

## Rare Refractory Kawasaki Disease in an Adolescent Boy With Cardiac and Diffuse Coronary Artery Involvement

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**Key Words:** Kawasaki disease; coronary artery aneurysm; infliximab.

**Summary.** Kawasaki disease is an acute multisystemic vasculitis occurring predominantly in infants and young children and rarely in adolescents and adults. At elderly age, Kawasaki disease may remain unrecognized with a subsequent delay in appropriate therapy and an increased risk of coronary artery aneurysms. We report a case of intravenous immunoglobulin- and aspirin-resistant Kawasaki disease and severe cardiovascular damage in an adolescent boy. The article discusses major issues associated with the management of refractory Kawasaki disease.

### Introduction

Kawasaki disease (KD) is an acute necrotizing vasculitis of medium- and small-sized vessels with a life-threatening predisposition to involve coronary arteries, predominantly occurring in children aged from 6 months to 5 years (1, 2). Acute KD is rare in adolescents and adults (3, 4), and therefore, this disease can be easily misdiagnosed in a patient presenting to a primary health care clinic. As specific laboratory tests are unavailable, the diagnosis of KD still relies on clinical criteria (5). KD shares symptoms and signs with other more frequent illnesses (e.g., viral infections, scarlet fever, toxic shock syndrome, and others) with a subsequent delay in appropriate therapy and a possible increased risk of coronary artery aneurysms (CAAs). We report a case of KD in an adolescent boy who was admitted to our hospital on day 12 of the illness with a high fever and signs of congestive heart failure. Though the diagnosis was made on the first day of hospitalization and the treatment with intravenous immunoglobulin (IVIG) and high-dose aspirin was started, the patient failed to defervescence, and thus, additional therapy with steroids and antitumor necrosis factor alpha was administered.

### Case Report

The 17-year-old boy was admitted to our hospital in January because of fever lasting for 12 days. He had abdominal pain, nausea, and diarrhea during the first days of the illness and was treated symptomatically. The patient noted an erythematous diffuse skin rash on his torso, which was spreading to his

extremities. The boy had previously been healthy and reported no drug allergies. On day 9 of high fever (39°C–40°C) and shortness of breath, the boy was admitted to the local hospital. Pneumonia and pleurisy were diagnosed and cephalosporin was prescribed, but fever remained high, the symptoms of acute heart failure appeared, and the boy was transferred to the university hospital.

On admission, he was febrile (40°C) and suffered from abdominal and chest pain. A physical examination revealed the following: bilateral non-suppurative conjunctivitis, dry mucus membranes with erythematous pharynx, strawberry tongue, and fissured lips. His skin desquamated from fingernails. A soft heart murmur was audible at the apex with irradiation to the left axillary area. The heart rate was 126 beats per minute. A soft liver edge was palpable 2 cm below the costal margin.

Laboratory tests disclosed leukocytosis ( $39.44 \times 10^9/L$ ) with a predominance of polymorphonuclear cells (93.99%) and thrombocytosis ( $431 \times 10^9/L$ ). His erythrocyte sedimentation rate (ESR) was 120 mm/h, and the C-reactive protein (CRP) level was 444.24 mg/L. Blood, urine, and throat cultures were negative for bacteria. The results of the serologic tests for *Yersinia* and the antistreptolysin test O were negative. A moderate increase in the troponin T level was observed ( $0.62 \mu g/L$ ; reference,  $0.01 \mu g/L$ ). The results of the test for antinuclear antibodies were positive with a titer of 1:40 and nucleolar pattern (++), and the level of anti-DNA antibodies was slightly increased ( $52.93 kU/L$ ; reference value,  $50 kU/L$ ). The results of the renal and liver function tests were normal, and the bone marrow aspirate demonstrated reactive inflammatory changes with no evidence of malignancy.

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The electrocardiogram showed sinus tachycardia and negative T waves in all the precordial leads. Echocardiography revealed a decreased ejection fraction (EF) of 32%, an increased left ventricle end-diastolic diameter (55 mm, 29 mm/m<sup>2</sup>); hypokinesia of the basal segment of the left ventricular (LV) anterior wall and the basal and middle segments of the septum; mitral and tricuspid regurgitation (2nd and 3rd degree, respectively) and dilatation of the proximal segment of the right and left coronary arteries (7 and 8 mm, respectively) (Fig. 1).

