

Kawasaki disease shock syndrome: A report of two cases and literature review

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ABSTRACT

Importance: Kawasaki disease shock syndrome (KDSS) is a rare Kawasaki disease (KD) manifestation. The pediatricians are not aware of the full range of clinical characteristics of KDSS.

Objective: We aimed to investigate the clinical features, diagnosis and treatment of KDSS in two patients and we included a literature review.

Methods: We collected and analyzed the clinical data for two patients with KDSS. Additionally, using “Kawasaki diseases shock syndrome” as a key phrase, we searched PubMed, Biotechnology Information and Wanfang Data Knowledge Service Platform databases for any similar reports between January 2009 and March 2017.

Results: Both of our patients diagnosed with KD developed sustained hypotension during the course of intravenous immunoglobulin treatment, as well as hypoalbuminemia, and increased C-reactive protein and brain natriuretic peptide levels during hypotension. Both patients responded well to fluid resuscitation and inotropic support. No aneurysms formed in either patient during follow-up. We reviewed two related studies in Chinese and 11 studies in English.

Interpretation: KD may present with severe shock, and requires proper diagnosis and rapid treatment. The prognosis for most patients with KDSS is excellent.

KEYWORDS

Brain natriuretic peptide, Children, Kawasaki disease, Shock

INTRODUCTION

The etiology of Kawasaki disease (KD), a self-limiting systemic vasculitis in children, remains unknown. KD diagnosis depends on the clinical pictures, including fever, rash, conjunctivitis, edema of the hands and feet, erythema, cracked oral mucosa and lips, and cervical lymph node enlargement.¹ Kanegaye et al² were the first to report Kawasaki disease shock syndrome (KDSS), a rare KD manifestation. The characteristics of KDSS are systolic hypotension or shock. Multiple factors lead to KDSS, and may include vasculitis with ongoing leakage

of plasma and proteins into the interstitial compartment, myocardial damage causing dysfunction, and high levels of cytokine.²⁻⁵ In this report we describe two patients with KDSS and review the literature, to increase awareness of this rare cause of shock.

METHODS

We collected and analyzed clinical information of two patients with KDSS. Using “Kawasaki disease shock syndrome” as a key phrase, we searched PubMed, Biotechnology Information and Wanfang Data Knowledge

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Service Platform databases for similar reports (between January 2009 and March 2017).

RESULTS

Case 1

A 1-year-5-month-old boy presented with poor general condition and 5 days of high-grade fever. He had developed a diffuse erythematous maculopapular rash on his trunk, edema of the hands and feet and injected and dry fissured lips, but no bulbar conjunctival injection. He had no contact history for infectious diseases. In a local hospital, a diagnosis of incomplete Kawasaki disease was suspected, and he received intravenous immunoglobulin (IVIG) and moderate-dose acetylsalicylic acid treatment. However, during treatment, the high-grade fever persisted, and his blood pressure decreased from 90/60 mmHg to 70/30 mmHg. He was then transferred to our department. Physical examination revealed a febrile ill child with diffused erythematous rash on his trunk and face. He was irritable and anorexic, with tachypnea and tachycardia (heart rate: 180 beats/min), and his O₂ saturation was > 95% without supplemental oxygen. His blood pressure was 73/40 mmHg with capillary refill time > 5 s. Blood tests on the first day of admission showed a white blood cell count (WBC) of 6.63×10^9 /L (band form: 11%); low hemoglobin: 91 g/L; platelets: 130×10^9 /L; C-reactive protein (CRP): 171 mg/L; and erythrocyte sedimentation rate (ESR): 40 mm/1st hour. Additional laboratory results included serum aspartate aminotransferase: 24 U/L; alanine aminotransferase: 14 U/L; albumin: 23.6 g/L; and sodium: 129 mmol/L. Serum brain natriuretic peptide (BNP) level was 2545 pmol/L and cardiac troponin level was 0.06 ng/mL. Echocardiography revealed left main coronary artery (LMA) dilatation with normal cardiac function and no pericardial effusion. LMA diameter was 2.0 mm, and the right main coronary artery diameter was 2.2 mm. Perivascular brightness in both LMA and right main coronary artery was also seen. Despite fluid resuscitation with normal saline (20 mL/kg), the patient's blood pressure remained low at 63/23 mmHg. We then administered inotropic agents to treat sustained hypotension and shock syndrome [(dopamine and dobutamine at up to 10 µg/(kg · min)]. Although the suspected diagnosis was incomplete KD, the patient's high-grade fever persisted despite appropriate therapy. IVIG (2 g/kg for 24 h) was repeated, and moderate-dose of acetylsalicylic acid [40 mg/(kg · day), divided into four doses] was continued. After 24–48 h of treatment, the patient's general condition and hemodynamic status gradually improved. On day 10, periungual desquamation appeared. Fourteen days after admission, repeat echocardiography showed a dilated LMA (2.7 mm) without aneurysm formation. Two months later, the patient was symptom-free and repeat echocardiography showed a mildly-dilated LMA (2.6 mm) without aneurysm

