HK J Paediatr (new series) 2016;**21**:197-200

Two Cases of Kawasaki Disease Shock Syndrome

SWY ***To***, CLS ***Yan***, NC ***Fong***, CW ***Leung***

Abstract Kawasaki disease shock syndrome (KDSS) is a newer entity being better recognised recently, which is defined as Kawasaki disease features plus systolic hypotension or clinical signs of poor perfusion. Patients with KDSS typically have more heightened levels of inflammatory markers and greater risks of coronary artery abnormalities, mitral regurgitation and persistent myocardial dysfunction. They also have greater likelihood of intravenous immunoglobulin (IVIG) resistance requiring additional anti-inflammatory treatment. We report two cases of KDSS presenting with shock, both with IVIG resistance and coronary arteries involvement. Clinicians should maintain high index of suspicion for KDSS to avoid delay in diagnosis and to facilitate timely treatment by IVIG.

Key words Complications; Immunoglobulins; Kawasaki disease; Paediatric intensive care units; Shock

Introduction

Haemodynamic disturbance manifesting as shock has recently been recognised as a potential complication of Kawasaki disease (KD).[1] We report here 2 cases of Kawasaki disease shock syndrome (KDSS) requiring intensive care in a regional referral centre.

Case 1

A previously healthy 7-year-old Chinese girl was referred from a private hospital in July, 2014 for septic shock. She presented with fever for four days, sore throat and cough. On admission she was lethargic and required 2 L/min of supplemental oxygen. She had a temperature of 38.7°C, cool extremities, blood pressure (BP) of 85/50 mmHg (systolic BP at 5th percentile for age) (Table 1) and pulse rate of 135/min. Other physical findings included bilateral non-suppurative conjunctival injection, strawberry tongue, red and cracked lips, unilateral cervical lymph node enlargement 3 cm in diameter, maculopapular rash over trunk, but no oedema or erythema over distal extremities. There was hepatomegaly of 3 cm below the right costal margin but no splenomegaly. Chest and cardiovascular examination was unremarkable. Initial investigations showed a slightly elevated absolute neutrophil count (ANC) of 9.2 x 10^9/L and deranged liver function with alanine aminotransferase (ALT) 195U/L, aspartate aminotransferase 168U/L, total bilirubin (TB) 65 umol/L. Albumin level was decreased to 32 g/L and renal function test was normal. C-reactive protein (CRP) was markedly raised to 238 mg/L and erythrocyte sedimentation rate (ESR) was 91 mm/hr. Microbiological workup was non-contributory except for the detection of adenovirus in the nasopharyngeal aspirate by nucleic acid amplification. Chest X-ray showed bilateral interstitial infiltrates. Ultrasonography of the hepatobiliary system was unremarkable. Cervical ultrasonography did not reveal abscess formation of the enlarged lymph node.

Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Kwai Chung, N.T., Hong Kong, China

SWY **To** (杜詠恩) *MBBS, MRCPCH*
CLS **Yan** (甄麗嬋) *MBBS, MRCPCH*
NC **Fong** (方乃聰) *FHKCPaed, FHKAM (Paed)*
CW **Leung** (梁志偉) *FRCP, FRCPCH*

Correspondence to: Dr SWY **To**

Received July 9, 2015

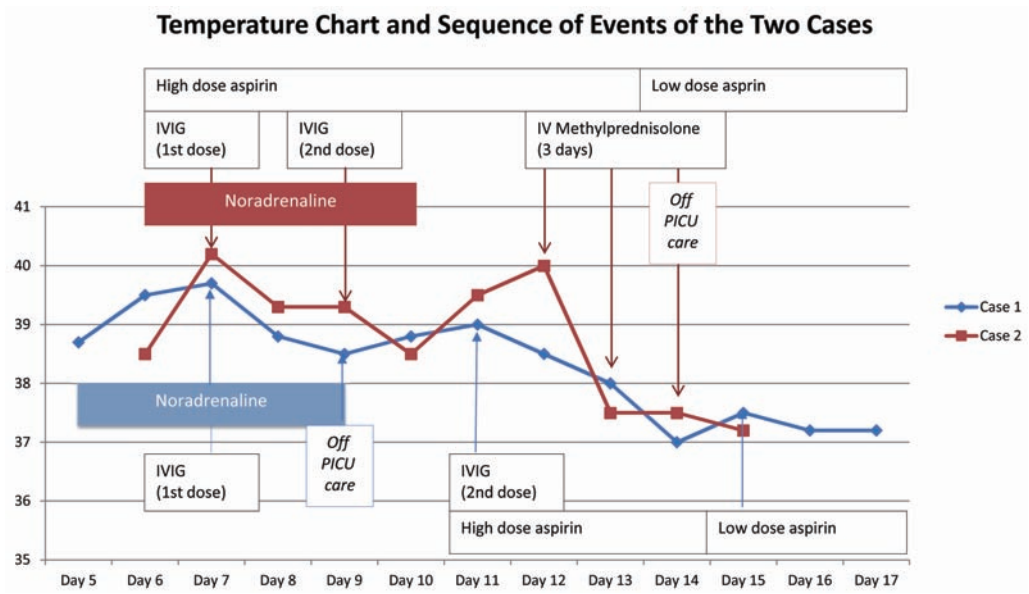
She was given fluid resuscitation with bolus normal saline (NS) infusion (total 20 ml/kg) and inotropic support with noradrenaline up to 0.15 mcg/kg/min (Figure 1). Intravenous ceftriaxone, vancomycin and clindamycin were administered. Intravenous immunoglobulin (IVIG) was given on day 7 of illness for suspected Toxic shock syndrome (TSS). With possible Kawasaki disease in mind, Echocardiogram was performed on day 7 which showed mild mitral regurgitation, no pericardial effusion, normal cardiac contractility and unremarkable coronary arteries. Her BP gradually stabilised with inotropic support discontinued on day 9.

