



## Kawasaki Disease Shock Syndrome, Unique Type with Giant Coronary Artery Dilatation – Presentation of Two Cases and a Literature Review

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### Abstract

**Introduction:** Kawasaki disease is an acute, self-limited vasculitis of childhood characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in approximately 15% to 25% of untreated children with the disease and may lead to myocardial infarction, sudden death, or ischemic heart disease. Despite an overlap of clinical features with toxic shock syndrome, children with Kawasaki disease generally do not develop shock.

**Cases:** Two adolescent children who presented with a toxic shock-like illness, and were subsequently diagnosed with Kawasaki disease shock syndrome when coronary artery abnormalities were found on transthoracic echocardiography.

**Conclusion:** Pediatricians and pediatric cardiologists alike should be aware of this potentially severe form of manifestation of the Kawasaki disease which needs to be differentiated from the multisystem inflammatory syndrome in children.

**Keywords:** Kawasaki disease; Kawasaki disease shock syndrome; Coronary artery aneurysm; Intravenous immunoglobulin

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### Introduction

Kawasaki Disease (KD) constitutes an acute febrile vasculitis of unknown etiology associated with the development of arterial Coronary Artery (CA) abnormalities and myocardial infarction. Its etiology remains unknown, although specific viral agents or virus-like cytoplasmic inclusion bodies in the tissue of Kawasaki disease patients have been implicated [1,2]. Although standard treatment comprises intravenous immunoglobulin and aspirin, some children exhibit refractory disease, necessitating the use of alternative therapies such as corticosteroids and anti-tumor necrosis factor-alpha.

The "Kawasaki Disease Shock Syndrome" (KDSS) is characterized by myocardial dysfunction, earlier-onset and more severe CA involvement, and poor response to standard therapy [3,4]. In recent years during the COVID-19 pandemics there have been overlapping cases presenting with hemodynamic instability, hypotension, shock and coronary artery involvement leading to a diagnostic dilemma between KDSS and Multisystem Inflammatory Syndrome in Children (MIS-C) [5]. Here we present two adolescent boys who had KDSS and discuss their differentiating features from MIS-C.

### Case Series

#### Case 1

A previously healthy 13-year-old Kosovar Albanian, teenager boy weighing 64 kg presented with a 7-day history of high fever, headache, vomiting with diarrhea, myalgia, and generalized rash. There was a two-day history of abdominal pain, erythema of the oral mucosa, and bilateral conjunctivitis. On admission he was febrile (39.8°C), tachycardic (145/min), hypotensive (75/55 mmHg), poorly perfused, (capillary refill time 5s). He had bilateral non-exudative conjunctival injection without

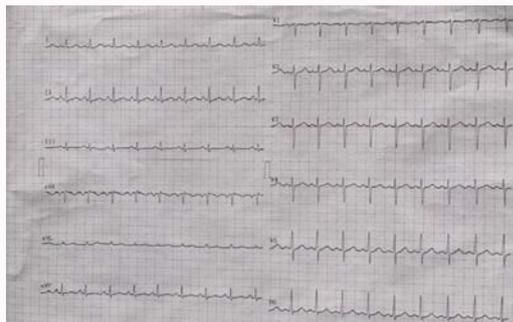


Figure 1: Normal echocardiogram.

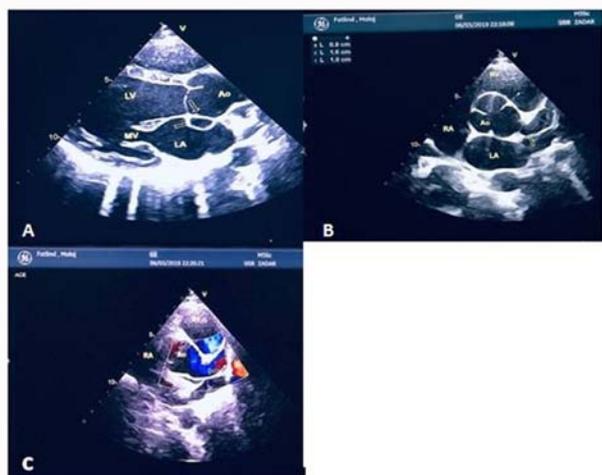


Figure 2: (A) 2D echocardiography at the long axis view showed giant dilatation of the LMCA (arrows); (B) Short axis view presented aorta and enormously dilated LMCA (arrow); (C) Short axis view with color Doppler showed laminar down flow in dilated LMCA (arrow).  
LA: Left Atrium; MV: Mitral Valve; LV: Left Ventricle; AO: Aorta; RA: Right Atrium; RV: Right Ventricle.

focal neurological signs, generalized lymphadenopathy, red lips and punctate ulcers on his buccal mucosa, red fissured lips, and a widespread maculopapular rash with target lesions. There was no evidence for periungual desquamation at any stage. Abdominal examination revealed right upper quadrant abdominal tenderness.