formation.

Case 2

High fever and a 2-day-duration maculo-papular cutaneous rash were the chief complaints of a previously healthy 7-year-old girl. Three days after the onset of her symptoms, the patient developed bilateral bulbar conjunctival injection without exudate, and mild pruritus. She was treated with a 2-day course of cefuroxime and cetirizine, but her symptoms did not improve. Physical examination revealed a diffuse congestive papular rash, cervical lymph node enlargement, brawny edema of the dorsa of the hands, inflamed lips with dryness and cracking and red strawberry tongue. Her extremities were warm, and heart rate was 112 beats/min. Her blood pressure was normal at 108/50 mmHg, and bilateral lung, neurological and abdominal examinations were also normal. She was initially managed for having bacterial infection and received cefotaxime treatment.

On day 5 of illness, the high fever had not resolved, and she now had a rash, bilateral nonexudative conjunctivitis, cracked and red lips, red strawberry tongue, cervical lymphadenopathy and edema of the dorsum of the hands and feet along with diffuse erythema. She was diagnosed as having typical KD. A dilated left anterior descending (LAD) artery and right coronary artery were seen on echocardiography; cardiac function was normal, and no pericardial effusion was seen. IVIG was administered at 2 g/kg as a single infusion over 12 hours, and acetylsalicylic acid was started at 40 mg/(kg · day) divided into four doses. However on day 7 of illness, agitation, tachycardia, hypotension (blood pressure: 77/33 mmHg), and cool extremities were noted. After fluid resuscitation with normal saline (20 mL/kg), inotropic agents were administered for the persistent hypotension and for shock syndrome [dopamine: up to 15 µg/(kg · min)]. Laboratory data revealed WBC: 5.42×10^9 /L; hemoglobin: 81 g/L; platelets 114×10^9 /L; albumin: 24.8 g/L; sodium: 127.52 mmol/L; aspartate aminotransferase: 19 IU/L; and alanine aminotransferase: 22 IU/L; BNP: 914 pmol/L; and cardiac-specific troponin-I: 0.265 ng/mL. Abdominal ultrasound revealed mild ascites without hepatosplenomegaly. After 36 hours of the IVIG infusion, the patient continued to have a fever >38.5°C, and retreatment with a single dose of IVIG (2 g/kg) was given. After the second dose of IVIG, her fever resolved, and her general appearance and blood pressure improved gradually. She underwent repeat echocardiography 15 days after admission, which revealed an LAD diameter of 2.9 mm, and right main coronary artery diameter of 2.6 mm. Perivascular brightness in both LAD and right main coronary artery was seen; with no aneurysm formation.

