



# Adolescent Kawasaki disease shock syndrome with inflammatory cell infiltration into the myocardium: a case report

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## Background

Kawasaki disease (KD) is a self-limiting form of systemic vasculitis. KD usually occurs in infants and young children and is rarely seen in adolescents. On rare occasions, KD is accompanied with reduced organ perfusion due to systolic hypotension, a condition known as Kawasaki disease shock syndrome (KDSS). The multifactorial causes of KDSS may include intensive vasculitis with capillary leak, myocardial dysfunction, and release of proinflammatory cytokines. However, the mechanisms underlying the pathophysiology of KDSS have not been fully elucidated.

## Case summary

A febrile 17-year-old male with cervical lymphadenopathy developed extreme shock with rapid cardiac dysfunction and reduced organ perfusion. Electrocardiogram revealed ST elevation in the precordial leads and increased serum levels of cardiac enzyme levels. Endomyocardial biopsy at the acute phase revealed CD3<sup>+</sup>, CD4<sup>+</sup> or CD8<sup>+</sup>, and CD20<sup>+</sup> lymphocytes and CD68<sup>+</sup> macrophages within infiltrates in the myocardium with mild interstitial fibrosis. He was treated with intravenous immunoglobulin (IVIg) and followed by glucocorticoids with mechanical circulatory support. His cardiac function recovered rapidly with no apparent adverse effects.

## Discussion

Our results suggest that KDSS may be a form of myocarditis, a condition in which inflammatory cells infiltrate the myocardium. Early immunosuppressive therapy, including IVIg and glucocorticoid therapy, may limit the severity of disease and improve the prognosis. As shown by this case, an accurate diagnosis of KD and KDSS will lead to early intervention and improved prognosis even among those in an older cohort.

## Keywords

Kawasaki disease • Shock • Endomyocardial biopsy • Inflammatory cell • Immunosuppressive therapy • Case report

## Learning points

- Kawasaki disease usually occurs in infants and young children; older children can present with low cardiac output and systemic shock [Kawasaki disease shock syndrome (KDSS)].
- KDSS is associated with infiltration of inflammatory cells into the myocardium.
- Early immunosuppressive therapy may control the myocardial inflammation associated with KDSS and result in an improved prognosis.

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## Introduction

The diagnosis of Kawasaki disease (KD) is based on specific clinical features, including fever persisting for five or more days, a polymorphous rash, oedema of dorsum of the peripheral extremities, bilateral conjunctivitis, cervical lymphadenopathy, and oropharyngeal changes.<sup>1</sup> KD is most frequently diagnosed in children less than 5 years of age; the main pathophysiology is a self-limited systemic vasculitis.<sup>2</sup> On rare occasions, KD is accompanied with reduced organ perfusion due to systolic hypotension; this condition is referred to as Kawasaki disease shock syndrome (KDSS).<sup>3</sup> However, the mechanisms underlying the pathophysiology of KDSS have not been fully elucidated. Here, we report a case of life-threatening KDSS in an adolescent male successfully treated with immunosuppressive therapy (IST) and mechanical circulatory support. We have used this case as a basis to investigate the mechanisms underlying KDSS from a clinicopathological point of view.

