alanine aminotransferase
  - iv. Sterile pyuria: >10 white blood cell/mm^3

KD: Kawasaki disease

Table 1b: Patient's initial biochemical data

Biochemical data[19,22]	The patient	Reference range
WBCs	6.2×10^9/L	5.5–15.5
Hgb	10.5 g/dL	11.5–14.5
Platelets	129×10^9/L	140–400
ALT	33 U/L	11–39
AST	99 U/L	22–58
Total bilirubin	507 mg/dl	90–396
Direct bilirubin	156.6 mg/dl	30.6–154.8
Albumin	28 g/L	35–48
CRP	105 mg/L	0–8
ESR	23 mm/h	0–10
CK-MB	0.9 ng/ml	0.6–6.3
Troponin-I	0.02 ng/ml	0.01–0.04

WBCs: White blood cells, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, CK-MB: Creatine kinase MB

respiratory rate and blood pressure. At that point, acute myocarditis was highly suspected. Cardiac panel, including creatine kinase MB and troponin-I, was initially within normal limits [Table 1b]. Echocardiogram was performed on day 2 and showed normal findings including coronary arteries [Figure 1]. For precautions and to avoid the risk of influenza B associated Reye's syndrome, warfarin (1 mg/day) substituted aspirin and patient were started on oseltamivir. By next day, he continued to be febrile, irritable, and ill-looking. Physical examination revealed heart rate of 130bpm with a blood pressure of 81/40 mmhg (wide pulse pressure), warm extremities and Glasgow coma scale of 11 (opening eye spontaneously, cries, and withdraw to pain). At this stage, he was transferred to the pediatric intensive care unit (PICU). Repeated cardiac enzymes were markedly increased this time [Table 2]. There were also some significant findings in the repeated echocardiogram with mildly depressed left ventricular function with ejection fraction of 47% and mild degree of mitral and tricuspid regurgitation with normal coronary artery dimensions and normal *Z* scores. Ultrasound study showed thickening of gallbladder wall, pericholecystic edema, and bilateral pleural effusions. Fluid resuscitation, inotropes, and broad-spectrum antibiotics were started for possible staphylococcal toxic shock syndrome (TSS). The patient was also complaining of neck stiffness and difficulty in swallowing. Examination of the neck showed right-sided tender cervical lymphadenopathy. Ultrasound confirmed enlargement of neck lymph node bilaterally. On the 5th day of admission, the fever subsided after the second dose of IVIG and the overall clinical picture of the patient started to improve. He developed thrombocytosis (platelet: 569,000/mm^3) on the 14th day. Echocardiogram was normal on the 4th week without coronary abnormalities. The patient has been following with cardiology clinic on low dose aspirin without any complications. The repeated echocardiographs were all normal.

DISCUSSION

KD remains to be of unclear etiology. To dates, there is no single pathognomonic clinical or laboratory finding to confirm the diagnosis. Our patient had incomplete KD, as he was not fulfilling the principle criteria. Furthermore, his condition got complicated by KDSS with hemodynamic instability. This clinical deterioration necessitated transfer to PICU for closer observation and inotropic support. In fact, there seem to be many similarities between KDSS and TSS. It has been speculated that a certain super-antigen mediates the interactions in both conditions.[15,16] The exact role of IVIG in KD is still not clearly understood, but it is known to have anti-inflammatory effects including reduction of fever, modulating cytokine levels, as well as downregulating antibodies synthesis. There have been many recent reports of IVIG failure or non-responsiveness in patients with KDSS.[17-19] On reviewing the temperature profile of the patient during IVIG infusion, his temperature subsided then re-appeared with a high grade in <24 h. Therefore, he was labeled as partial non-responder to the initial treatment.[19] Several scores have been developed to predict the risk of IVIG resistance/failure.[20,21] Unfortunately, our patient scored high in all the three scores and indeed required a second dose of IVIG [Table 3]. KDSS, IVIG resistance, and acute myocarditis may exist together. Therefore, there was an interesting debate whether the sudden deterioration (hypotension, tachycardia, delayed capillary refill, etc.) was due to by KDSS or due to acute heart failure due to acute viral myocarditis secondary to influenza. Recent articles showed that patients with KDSS seem to be at higher risk for gastrointestinal manifestations, incomplete presentation, IVIG resistance, and myocardial infarction.[23,24] Interestingly, the child did not have any involvement of coronary arteries during acute, convalescent phase and follow-up, though he had the rare and the severe form of KD. Chen and Chi published a case-controlled study in 2015 that reviewed hospitalized patients (2001–2011) who were diagnosed with KD and KDSS. They concluded that patients with KDSS presented with atypical features that could have been missed and were managed in the intensive care unit for hemodynamic support.[24] Another case report from Turkey by Işgüder *et al*. revealed that misdiagnosing KDSS is likely as pediatricians and intensive care unit practitioners are unaware of this condition and its damaging sequelae.[5]

