Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9044-21
Intern Med 61: 3525-3529, 2022
http://internmed.jp

【 CASE REPORT 】

Two Distinct Cases of Adult-onset Kawasaki Disease

Takehiko Onoki[1], Takaya Metoki[2], Shinya Iwasawa[1], Kengo Kawano[2], Masato Kimura[3], Shigeo Kure[1] and Chiharu Ota[1]

Abstract:
Kawasaki disease (KD) is a systemic vasculitis syndrome that mostly affects children under 4 years old. Among the reported KD cases, only 1% were over 10 years old. We herein report 2 cases of adult-onset KD (AKD) in 19- and 17-year-old boys diagnosed with a persistent fever and cervical lymphadenitis. Both patients showed cardiac complications, such as coronary artery dilation and myocarditis. Repeated intravenous immunoglobulin therapy was effective in the 19-year-old, while plasma exchange therapy was needed for the 17-year-old, with no sequelae noted at discharge. KD should be considered as a differential diagnosis for persistent fever in adults.

Key words: adult-onset Kawasaki disease, persistent fever, lymphadenitis, coronary artery lesion, myocarditis

(Intern Med 61: 3525-3529, 2022)
(DOI: 10.2169/internalmedicine.9044-21)

Introduction

Kawasaki disease (KD) is a systemic vasculitis syndrome first reported by Kawasaki et al. in 1967 (1) that mostly affects infants and younger children.

Indeed, among the reported KD cases in the epidemiologic survey in Japan, 80% were in infants and children under 4 years old, while 1% were in patients over 10 years old.

Adult-onset KD (AKD) is characterized by a delayed diagnosis, disease that is refractory to initial intravenous immunoglobulin therapy (IVIG), and cardiac complications (2, 3).

We herein report two distinct cases of AKD in 19- and 17-year-old boys. The 19-year-old presented with typical KD that was refractory to the initial treatment of IVIG but responsive to the repeated IVIG, while the 17-year-old developed KD with myocarditis (KD-myocarditis) that was refractory to initial IVIG and thus underwent plasma exchange (PEx) for 5 days.

Case Reports

Case 1

A 19-year-old boy was admitted to the otolaryngology department of our university hospital with a diagnosis of cervical cellulitis. Five days before admission, he had a sore throat, right neck pain with torticollis, and high fever of 39°C. Three days before admission, he visited a general practitioner and underwent a blood examination, revealing elevated inflammatory markers: white blood cell (WBC) count, 12×10^9/L; and C-reactive protein (CRP) level, 129 mg/L. On the day of admission, he visited an emergency room at a local hospital due to exacerbated cervical pain and inflammation. He underwent neck computed tomography (CT) and was referred to our hospital (Fig. 1A). The patient was diagnosed with cervical cellulitis and treated with sulbactam/ampicillin for four days, although this was ineffective. Three days after admission, he developed conjunctival congestion, red lips, and strawberry tongue, along with a high fever and cervical pain. He was referred to our department with suspected KD.

The patient was 175 cm tall and weighed 52 kg. He showed a clear consciousness, with a body temperature of

[1]Department of Pediatrics, Tohoku University Hospital, Japan, [2]Department of Pediatrics, Yamagata Prefectural Central Hospital, Japan and [3]Department of Cardiology, Miyagi Children's Hospital, Japan
Received: November 21, 2021; Accepted: March 6, 2022; Advance Publication by J-STAGE: April 23, 2022
Correspondence to Chiharu Ota, chiharu.ota.e8@tohoku.ac.jp