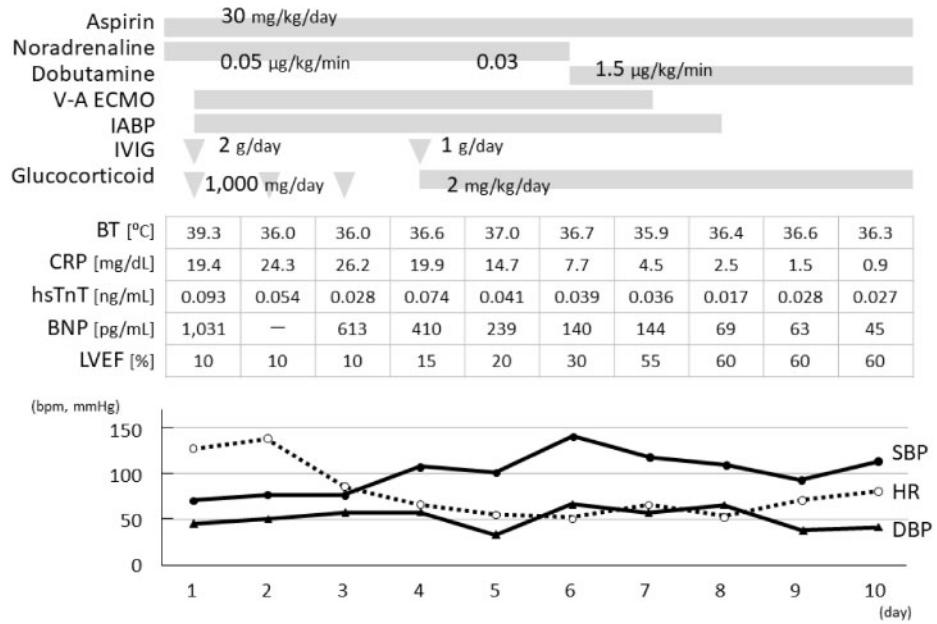
## Timeline

Time	Clinical presentation and treatments
Three days earlier	Fever at 40.2°C, headache, and dyspnoea on effort
Day 1	Polymorphous rash, peripheral oedema, cracked lips, bilateral conjunctivitis, and strawberry tongue Hospitalized due to Kawasaki disease Intravenous immunoglobulin (IVIG) (2 g/kg) and oral aspirin therapy (30 mg/kg/day)
Shortly thereafter	Shock vital (blood pressure 74/38 mmHg, heart rate 133 beats/min) Diagnosed as Kawasaki disease shock syndrome ST-segment elevation in V <sub>2-4</sub> precordial leads, left ventricular ejection fraction (LVEF) 10% Elevated brain natriuretic peptide and troponin T levels Initiated intra-aortic balloon pumping (IABP) and veno-arterial extracorporeal membrane oxygenation (V-A ECMO) support Endomyocardial biopsy: inflammatory cell infiltrates with mild myocardial interstitium fibrosis Steroid pulse therapy (methylprednisolone 1000 mg/day for 3 days)
Day 4	IVIG (1 g/kg) and oral steroid therapy (2 mg/kg/day)
Day 5	LVEF 20%
Day 7	LVEF 55%, terminated V-A ECMO support
Day 8	Terminated IABP support
Day 30	No coronary aneurysms, LVEF 60%
Six months later	LVEF 66%