Laboratory evaluation showed an erythrocyte sedimentation rate of 112 mm/h and a C-reactive protein level of 232 mg/dl. Other laboratory investigations showed mild thrombocytopenia ( $142 \times 10^9$ ), mild neutrophilia ( $11 \times 10^9$ ), decreased level of serum sodium (123 mmol/l), and potassium (3.4 mmol/l), mild renal impairment (urea 7.2 mmol/l and creatinine (92  $\mu$ mol/l), slightly increased liver transaminases (gamma-glutamyl transferase 69 IU/l and alanine transaminase 72 UI/l). *Staphylococcus aureus* was detected from nasal and pharyngeal swabs. A coagulopathy workup yielded a negative result.

Because of his hypotension patient was admitted to the Intensive Care Unit (ICU) due to ongoing hemodynamic instability. Initially, fluid resuscitation and electrolytes correction was done (20 ml/kg in the first hour and 10 ml/kg in the next two hours). Broad-spectrum antibiotics were administered (Ceftriaxone and Amikacin). Due to persistent hypotension one dose of fresh serum plasma was given (10 ml/kg). His hypotension remained problematic despite adequate volume expansion and inotropic support (Dopamine).

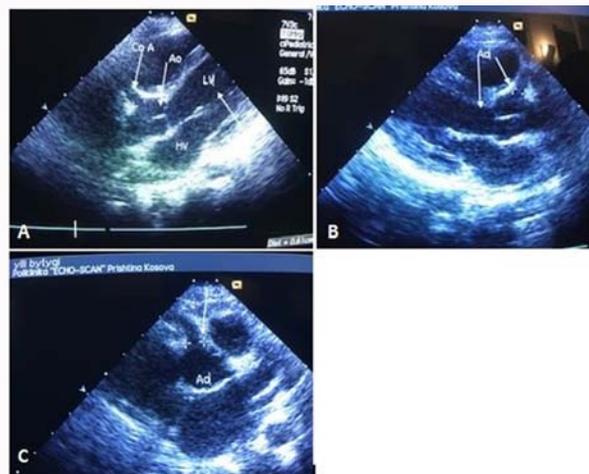


Figure 3: (A) 2D transthoracic echocardiography at the five; (B) long; and (C) short axis view shows dilated right coronary artery.  
Ao: Aorta; MV: Mitral Valve; LV: Left Ventricle; CoA: Coronary Artery.

Clinical suspicion was between Kawasaki disease and multisystem inflammatory syndrome. The possibility of KD was raised, and clinical investigations were continued. There were no features of heart ischemia on the electrocardiogram (Figure 1). A chest X-ray showed significant cardiomegaly and pulmonary stasis. Abdominal ultrasound examination revealed a normal liver, pancreas, and both kidneys, with slightly drops of the gallbladder. Transthoracic echocardiography on the second day of admission (day 9 of illness) was performed. Echocardiography examination showed a small pericardial effusion and mild AV valve regurgitation. Biventricular systolic dysfunction was noted. 2-D echocardiography showed a giant and generalized dilatation and loss of normal tapering of the Left Main Coronary Artery (LMCA), measuring in the proximal to distal part from 9 mm to 16 mm (Boston z-score +9.3) (Figure 2A, 2B). Pulse and color Doppler examinations showed sluggish anterograde flow (Figure 2C). Both branches of the LCA were dilated: The Left Anterior Descending (LAD) artery diameter was 8 mm (Boston z-score +7.8), and the circumflex artery measured at 7 mm (Boston z-score +7.1). Right Coronary Artery (RCA) diameter was normal.