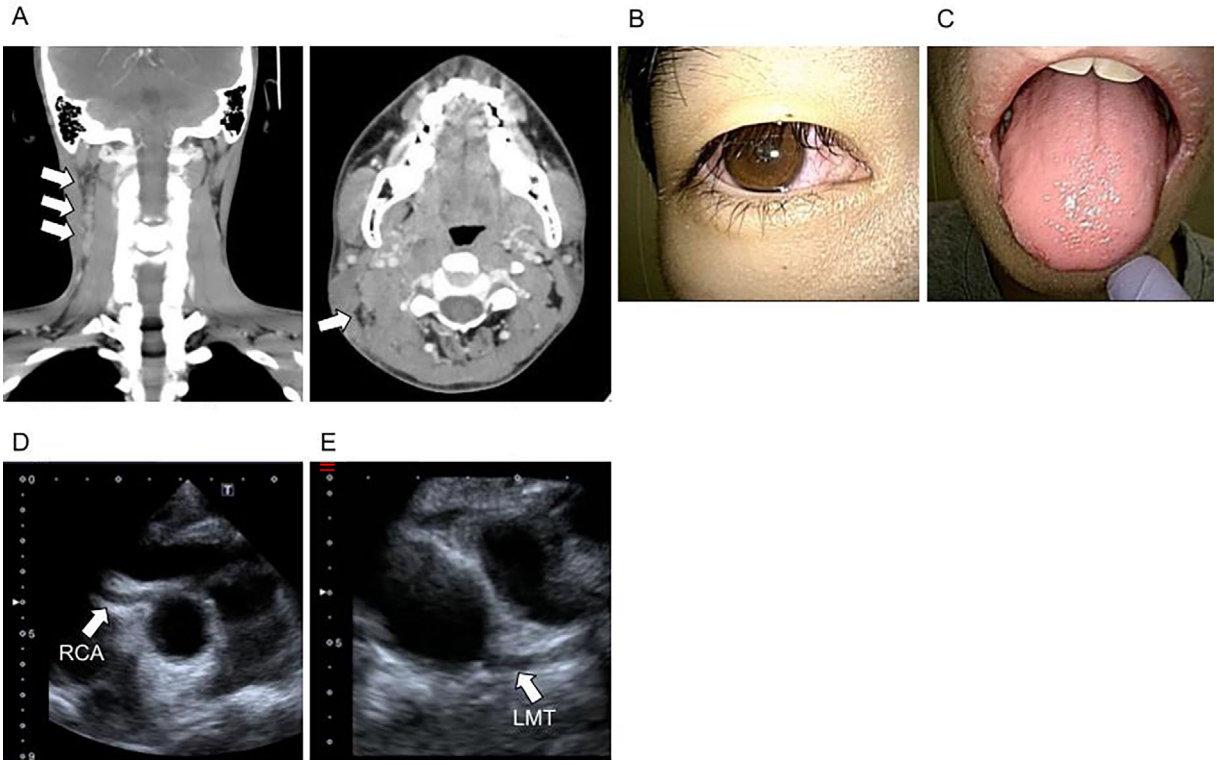

Figure 1. Findings of the case 1 at admission. A: Neck CT with right lymphadenitis. B: Conjunctival hyperemia. C: Strawberry tongue, and injected lips. D: TTE: RCA. E: TTE: LMT.

38-39°C, blood pressure of 120/70 mmHg, heart rate of 100 bpm, and oxygen saturation of 99% at room air. He presented with right lymphadenitis, bilateral conjunctival hyperemia, strawberry tongue, and injected lips (Fig. 1B, C). No heart murmurs were audible. A laboratory examination revealed an elevated WBC count 13.5×10^9/L with 78% neutrophils, CRP 162.2 mg/L, fibrinogen (FBG) 8.7 g/L, brain-type natriuretic peptide (BNP) 21.6 pg/mL, decreased serum albumin 26 g/L, and normal range of serum sodium 142 mmol/L. An Epstein-Barr virus (EBV) test showed a past-infection pattern.

Chest radiography showed a 49% cardiothoracic ratio (CTR) without a change in the costophrenic angle. Transthoracic echocardiography (TTE) revealed a good left ventricular ejection fraction (LVEF) of 65% without the accumulation of pericardial effusion. TTE also revealed a right coronary artery diameter of 4.5 mm (RCA, Z-score: +2.7) (Fig. 1D), 3.9 mm in diameter of the left main trunk (LMT, Z-score: +0.7), and 3.2 mm in diameter of the left anterior descending artery (LAD, Z-score: +0.7) (Fig. 1E) without any signs of aneurysmal changes in the coronary arteries. Each Z-score is calculated by the scoring system generated and validated using a large pediatric population (http://raise.umin.jp/zsp/calculator/).

The patient was diagnosed with KD due to four main symptoms, including lymphadenitis, conjunctival hyperemia, strawberry tongue and injected lips with a mild coronary artery lesion (CAL). We administered 2 g/kg of IVIG in 24 h with 18 mg/kg of oral acetylsalicylic acid (ASA) on day 9 from the initial symptoms. On day 10, the patient still had a low-grade fever with cervical pain. On day 11, he showed a recurrent high fever (39°C) with polymorphous erythema on his trunk. Laboratory data showed an elevated WBC count of 10.4×10^9/L, CRP of 114.2 mg/L, FBG of 7.1 g/L, and low albumin level of 23 g/L. We added another 2 g/kg IVIG on day 11. On day 12, his fever subsided, and his laboratory examination findings improved with a WBC count of 6.1×10^9/L, CRP of 8.3 mg/L, serum albumin of 33 g/L, and FBG of 4.9 g/L, and CAL attenuated the RCA to 3 mm (Z-score: +0.1) and LMT to 3 mm (Z-score: -0.9) on day 16. He did not show any mucocutaneous symptoms but presented with desquamation. We diagnosed the patient with complete/classical KD with desquamation in the subacute phase (4).