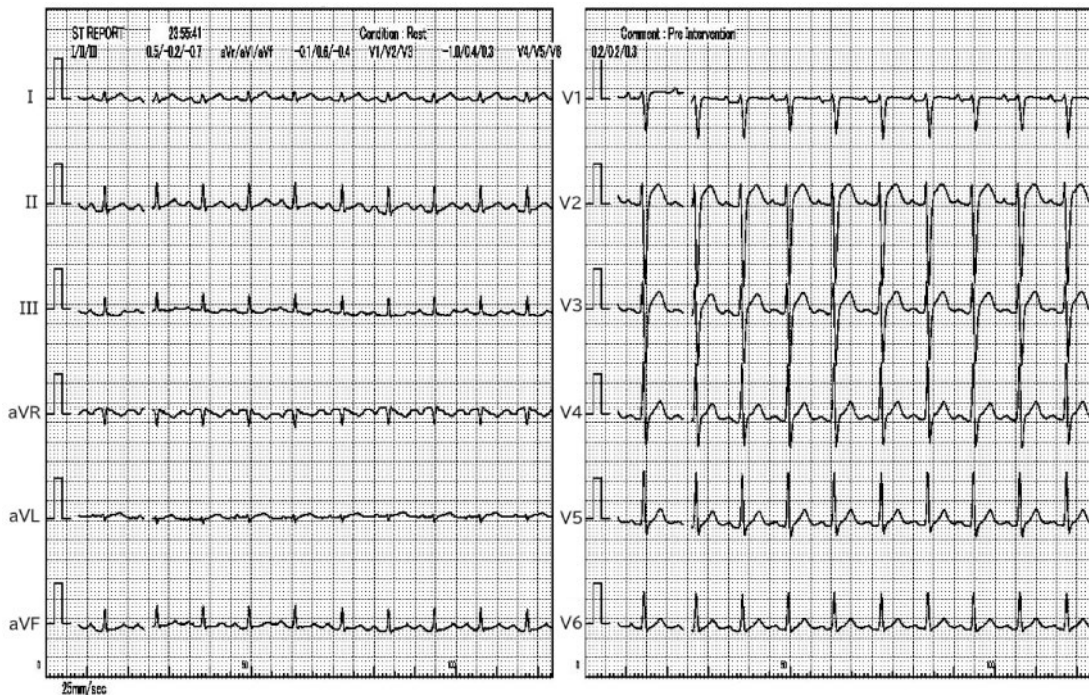
## Case presentation

A 17-year-old male initially presented with chief complaints of a fever (at 40.2°C), headache, dyspnoea on effort, and cervical lymphadenopathy. Three days later, he was diagnosed with KD based on the appearance of polymorphous rash, peripheral oedema, cracked lips, bilateral conjunctivitis, and a swollen and bumpy 'strawberry' tongue. He had no noteworthy previous medical history or family history. The antinuclear antibody level was below 1:40 and the rheumatoid factor was negative. Both the myeloperoxidase-anti-neutrophil cytoplasmic antibody (ANCA) and proteinase-3-ANCA levels were within normal limits and no suspicious findings regarding other immune diseases were observed. He was hospitalized at this time and received a single dose of intravenous immunoglobulin (IVIG; 2 g/kg) together with oral aspirin therapy (30 mg/kg/day) in an effort to prevent the development of a coronary artery lesion (Figure 1). Shortly thereafter, his blood pressure dropped to 74/38 mmHg and his heart rate increased to 133 beats/min. Chest radiograph was notable for bilateral lung congestion and cardiac enlargement (cardiothoracic ratio = 59%). An electrocardiogram included ST-segment elevation in V<sub>2-4</sub> precordial leads (Figure 2). At this time, his ejection fraction had dropped to 10% (Figure 3A), and accumulated pericardial fluid was detected in an echocardiogram. Likewise, plasma levels of brain natriuretic peptide (BNP) increased markedly to 1.031 pg/mL (normal < 18.4 pg/mL); serum levels of troponin-T were mildly elevated at 0.093 ng/mL (normal < 0.014 ng/mL). These findings suggested acute myocardial injury in association with KD. Emergency coronary angiography was performed, followed by right heart catheterization and endomyocardial biopsy under inotrope infusion, intra-aortic balloon pumping (IABP), and peripheral veno-arterial extracorporeal membrane oxygenation (V-A ECMO) support. He had no valvulitis, but his age-adjusted haemoglobin level was normal and platelet count was preserved (160 000/mm<sup>3</sup>). In addition, blood cultures showed no bacterial involvement and plasma endotoxin levels were within normal limits. He was diagnosed as KDSS as per the recently proposed criteria.<sup>3,4</sup>