The diagnosis of KD was based on the presence of all the diagnostic criteria for the disease. On day 13 of the illness, the patient received treatment with IVIG (2 g/kg, 140 g) and aspirin (75 mg/kg, 5.25 g). Heart failure was treated with furosemide and spironolactone. On the next day, the boy was still febrile (39°C–39.5°C), so the second dose of IVIG (1 g/kg, 70 g) was used, but fever, leukocytosis, thrombocytosis, CRP level, and ESR remained pronounced. At this point, the boy was given intravenous methylprednisolone (1 g per day), and fever disappeared during the following 12 hours. Two boluses of methylprednisolone (1 g daily) for 2 consecutive days followed by oral prednisolone (1 mg/kg, 70 mg) per day thereafter weaning by 5 mg per week were given. Aspirin was given at a dosage of 250 mg per day. An improvement in clinical and laboratory results was achieved due to this treatment. On day 56 of the illness, when the treatment with oral prednisone was stopped, fever recurred (38°C–38.5°C), arthralgia appeared without ostensible arthritis, and the laboratory findings were as follows: CRP, 116 mg/L; ESR, 75 mm/h; and hemoglobin, 99 g/L. Blood, urine, and throat cultures were negative for bacteria again. Echocardiography showed a slightly decreased EF (54%), and the dilatation of coronary arteries remained. In view of persisting systemic inflammation and coronary artery damage, infliximab at a dose of 5 mg/kg (400 mg) was given. This treatment was effective, and the patient showed defervescence within 1 day; he had no complaints and laboratory values were within reference ranges. Echocardiography showed no abnormalities.

Six months later, coronary computed tomography angiography (CCTA; General Electric, Light Speed Pro 16, Milwaukee, WI, USA) revealed multiple giant aneurysms of the right and left anterior descending and circumflex coronary arteries with a mural thrombus of the right and left anterior descending coronary arteries (Fig. 2).

Warfarin at a dose of 0.1 mg/kg (7.5 mg) (desired international normalized ratio, 2.5) was recommended, and aspirin at a dosage of 250 mg per day was continued.

At that time, a gated rest test and a myocardial

perfusion scan were performed with intravenous <sup>99m</sup>Tc MIBI (methoxyisobutyl isonitrile) according to the standard protocols (gamma camera equipped with low-energy high-resolution collimators, Siemens E-CAM, Germany). This examination did not reveal the signs of perfusion abnormality but showed inhomogeneous perfusion in the segments of the LV (Fig. 3), nonsynchronous contraction of the LV, insufficient thickening of the basal and middle segments of the septum, and decreased LV EF (56%). These alterations were assessed as an initial stage of cardiomyopathy due to myocarditis.  $\beta$ -Blockers (carvedilol, 6.25 mg twice daily), angiotensin-converting enzyme inhibitors (enalapril, 2.5 mg per day), and aldosterone antagonists (spironolactone, 50 mg per day) were prescribed for the patient.

At 1 year and 5 months of follow-up, the patient was alive, had no complaints, and was studying at university. CCTA and a myocardial perfusion scan were repeated and demonstrated persisting aneurysmatic dilatation of 3 coronary arteries, fewer signs of parietal thrombosis, and inhomogeneous perfusion zones of the LV remaining. Now the patient is followed up by cardiologists and rheumatologists; he still receives treatment with warfarin, aspirin, carvedilol, and enalapril. The further follow-up is needed.

## Discussion

First described in Japan in 1967, KD is most common among children of Asian and Pacific Islander populations (1, 5). The cases of KD are reported in almost every country all over the world with a peak incidence being in winter (1, 5). Adult and adolescent KD is a rare condition that may remain unrecognized. In Lithuania, KD is rare; there were no cases of adolescent and adult KD during the last 20 years. There is no specific diagnostic test available for KD; the diagnosis in both adults and children is based on the presence of characteristic findings, i.e., fever lasting for 5 days or more and at least 4 of the 5 following clinical signs: 1) nonexudative bilateral conjunctivitis; 2) diffuse erythema of the oropharyngeal mucosa, fissured lips, or strawberry tongue; 3) cervical adenopathy; 4) polymorphic rash; and 5) erythema or edema of the palms and the soles progressing to a periungual desquamation in the subacute phase. If a patient presents only with a fever, and the symptoms and signs of KD appear over a protracted period, the diagnosis is more difficult and delayed. In addition, classical KD in an adolescent patient often manifests with a fever and not specific gastrointestinal symptoms as vomiting, diarrhea, and abdominal pain, which mimic more common childhood diseases (6). Patients with KD diagnosed 10 days later are more likely to develop CAAs (7). The pri-