She had persistent swinging fever despite antibiotics and IVIG treatment and a second dose of IVIG was given on day 11. High-dose aspirin was also administered for suspected KD. Defervescence occurred within 48 hours with rapid disappearance of the peripheral signs of KD. Repeated blood tests showed a decline of ESR and ANC, as well as thrombocytosis of 575 x 10^9/L and hypoalbuminaemia of 19 g/L. She was switched to low-dose aspirin therapy on day 15. Echocardiography performed at 2 weeks of illness showed trace mitral regurgitation, left anterior descending coronary artery aneurysm of 6 mm, mild dilatation of right coronary artery to 3.5 mm, a thin rim of pericardial effusion and normal ventricular function. She was discharged on day 17 of illness to be followed up by paediatric cardiologist.

Table 1 Clinical and laboratory findings of the two cases of KDSS

	Case 1	Case 2
Age	7 years old	26 months
Gender	Female	Female
Ethnicity	Chinese	Chinese
Febrile duration (days)	13	13
Highest body temperature (°C)	39.7	40.2
Lowest blood pressure (mmHg)	85/50	60/30
Requiring inotropes	Yes	Yes
WBC count (x 10^9/L)	10.2	4.7
Absolute neutrophil count (x 10^9/L)	9.2	3.8
Haemoglobin (g/dL)	12.8	9.9
Platelet count (x 10^9/L)	234	39
Albumin (g/L)	32	28
ESR (mm/hr)	91	Normal
CRP (mg/L)	239	181
Received IVIG dose	2	2
Additional anti-inflammatory treatment	Nil	Methylprednisolone
Coronary artery dilatation	RCA 3.5 mm	LCA 3.2 mm
Coronary artery aneurysm	LAD 6 mm	Nil
Mitral regurgitation	Trace	Moderate

WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IVIG: intravenous immunoglobulin; RCA: right coronary artery; LCA: left coronary artery; LAD: left anterior descending coronary artery



IVIG: intravenous immunoglobulin; PICU: paediatric intensive care unit

Figure 1 Temperature chart and events sequence of the two cases.

Case 2

A 27-month-old previously healthy Chinese girl was transferred from a private hospital in July 2014 with a history of fever for six days and rash. Physical examination showed a temperature of 38.5°C, BP of 60/30 mmHg (systolic BP below 5th percentile for age) (Table 1), and a pulse rate of 150/min. She had cool extremities, puffy eyelids, generalised oedema and confluent erythematous macular rash over the face, trunk and lower limbs. There was no conjunctivitis, lip changes or enlarged cervical lymph nodes. Abdominal examination revealed hepatomegaly of 3 cm below right costal margin but no splenomegaly. NS bolus infusion (total 35 ml/kg) and noradrenaline up to 0.6 mcg/kg/min were administered to combat shock. Intravenous vancomycin, ceftriaxone and clindamycin were commenced for suspected TSS. Initial investigations showed an ANC of 3.8 x 10^9/L, platelet count 39 x 10^9/L and haemoglobin 9.9 g/dL. Sodium level was low at 128 mmol/L with normal renal function. There was hypoalbuminaemia of 17 g/L with normal ALT and TB. INR was increased to 1.4 and APTT level was prolonged to 50.7 seconds. CRP was markedly raised to 181 mg/L but ESR was normal. Urinalysis was normal.

She developed bilateral conjunctival injection, red lips and bilateral cervical lymph node enlargement up to 1.5 cm diameter one day after admission. Echocardiogram showed moderate tricuspid and mitral regurgitation, mildly dilated left atrium and ventricle with normal contractility, and coronary arteries were of normal size but echogenic. KD was diagnosed and she was administered IVIG and high-dose aspirin on day 7 of illness (Figure 1). Fever persisted despite a second dose of IVIG on day 9. She was then commenced on a 3-day course of intravenous high-dose methylprednisolone from day 12 to 14 of illness. Her BP gradually stabilised and inotrope was taken off on day 10. Defervescence occurred on day 14 and she was subsequently switched to low-dose aspirin. The rash rapidly subsided and desquamation developed over her left hand. CRP declined rapidly to 17 mg/L with normalisation of platelet count and albumin level increased to 27 g/L. Microbiological workup was negative. Echocardiography performed at 2 weeks of illness showed mildly dilated left main coronary artery up to 3.5 mm.