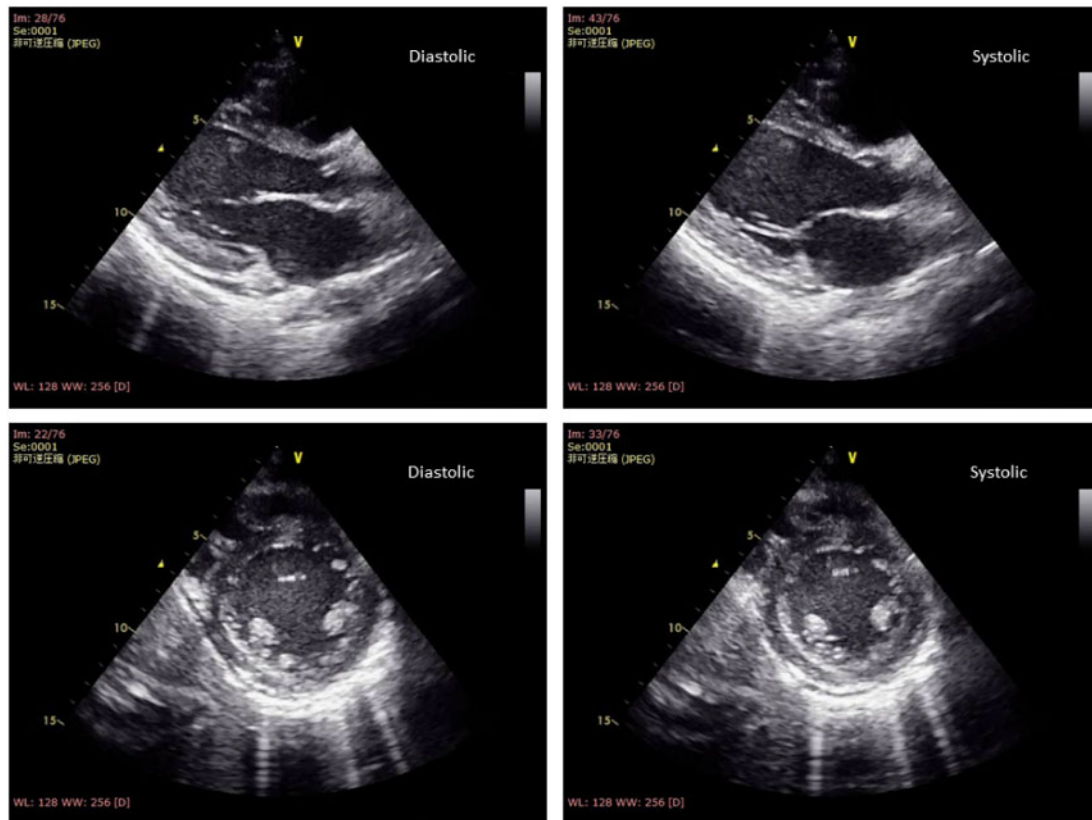
Pathological findings in the endomyocardial biopsy specimen are shown in Figure 4. Inflammatory cell infiltrates were detected in the myocardial interstitium in association with mild fibrosis, consistent with a diagnosis of myocarditis. Immunostaining revealed a small number of CD3<sup>+</sup>, CD4<sup>+</sup> or CD8<sup>+</sup> and CD20<sup>+</sup> small lymphocytes together with a few CD68<sup>+</sup> macrophages. The serological analysis with paired serum samples did not reveal any viral involvement. No stenosis or aneurysms were noted at the coronary arteries. As his cardiac index had decreased to 1.6 L/min/m<sup>2</sup>, we treated his IVIG-resistant KDSS and myocardial inflammation with pulse IST using methylprednisolone 1000 mg/day for 3 days; oral steroids were added because the troponin-T level remained high on hospital Day 4 (Figure 1). Left ventricular systolic function had slightly improved by hospital Day 5 and had normalized by hospital Day 7 (Figure 3B), with a left ventricular ejection fraction (LVEF) of 55%. V-A ECMO was discontinued on hospital Day 7 as was IABP support on hospital Day 8. During right heart catheterization, cardiac index, and pulmonary artery wedge pressure was maintained at 3.5 L/min/m<sup>2</sup>. A repeat coronary angiography on hospital Day 30 revealed no abnormal findings and notably



**Figure 1** Clinical course in the acute phase of KDSS. BNP, brain natriuretic peptide; BT, body temperature; CRP, C-reactive protein; DBP, diastolic blood pressure; HR, heart rate; hsTnT, high-sensitivity troponin-T; IABP, intra-aortic balloon pumping; IVIG, intravenous immunoglobulin; KDSS, Kawasaki disease shock syndrome; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.