Literature Review

We used “Kawasaki disease shock syndrome” as a key

phrase and searched the English literature in PubMed, and the related literature in Chinese from the Biotechnology Information and Wanfang Data Knowledge Service Platform databases for similar cases reported between January 2009 and March 2017. We examined the title and abstract of each article discovered in the search, and if the article appeared potentially eligible for inclusion, we then examined its full text. Patients with a definitive diagnosis of KDSS in the included studies were enrolled in our study. We excluded patients with other diagnoses such as KD with cardiac shock, septic shock, or multiple organ dysfunction. We found two studies in the Chinese literature and 11 studies in the English literature. The full text of each of these 13 articles was then assessed in greater detail (Table 1).

DISCUSSION

KDSS was first described by Kanegaye et al,² but disorder has become more familiar to pediatricians only the past few years. Patients with KDSS are often misdiagnosed as having KD with septic shock, cardiogenic shock, toxic shock, or others. The reported incidence rate of KDSS ranges from 2.60%–6.95% for children in western countries.^{2,3,6} In Taiwan, the incidence of KDSS in children is 1.45 per 100 cases of KD, which is lower than in previous reports from western countries.⁷

According to Kanegaye et al's definition, KDSS is defined as hemodynamically-unstable KD, and includes the occurrence of hypotension and shock. The following criteria describe the diagnostic definition of KDSS generally accepted worldwide: systolic hypotension at different ages in children or clinical manifestations of hypoperfusion such as tachycardia, delayed capillary refill time, cool extremities, weak pulse, decreased urine output, or consciousness disturbance occurring regardless of blood pressure measurement.²

Both of our patients fulfilled the criteria for a diagnosis of KDSS. Patient 1 had exanthema, red and cracked oral mucosa, erythema, and edema of the extremities, but no conjunctival injection or cervical lymph node enlargement, which made the diagnosis of incomplete KD. However patient 2 had the typical symptoms of KD. Both patients deteriorated to shock during the first IVIG treatment, and then received fluid resuscitation and vasoactive agents.

According to previous studies, patients with KDSS are more likely to be female, and have atypical presentation, predominant gastrointestinal tract involvement, and laboratory findings consistent with inflammation. Previous patients had significantly increased WBC, low platelet counts, and low hemoglobin and serum albumin levels but high CRP levels. These patients also tended to not respond to IVIG, and also had higher incidence of coronary artery dilatation or evolving aneurysms.^{2,3,6-10} Both of our patients met these characteristics. Both patient 1 vs

patient 2, respectively had high CRP levels: 171 mg/L vs 132 mg/L; hypoalbuminemia: 23.6 g/L vs 24.8 g/L; and low hemoglobin: 91 g/L vs 81 g/L. Both patients were IVIG-resistant and required a second dose of IVIG. Both also showed coronary artery dilation in the acute phase of illness, but neither had a permanent coronary aneurysm.

In addition to the above characteristics, our patients also had interesting clinical findings. One finding was that the hypotension in both patients occurred during the period of most severe inflammation and both showed myocardial damage, shown by the high CRP, serum cardiac troponins, and BNP levels. The most severe hypoalbuminemia also occurred at that time. These findings are consistent with the etiology of KDSS.

Although the exact mechanism for KDSS is unknown, most reports discuss the suspected development of systemic capillary leak syndrome secondary to intense vasculitis, proinflammatory cytokine overexpression, and myocardial dysfunction secondary to acute myocarditis or transient valvular regurgitation as the main causes of KDSS.⁴⁻⁷ The high inflammatory marker levels and severe hypoalbuminemia suggest increased capillary leakage secondary to intense vasculitis, and the high serum troponins and BNP levels suggest acute myocarditis leading to myocardial dysfunction. Based on these factors, the key treatments for KDSS should include timely administration of colloid (albumin infusion) and vasoactive agents.