Discussion

Recently, the clinical entity of Kawasaki Disease Shock Syndrome is described in case reports.[2-4] KDSS was first described by Kanegaye et al in 2009[1] and was quoted to account for around 7% of all KD cases. Its diagnostic criteria being KD features together with systolic hypotension for age (infants 0-28 days of age ≤60 mm Hg; infants 1-12 months of age <70 mm Hg; children 1-10 years of age <70 + [2 x age] mm Hg; youths >10 years of age, <90 mm Hg), a sustained decrease in systolic blood pressure from baseline of ≥20% or clinical signs of poor perfusion (tachycardia, prolonged capillary refill time, cool extremities, diminished pulse volume, oliguria) requiring use of volume expansion, vasoactive agents, or transferal to an intensive care setting. Whereas for TSS, there is also multi-organ failure involving 3 or more organ systems.[5] Misdiagnosis may lead to delay in diagnosis of KD and thus delay in giving IVIG. Both cases were suspicious of TSS initially and antibiotics were promptly administered. However, for the first case, IVIG was given early on before the diagnosis of KDSS as an adjunctive treatment for TSS to neutralise superantigens.[6] Aspirin was started later when KD features were more prominent.

Patients with KDSS have some common characteristics including female predominance, greater proportion of band forms in white cells, lower platelet count with evidence of consumptive coagulopathy, lower haemoglobin level, and higher CRP level.[1] KDSS is associated with higher risk of cardiac complications including coronary artery dilation and aneurysm formation, mitral regurgitation, and persistent ventricular diastolic dysfunction.[1,7] Gastrointestinal symptoms including abdominal pain, vomiting, diarrhea and gastrointestinal bleeding were also more prominent.[7] They have higher risk of IVIG resistance as defined by persistent fever after 48 hours of starting IVIG.[8] By definition, both cases were IVIG-resistant and for the second case, methylprednisolone was required to achieve defervescence. Postulations for higher risk of IVIG resistance and development of cardiac complications include more intense underlying inflammation as suggested by heightened levels of inflammatory markers and also delay in diagnosis thus delay in giving IVIG and aspirin.

The pathogenesis of KDSS is not fully understood. Proposed mechanisms include proinflammatory cytokine over-expression (cytokine storm), vasculitis with systemic capillary leak syndrome and myocardial dysfunction.[9] Both patients had severe hypoalbuminaemia with capillary leak. Vasodilation related to toxin or cytokine may also be present, as evidenced by low diastolic blood pressure in both patients. For TSS, it is an acute exotoxin-mediated multisystem disorder caused by superantigens produced by *Staphylococcus aureus* or *Streptococcus pyogenes*. Some

experts suggested a similar pathogenetic mechanism of superantigen (SAg)-mediated inflammation for both TSS and KDSS given their overlapping clinical features. Researchers have found SAg-producing microbes in the gastrointestinal tract of patients with KD and some even investigated into SAg genes in the stool of patients with KD.[10] Nonetheless, no specific bacterial superantigens were proven to be the direct trigger of KD.

Paediatricians, intensivists and accident and emergency personnel are advised to have increased awareness of KDSS and to diligently looking for Kawasaki features in patients presenting with fever, rash and shock, to avoid delay in instituting appropriate specific management. Also, additional research is required to elucidate the pathogenesis of this phenomenon, to identify the risk factors and predictors for the development of KDSS, and to characterise more fully the long-term abnormalities of cardiac diastolic dysfunction.

References

1. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics 2009;123:e783-9.
2. Yim D, Ramsay J, Kothari D, Burgner D. Coronary artery dilatation in toxic shock-like syndrome: the Kawasaki disease shock syndrome. Pediatr Cardiol 2010;31:1232-5.
3. Thabet F, Bafaqih H, Al-Mohaimeed S, Al-Hilali M, Al-Sewairi W, Chehab M. Shock: an unusual presentation of Kawasaki disease. Eur J Pediatr 2011;170:941-3.
4. İşgüder R, Doksöz Ö, Bağ Ö, et al. Kawasaki disease shock syndrome: a severe form of Kawasaki. Turk J Pediatr 2013;55: 319-21.
5. Centers for Disease Control and Prevention. Toxic shock syndrome (other than Streptococcal) (TSS): 2011 Case Definition. [Online] Available from: http://wwwn.cdc.gov/nndss/script/casedef.aspx?CondYrID=869&DatePub=1/1/2011 [Accessed 10th February 2015]
6. Darenberg J, Ihendyane N, Sjölin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2003;37:333-40.
7. Gámez-González LB, Murata C, Muñoz-Ramírez M, Yamazaki-Nakashimada M. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children. Eur J Pediatr 2013;172:337-42.
8. Guidelines for medical treatment of acute Kawasaki disease: Report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version). Pediatr Int 2014;56:135-8.
9. Gatterre P, Oualha M, DupicL, et al. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. Intensive Care Med 2012;38:872-8.
10. Nagata S, Yamashiro Y, Ohtsuka Y, et al. Heat shock proteins and superantigenic properties of bacteria from the gastrointestinal tract of patients with Kawasaki disease. Immunology 2009;128: 511-20.