**Figure 2** A 12-lead electrocardiogram in patient diagnosed with KDSS. KDSS, Kawasaki disease shock syndrome; ST-segment was elevated in V<sub>2-4</sub> precordial leads.



**Figure 3** Systolic function on echocardiogram. (A) Echocardiogram during the acute phase of disease revealed a marked decrease in systolic function. (B) Systolic function returned to normal in response to glucocorticoid therapy.

no coronary aneurysms. At follow-up 6 months after discharge, echocardiography was notable for normal systolic function (LVEF 66%). Troponin-T and plasma BNP level were within normal range without oral steroid therapy (0.005 ng/mL and 7.0 pg/mL, respectively).

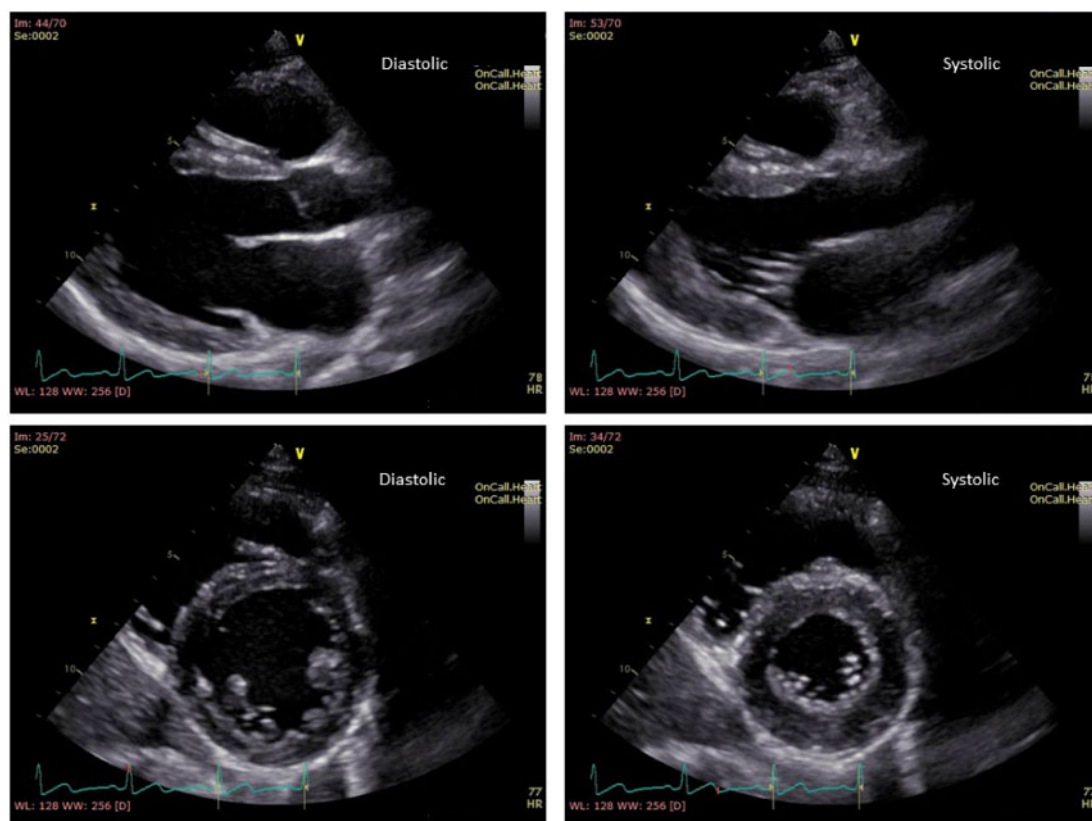
## Discussion

KD is diagnosed frequently in the Asian paediatric populations, and it is especially common in Japan, where its prevalence is 10 times greater than in Western countries. Almost all cases are diagnosed in children between the ages of 6 months and 8 years; the disease is rarely seen in anyone over 9 years of age.<sup>5</sup> After the peak age of onset, the diagnosis of KD is not often considered and is probably underdiagnosed to some degree. Interestingly, age >10 years has been reported as one of the risk factors for progression to KDSS.<sup>6</sup> As such, KD is usually not implicated in what has been called adolescent shock syndrome. In patients with shock, KDSS may also be underdiagnosed.

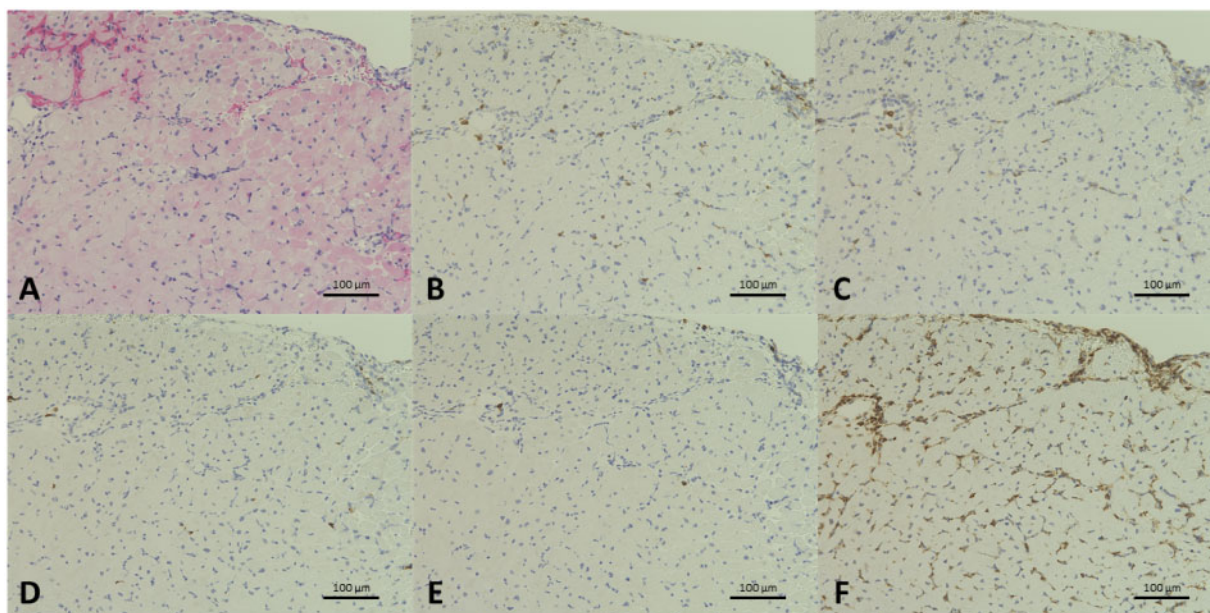