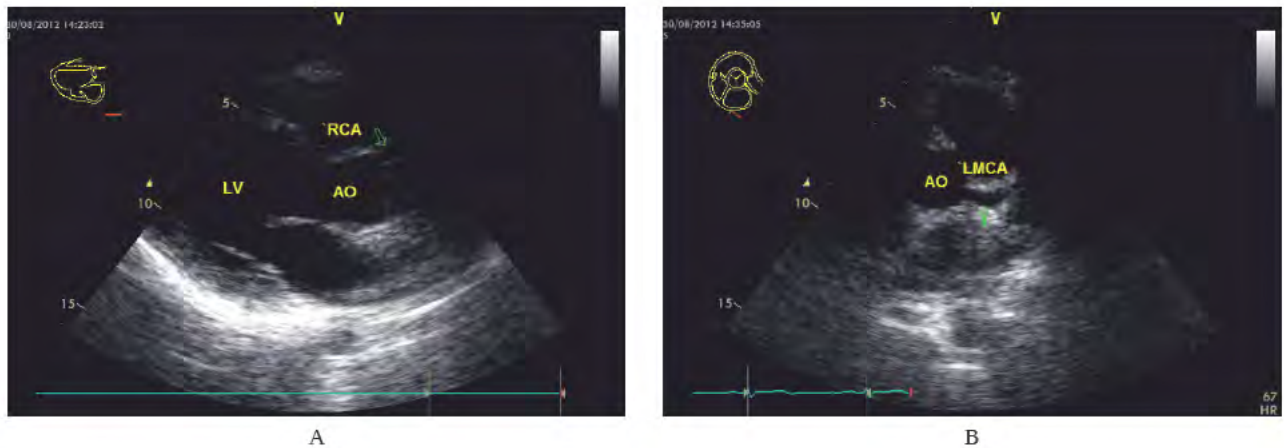


Fig. 1. Echocardiographic findings

A, a parasternal long-axis image demonstrating right coronary artery (RCA) enlargement (arrow); B, a parasternal short-axis image demonstrating left main coronary artery (LMCA) enlargement (arrow). AO, aorta; LV, left ventricle.