After transthoracic echocardiography findings, a diagnosis for KDSS was made, and the patient was treated immediately with Intravenous Immunoglobulin (IVIG) (2 g/kg), divided into two doses. Also, a high dose of Aspirin (70 mg/kg) was added. His general condition improved during the next 48 h and subsequently became afebrile. He was normotensive and with a normal capillary refill time. There was resolution of the fever, conjunctivitis, and oral mucositis by day 10 of admission. The transthoracic echocardiography was repeated every two days which showed pericardial effusion being completely resolved with improved left ventricular systolic function. Persistent proximal LCA, LAD, and circumflex artery dilatation were noted. Serial blood results showed resolution of inflammatory markers with transient anemia (Hgb – 92 g/l). He was discharged on low-dose aspirin (2 mg/kg). Repeated transthoracic echocardiography 4 weeks later showed normal systolic function of both ventricles with an unchanged dimension of the LCA.

**Case 2**

A previously healthy 11-year-old Kosovar Albanian adolescent boy presented to the Pediatric Emergency Department with a 4-day

history of high fever, headache, generalized arthralgia, and rash, with nausea, vomiting, and diarrhea. He required ICU admission for ongoing hemodynamic instability. At the admission, he was febrile (40.4°C) and unwell, with hypotension (70/55 mmHg), tachycardia (142/min), and poor capillary refill time (5 sec). Neck stiffness was noted without local or generalized neurological signs. During the clinical examination bilateral non-purulent conjunctivitis, erythematous rash over the trunk and extremities, red lips, strawberry tongue, and punctate ulcers on his buccal mucosa were noted. He was the second child of non-consanguineous healthy parents, born at full term with unremarkable past medical history.

Laboratory investigations showed an erythrocyte sedimentation rate of 122 mm/h, C-reactive protein level of 288 mg/dl, borderline thrombocytopenia ( $42 \times 10^9/l$ ), leukocytosis ( $14.3 \times 10^9$ ), hyponatremia (119 mmol/l), hypokalemia (3.1 mmol/l) and hypochloremia (89 mmol/l). Renal impairment was manifested with high levels of urea (15.6 mmol/l) creatinine (134  $\mu$ mol/l). His B-natriuretic peptide was 5.560 ng/l (normal range <100 ng/l) and his troponin-I level 1.10  $\mu$ g/l (normal range <0.04  $\mu$ g/l). Microbial cultures were negative. His hypotension persisted despite adequate fluid resuscitation (50 ml/kg in total for 24 h) and inotropic support (Dopamine). The diagnosis of KD was considered in view of his clinical features. Electrocardiogram was normal. X-ray of the chest revealed cardiomegaly with increased bronchopulmonary markings. The abdominal ultrasound examination was normal. Transthoracic echocardiogram on day 7 of illness revealed severe biventricular dysfunction with a fractional shortening of 19%, moderate AV valve regurgitation, and diffuse dilatation of the right coronary artery of 6.1 mm (z-score +6.2) (Figure 3A-3C). The LCA system was normal in appearance and dimensions.

The patient was treated with 2 g/kg IVIG divided into two doses, and antiplatelet therapy (Clopidogrel and Aspirin -70 mg/kg/d) was administered. Two broad-spectrum antibiotics (Cefotaxim and Amikacine) and methyl-prednisolone (3 mg/kg/d) divided in three doses were included in the drug treatment. Omeprazole was given parenterally to prevent gastric injury. His general condition improved during the next 36 h and subsequently became afebrile. In the next three days, he was normotensive and with normal capillary refill time. Except for clinical condition, there was an echocardiographic improvement of global heart function over the subsequent days. After 2 weeks of admission a repeat transthoracic echocardiogram showed normal biventricular function with persistent RCA dilatation. At day 18 of the illness patient was discharged home as being clinically well, and on low-dose aspirin (3 mg/kg/d).

The above reported cases were presented during early winter, from different places of Kosovo, respectively, within 4 weeks of each other to different outer metropolitan hospitals.

## Discussion

Kawasaki Disease (KD) is an acute vasculitis of unknown origin that involves predominantly the coronary arteries, is the leading condition causing acquired heart disease in industrialized countries and an important cause of long-term cardiac morbidity [4]. Its etiology remains unknown, although specific viral agents or virus-like cytoplasmic inclusion bodies in tissues of KD patients have been implicated [5,6].