The aetiology of severe hypotension in KDSS is unknown, but it is probably multifactorial and may relate to intensive vasculitis with capillary leak, myocardial dysfunction, and release of proinflammatory cytokines.<sup>3</sup> Interestingly, in KDSS patients, serum C-reactive protein levels are high and 80% of patients have elevated levels of

cardiac enzymes (troponin-T and creatine kinase-MB)<sup>6</sup> which suggests acute injury to the myocardium. In our case, immunostaining of endomyocardial biopsy samples suggested infiltration of the interstitial myocardium with T-lymphocytes and macrophages with mild fibrosis, a pathological picture that is consistent with a diagnosis of myocarditis. Taken together, these findings suggest that the pathophysiology of KDSS might relate directly to an underlying inflammatory response with profound myocardial involvement. Actually, before the concept of KDSS was established, histological characteristics consistent with myocarditis were identified in most if not all patients with KD.<sup>7</sup> Furthermore, while most KD-associated myocarditis involved only mild symptoms, there were occasional reports of severe haemodynamic impairment that required mechanical circulatory support.<sup>8,9</sup> We need to remain vigilant for rapidly progressive haemodynamic disruption even in the early stages of KD, and in case of refractory KDSS, it is necessary to introduce mechanical circulatory support at the appropriate moment.