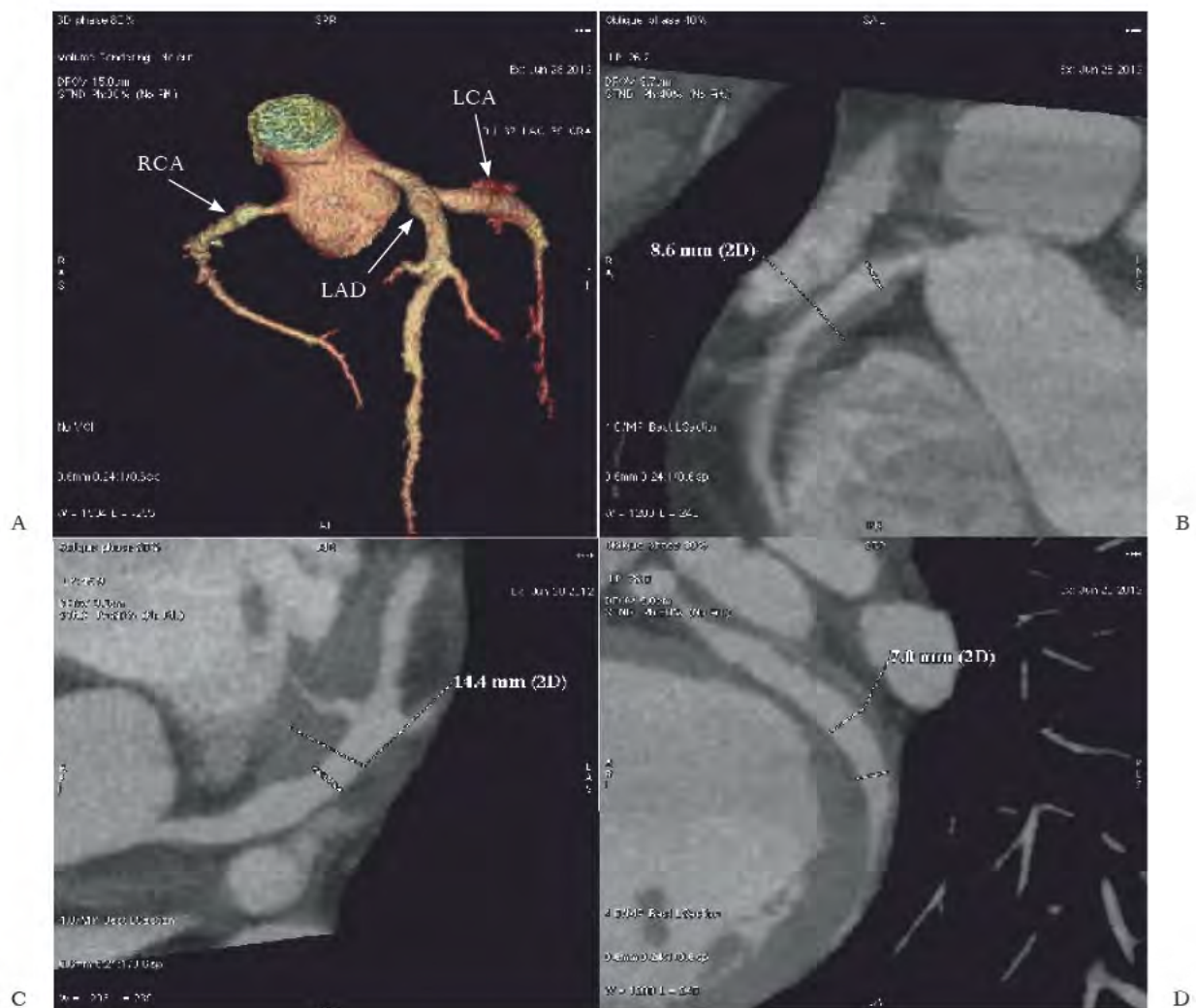


Fig. 2. Findings of coronary computed tomography angiography

A, volume rendering image shows dilated all 3 major coronary arteries; B–D, multiplanar reformation images showing the lumen of aneurysmatically dilated segments: a giant aneurysm of right coronary artery (RCA) with a mural thrombus (B), a giant aneurysm of left anterior descending artery (LAD) with a mural thrombus (C), and an aneurysm of left circumflex artery (LCA) (D).