Kawasaki disease is the main cause of childhood-acquired cardiac disease in developed countries, with an incidence of 174 in 100,000 per year in children less than 5 years of age, such as Japan. Children

in the age group of 6 months to 5 years are the most susceptible. The diagnosis of KD is based on clinical criteria established in 1993 by the American Heart Association, according to which the most important criterion was the presence of fever for more than 5 days, together with at least four of the five principal criteria: bilateral non-purulent conjunctivitis, erythematous oral cavity, red fissured lips and “strawberry” tongue, polymorphous skin rash, cervical lymphadenopathy (usually unilateral), erythema, and edema of the hands and feet. Additional findings in children with KD include irritability, mood alterations, gastrointestinal discomfort, diarrhea arthralgia/arthritis affecting large joints (30%), hydrops of the gallbladder, and liver dysfunction.

CA involvement can range from transient mild dilatation or ectasia, occurring in up to 40% of patients, to giant Coronary Artery Aneurysms (CAA) [7].

Standard treatment with intravenous immunoglobulin and aspirin reduces the incidence of coronary artery lesions from 20% to 5% [8].

The mortality rate among children is less than 1%, with the most significant complications from ischemic cardiomyopathy presenting during the convalescent phase [9].

In the absence of diagnostic tests, identification of KD requires a high index of suspicion for the cardinal diagnostic features [1]. In addition to fever lasting  $\geq 5$  days, the diagnosis is made with clinical features which include polymorphous rash, palmar and plantar edema of the extremities, non-exudative conjunctival injection, oral mucous membrane changes, and lymphadenopathy. The risk of thrombosis is very high when giant coronary aneurysms develop promptly [10]. There is overlap in clinical features between TSS and KD, although shock and organ dysfunction are unusual features of KD. Non-invasive diagnostic imaging techniques, such as echocardiography and magnetic resonance imaging, may be helpful in diagnosing subclinical myocardial infarction [11]. Cardiac dysfunction is a feature of TSS but CA dilatation and aneurysms have not been previously reported in children and adults [11]. Although our two patients presented with clinical features highly suggestive for TSS, they did not meet the criteria for diagnosis. Clinical presentation, laboratory analysis, and transthoracic findings were similar to the recently described KDSS, which is distinguished from “classical” KD by shock, hypotension and myocardial dysfunction. Thrombocytopenia and coagulation abnormalities, which are rarely seen in KD, appear common in KDSS [12].

Similarly, COVID-19 related MIS-C associated with shock can lead to a delay in diagnosing KDSS as there are common presentation features such as hemodynamic instability, hypotension, and myocardial dysfunction with fever. MIS-C responds rapidly to steroids and inotropic agents leading to the complete resolution of clinical symptoms without the need for IVIG. Nonetheless, giant coronary artery aneurysms rarely occur in the course of COVID-19 antibody positive infants even after IVIG administration [13,14]. MIS-C-related shock commonly occurs with significantly elevated inflammatory markers, low platelet count, but without hypoalbuminemia, no peripheral extremity or mucosal changes, absent lymphadenopathy, and no evidence of sterile pyuria or thrombocytosis. Coronary artery involvement occurs more commonly with KDSS, and gallbladder hydrops is one of the characteristic features of KD [15].

However, the included studies were retrospective case-control

studies, and some of the data reported in the literature were irregular or incomplete with potential publication bias, making the included sample size and data incomplete. The exploration of KDSS still needs prospective, large sample, and multicenter-joint researches. The symptoms of children with KDSS are basically in line with typical KD, yet with a longer duration of fever, more severe inflammatory indicators, and more cardiac abnormalities than non-shocked KD.

## Conclusion

Our presented cases highlight that children with KD may present with a toxic shock-like illness. KDSS should be considered in all children with hemodynamic instability, hypotension and myocardial dysfunction. Echocardiography should be performed frequently to look CA involvement and aggressive treatment is warranted because rapid development of CA aneurysms in the acute stage of the illness and the long-term outcomes in patients with untreated KDSS and giant coronary artery aneurysms are poor.

## Key Points

What's known on this subject?

Hypotension and shock resulting in hemodynamic instability are exceptionally rare in the acute phase of Kawasaki disease without any trigger such as a complication of intravenous IVIG administration.

What this study adds?

These two cases presented with shock and hypotension in the context of newly diagnosed KD highlight the importance of differentiating similar clinical scenarios including MIS-C and TSS.

What are the characteristic signs of the KDSS?

Compared with uncomplicated KD, KDSS occurs predominantly in older males and is associated with hypotension, myocardial dysfunction, reduced albumin, increased inflammation, and rapid development of coronary artery aneurysms.

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