The patient was discharged from the hospital on day 17. ASA was reduced to 100 mg/day and continued for 2 months. We have been following the patient for the past two years, and there has been no recurrence of KD or progression of CAL on TTE.

Case 2

A 17-year-old boy was admitted to the otolaryngology department of a regional hospital with a high fever and cervical pain for the past 5 days. He did not have a specific history of vasculitis or familial history of KD. He was diagnosed with bacterial cervical lymphadenitis based on ultrasonographic findings and multiple lymphadenopathies in his right neck. Despite the intravenous administration of antibiotics for 2 days, his symptoms were complicated with bilateral conjunctival hyperemia, strawberry tongue, and poly-

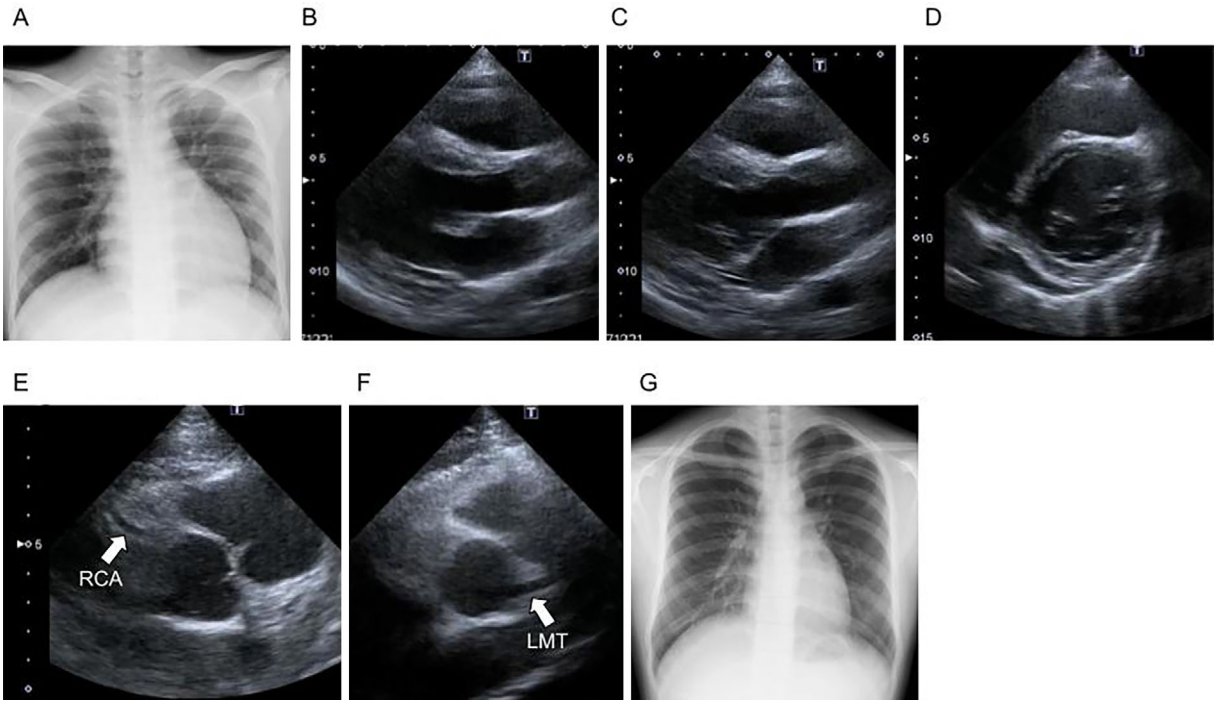

Figure 2. **Imaging findings of the case 2 at admission. A: Chest X-ray at admission. B: TTE: diastolic view of left ventricle, parasternal long axis view. C: TTE: systolic view of left ventricle, parasternal long axis view. D: TTE: pericardial effusion, parasternal short axis view. E: TTE: RCA. F: TTE: LMT. G: Chest X-ray at discharge.**

morphous exanthema, which led to the diagnosis of KD by a pediatrician consulted by an otolaryngologist. In addition, chest radiography showed cardiac enlargement with pleural effusion, and TTE revealed decreased LVEF with pericardial effusion. A laboratory examination showed an increased serum troponin I, at 6.56 ng/mL (normal range: 0-0.025 ng/mL). He was transferred to our university hospital with a diagnosis of KD-myocarditis.