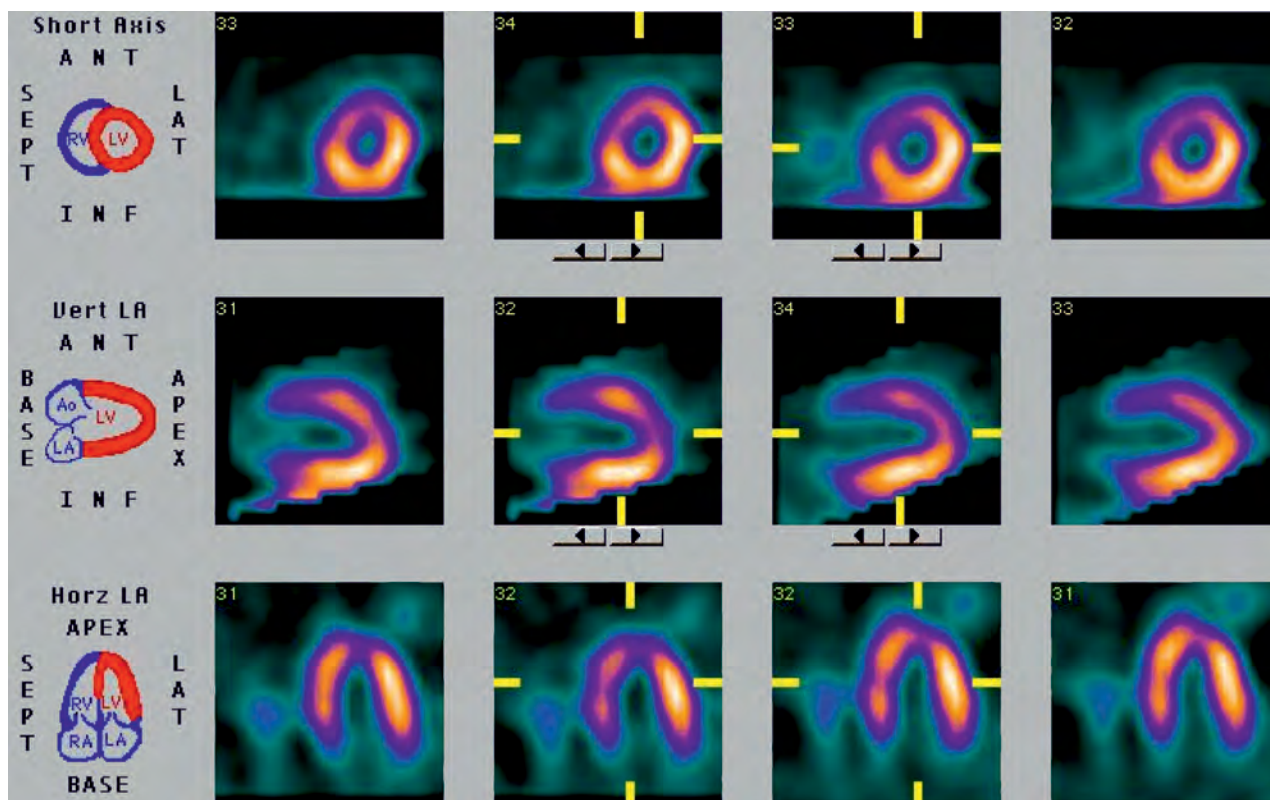


Fig. 3. The myocardial perfusion test showing inhomogeneous perfusion in the segments of the left ventricle; it is slightly decreased in the basal and middle segments of the septum and the anterior wall

mary goal for pediatricians and general practitioners should be early recognition of KD, irrespective of the patient's age and race, before coronary arteries are damaged.

Treatment of KD is aimed at reducing inflammation and preventing the formation of CAAs and arterial thrombosis. Current therapeutic regimens for KD include IVIG and aspirin (5, 6, 8). When KD diagnosis is delayed, but inflammatory parameters are still pronounced, it is, however, recommended to treat patients aggressively with IVIG and aspirin. Up to 15% of patients do not respond to a single dose of IVIG, and the second dose is recommended (5, 6, 8). Several variables seem to predict unresponsiveness to IVIG, and the clinical features include male gender, extremes of age, prolonged fever, delay in diagnosis, and persistent fever for more than 36 hours after treatment. The laboratory features include a low hemoglobin level, increased white blood cell count, high neutrophil count, very increased or persistently increased ESR or CRP, low platelet count, and low albumin level (6, 9).

If nonresponders remain febrile with a persistently high serum CRP level, leukocytosis, and high neutrophil counts, daily high-dose methylprednisolone is often administered (followed by oral corticosteroids progressively tapered until CRP normalization) (6, 9). Treatment with corticosteroids is

controversial and is not recommended for the initial management of KD due to an increased risk of CAA formation. Recent studies show that a combination of IVIG and methylprednisolone improves the clinical course and the coronary artery outcome, without causing side effects (10). However, Newburger and colleagues did not show a clear usefulness of steroids for routine primary treatment (5). There is no one accepted treatment algorithm for treatment-refractory KD patients.

Infliximab, a chimeric mouse-human monoclonal antibody targeting soluble and membrane-bound tumor necrosis factor alpha, has been successfully used in patients refractory to IVIG and corticosteroids, even with severe coronary artery involvement, without side effects (11, 12). Infliximab reduces cytokine-mediated inflammation and can be considered as a potential alternative drug for refractory KD (11). Based on the mechanism of endoarteritis, high-risk KD patients may benefit from early treatment with infliximab in conjunction with conventional IVIG therapy (13). In our case, it had a long-term treatment effect.

Long-term management of patients with KD is tailored according to the degree of coronary artery involvement and a relative risk of myocardial ischemia. Risk level stratification allows patient management to be individualized with respect to medi-

cal therapy, physical activity, frequencies of clinical follow-up, diagnostic testing, and indications for cardiac catheterization and coronary angiography. Patients with severe coronary artery involvement, mainly those with giant aneurysms, require long-term anticoagulation therapy to prevent intracoronary thrombus formation, myocardial ischemia, and a potential risk of sudden death. Current recommendations for systemic anticoagulation include the administration of a combination of aspirin and warfarin. Myocardial perfusion imaging by nuclear techniques should be performed annually; cardiac catheterization with selective coronary angiography is indicated if noninvasive studies suggest myocardial ischemia (5).

Approximately 50% of vascular segments with CAAs in KD show an angiographic regression of aneurysms within 1–2 years. However, in giant aneurysms (defined as >8 mm in diameter in children), regression is less likely, and they more often lead to myocardial ischemia (14). An abnormal endothe-

lial function may persist for many years after the resolution of CAAs or without detectable coronary artery damage. Endothelial dysfunction might also be the key event in the pathogenesis of premature atherosclerosis, coronary stiffness, and hypertension in these patients.

### Conclusions

We present a classic case of extremely refractory Kawasaki disease in the adolescent boy with a prolonged acute phase, which was never under control despite the administration of the first-line therapy, i.e., intravenous immunoglobulin and aspirin. Taking into account the lack of an evidence-based approach in refractory cases, we might cautiously suggest considering the administration of antitumor necrosis factor alpha as a potential alternative medicine for refractory Kawasaki disease.

### Statement of Conflict of Interest

The authors state no conflict of interest.

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