Pathological findings in the myocardium in the early phases of KD were characterized by acute peri-angiitis and vasculitis of microvessels and arterioles. Subsequently, infiltration of inflammatory cells, mainly monocytes, macrophages and lymphocytes, and oedema spread from the perivascular area to the interstitial myocardium to generate acute myocarditis.<sup>10</sup> Generally, inflammatory cell infiltration



**Figure 3** Continued.



**Figure 4** Pathological findings on endomyocardial biopsy. (A) Haematoxylin and eosin stained tissue with interstitial infiltration of inflammatory cells. Immunohistochemical staining revealed small number of (B) CD3<sup>+</sup> (C) CD4<sup>+</sup> or (D) CD8<sup>+</sup> and (E) CD20<sup>+</sup> small lymphocytes, and a few (F) CD68<sup>+</sup> macrophages within the myocardial infiltrates.

peaks at Day 10 of the disease and then gradually disappears by Day 20.<sup>11</sup>

IVIg has been recommended as a primary treatment for KDSS.<sup>6</sup> However, more than half of the KDSS patients have disease that is refractory to IVIg therapy and may ultimately require corticosteroids, monoclonal antibodies, or combination therapy.<sup>12</sup> Although the use of glucocorticoids has been controversial in this setting, we have found that early use of steroids with IVIg could be effective, particularly for IVIg-resistant KDSS.<sup>13</sup> Concomitant use of IVIg with steroid pulses did not suppress the development of coronary aneurysms in KD,<sup>14</sup> but several weeks of treatment with prednisolone decreased the risk for acute coronary lesions.<sup>15</sup> However, in this potentially fatal case, we considered it crucial to eliminate myocardial inflammation as early as possible. As such, we administered an intravenous steroid pulse followed by oral steroid therapy. On hospital Day 7, contractile function was successfully restored to normal without any apparent after-effects. In this case, pathologically, there was mild infiltration of inflammatory cells but no severe myocardial necrosis. Furthermore, we early performed aggressive IST. Thus, the responsiveness to the therapy might have been unspoiled and the cardiac function could have been improved earlier than usual.

As for the follow-up of patients without coronary artery lesions, the latest guidelines recommend electrocardiographic and echocardiographic follow-up on 1 month, 2 months, 6 months, 1 year, and 5 years after onset.<sup>16</sup> On the other hand, it has been pointed out that coronary artery lesions may occur more frequently in children with KDSS.<sup>17</sup> In KDSS cases, more careful follow-up of the development of coronary artery lesions might be warranted. We followed up for the first year according to the guidelines and then planned to follow-up on a yearly basis in more detail.

## Conclusion

The mechanism of KDSS may involve myocardial inflammation. Early intervention with IVIg, IST, and/or oral glucocorticoids may be effective in suppressing inflammation and thereby improving the prognosis of KDSS. We should carefully consider the possibility of KD as among the aetiologies of rapidly developing shock syndromes, regardless of the age of the patient. In this setting, a deliberate focus on extinguishing the myocardial inflammation in was clearly successful in our patient diagnosed with life-threatening KDSS.

## Lead author biography



Yuki Sugiura graduated in 2008 from Aichi Medical University. He is a research student in the Department of Cardiology at Nagoya University Graduate School of Medicine, Nagoya, Japan. His main interest is clinical research on heart failure and cardiomyopathy.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

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