Table 2: Repeated cardiac enzymes suggestive of acute myocarditis

Cardiac enzymes	The patient	Reference range
CK-MB	11.2 ng/ml	0.6–6.3
BNP	2107 pg/ml	0–35
Troponin-I	2.38 ng/ml	0.01–0.04

CK-MB: Creatine kinase MB, BNP: B-type natriuretic peptide

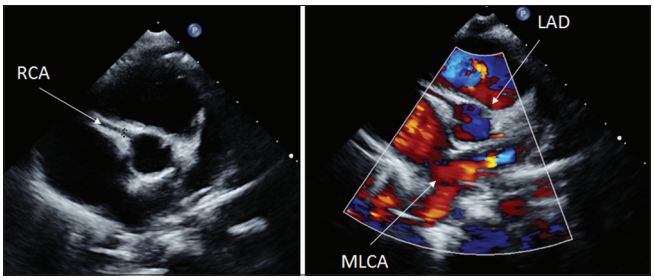

Figure 1: Echocardiogram finding in the patient with normal coronaries vessels dimension. Normal coronary arteries with normal z-score: (1) Main left coronary artery (MLCA): 2.7 mm. (2) Left anterior descending artery (LAD): 1.9 mm. (3) Right coronary artery (RCA): 2.3 mm

CONCLUSION

While the role of IVIG in TSS is controversial, it continues to play a major role in the management of KDSS. Hence, it is prudent that pediatricians and intensivists become familiar

Table 3: Representative scoring systems for evaluating potential IVIG resistance

IVIG resistance score	Cutoff point	Points	The patient	Point
Kobayashi score (≥5 points; 76% sensitivity, 80% specificity)[17,20,21]	Sodium≤133 mmol/L	2	132	2
	Day of illness at initial IVIG (=KD diagnosed) Day 4 or earlier	1	2nd day	1
	AST≥100 IU/L	2	83	0
	Neutrophil ratio≥80%	2	80%	2
	CRP≥10 mg/dL	2	164	2
	Platelet counts≤30.0×10⁴/mm³	1	76	0
	Age≤12 months	1	5 years	0
Total				7
Egami score (≥3 points; 78% sensitivity, 76% specificity)	ALT≥80 IU/L	2	48	0
	Day of illness at initial IVI G (=KD diagnosed) Day 4 or earlier	1	2nd day	1
	CRP≥8 mg/dL	1	164	1
	Platelet counts≤30.0×10⁴/mm³	1	76	0
	Age≤6 months 1	1	5 years	0
Total				2
Sano score (≥2 points; 77% sensitivity, 86% specificity)	AST≥200 IU/L 1	1		0
	Total bilirubin≥0.9 mg/dL	1	72	1
	CRP≥7 mg/dL	1	164	1
Total				2

IVIG: Intravenous immunoglobulin, KD: Kawasaki disease, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein

with this entity to be able to reach an early diagnosis and start the appropriate therapy on time.

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