The features of KDSS are similar to those of toxic shock syndrome (TSS), and differentiating KDSS from TSS is challenging in the early stages of a clinical diagnosis. Lin, et al stated that, echocardiographic abnormalities, especially coronary artery lesions, anemia, and thrombocytosis were highly suggestive of KDSS.¹⁰ However, in most studies, including in our two patients, in acute KDSS, lower platelet counts were more common.^{6-9,11-13} Given these considerations, it is very important to make a correct diagnosis using echocardiography to detect coronary artery lesions and to give appropriate treatment.^{2,6-9,11-13} In our two patients, we also found that serum BNP or N-terminal proBNP (NT-proBNP) might play an important role in differentiating KDSS from TSS, each of these values increased during hypotension. This phenomenon was also discussed by Qiu et al¹⁴ and Li et al,¹⁵ who found that high serum NT-proBNP level was an independent risk factor for KDSS. However, further studies of elevated NT-proBNP in KDSS are needed.

Schuster et al¹³ stated that hyponatremia was a feature of KDSS, reporting that hyponatremia occurred in 10/11 (91%) case-patients and 7/22 (33%) control-patients ($P < 0.003$). Similarly, both of our patients also had severe hyponatremia when hypotension occurred.

In conclusion, KDSS is a rare but severe form of KD

TABLE 1 Clinical features, vascular involvement, and IVIG resistance in patients with KDSS in the literature and in our reported cases

KDSS in literatures	Number of cases	Old age (>5 y) n (%)	Female/male	Incomplete KD n (%)	CRP (mg/L) [‡]	Reduced platelet count (<150 × 10 ⁹ /L) n (%)	IVIG resistance n (%)	Coronary involvement n (%)
Kanegaye et al ²	13 (187 patients with KD)	3 (23)	9/4	NA	184 (87–221)	7 (64)	6 (46)	8 (62)
Gómez-González et al ⁶	11 (214 patients with KD)	5 (45)	3/9	7 (64)	121.5	2 (18)	6 (60)	10 (91)
Chen et al ⁹	9	2 (22)	6/3	2 (22)	213	3 (33)	2 (22)	7 (78)
Lin et al ¹⁰	17 (Compared with TSS)	NA	6/11	NA	165 (70–352)	NA	NA	9 (53)
Qiu et al ¹⁴	8 (567 patients with KD)	5 (63)	3/5	NA	221	0 (0)	5 (63)	7 (88)
Kuo et al ⁷	19 (1065 patients with KD)	4 (15)	10/9	5 (26)	201	17 (89)	9 (47)	14 (74)
Schuster et al ¹³	12 (756 patients with KD)	NA	8/4	1 (1)	186	NA	7 (58)	3 (25)
Li et al ¹⁵	6	NA	2/4	0 (0)	258 (141–414)	NA	4 (67)	4 (67)
Taddio et al ⁸	5 (84 patients with KD)	NA	1/4	5 (100)	278 (233–960)	NA	3 (60)	3 (60)
Sinhabahu et al ¹⁶	1	1	1/0	1	289	1	0	1
Thabet et al ³	1	0	1/0	1	184	1	1	1
Marrani et al ¹⁷	1	0	0/1	1	NA	NA	0	0
Tissandier et al ¹¹	1	1	0/1	0	255	0	Cannot be evaluated [†]	0
Our reported cases	2	1 (50)	1/1	1 (50)	152	1 (50)	2 (100)	2 (100)

KDSS, Kawasaki disease shock syndrome; KD, Kawasaki disease; TSS, toxic shock syndrome; CRP, C-reactive protein; NA, not available; IVIG, intravenous immunoglobulin.

[†]The reported case was treated immediately as IVIG-resistant KD.

[‡]Data are presented as median (interquartile range) or mean.

with hemodynamic instability, and the diagnosis is often missed because of its atypical presentation. Our case report highlights that KD may be a rare etiology for shock in childhood, emphasizing that pediatricians be aware of the full range of clinical manifestations of KDSS. Patients with KD presenting in shock appear to have higher inflammatory marker levels, severe myocardial damage, hypoalbuminemia, hyponatremia, and higher serum BNP levels. Early recognition of KDSS and providing adequate therapy are critical.

CONFLICT OF INTEREST

None.

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