On admission, he was 175 cm tall and weighed 63 kg. He had a clear consciousness with a body temperature of 39.5°C, a blood pressure of 86/52 mmHg, a heart rate of 100 bpm, and oxygen saturation of 98% at room air. He presented with right lymphadenitis, bilateral conjunctival hyperemia, strawberry tongue, injected lips, and polymorphous exanthema on his trunk. No heart murmurs were audible. A laboratory examination revealed an increased WBC count of 7.7×10^{9}/L with 94.5% neutrophils, CRP of 226 mg/L, FBG of 5.4 g/L, creatine kinase (CK) of 156 IU/L with CK-muscle/brain (MB) of 6 IU/L, BNP of 1,157 pg/mL, and decreased serum albumin and sodium levels of 25 g/L and 131 mmol/L, respectively. Examinations for collagen diseases showed negative values, with antinuclear antibody (ANA) 40 times, rheumatoid factor (RF) <5.0, C3 115 mg/dL, C4 26.0 mg/dL, and CH 50 41.8 U/mL.

Chest radiography showed 57% CTR with a dull costophrenic angle on the left side (Fig. 2A). An electrocardiogram (ECG) showed sinus tachycardia of 107 bpm with flattened T waves in leads V4-V6. TTE exhibited a decreased LVEF of 50% (Fig. 2B, C), mild mitral valve regurgitation, and accumulation of pericardial fluid with a thickness of 10 mm (Fig. 2D). TTE also showed 3.7 mm of RCA (Z-score: +0.81) (Fig. 2E), 3.6 mm of LMT (Z-score: +0.15) (Fig. 2F), and 3.2 mm of LAD (Z-score: +0.41), without any signs of aneurysmal changes in the coronary arteries.

We diagnosed the patient with KD-myocarditis, showing five out of the six main symptoms of KD (a continuous high fever, cervical lymphadenitis, bilateral conjunctival hyperemia, strawberry tongue, and polymorphous exanthema) with pericardial effusion, changes in T-waves on an ECG, and increased serum troponin-I and plasma BNP.

We administered 2 g/kg of IVIG with 30 mg/kg oral ASA on day 6 of the initial symptoms. IVIG infusion took 27 h with the administration of diuretics to avoid volume overload. On day 9, he still had a high fever with bilateral conjunctival hyperemia, polymorphous exanthema, high CRP (257 mg/L), low serum albumin (2.1 g/L), and high BNP (969 pg/mL). We evaluated his status as IVIG-refractory KD-myocarditis and started PEx with human serum albumin and fresh-frozen plasma for 5 days. On day 12, after 4 days of PEx, his fever subsided, and his CRP level decreased to 12.7 mg/L. On day 14, we added 1 g/kg IVIG due to the reduced serum IgG level of 341 mg/dL after PEx. On day 15, chest radiography showed a decreased CTR of 43% (Fig. 2G) without accumulated pleural effusion; improved laboratory examination findings with a CRP level of 0.35 mg/L, serum albumin of 4.9 g/L, CK of 15 U/L, and BNP of 53 pg/mL; and decreased pericardial effusion with an LVEF of 52% without a coronary artery lesion (Figure not

shown).

The patient was discharged from the hospital on day 16. His cardiac function gradually improved within six months after discharge without any signs of recurrent KD or myocarditis.

Discussion

In the present study, we described two distinct cases of AKD, with the main manifestation of the first case being KD-associated cervical lymphadenitis with CAL and that of the second case being KD-induced myocarditis. The median age of the onset of AKD is the 20s, and the ratio of complete/classical KD cases (4) is approximately 80%, with a delayed diagnosis occurring over 10 days from the onset (2, 3).

Both of the present cases showed complete/classical KD symptoms of a persistent fever, cervical lymphadenitis, bilateral conjunctival hyperemia, strawberry tongue, polymorphous exanthema, or limbal changes. Cases 1 and 2 were diagnosed on days 9 and 8, respectively, by pediatricians consulted by otolaryngologists. Cervical lymphadenopathy, conjunctivitis, desquamation, and a persistent fever are found in more than 90% of AKD patients (3), followed by red pharynx, strawberry tongue, and erythema/edema in extremities in 80% (5). Therefore, otolaryngologists, general physicians, hematologists, and dermatologists can identify patients with AKD. If adult patients show a persistent fever without signs of infection, the presence of three to four of the aforementioned symptoms and laboratory data indicating vasculitis, i.e. increased CRP and FBG levels and decreased albumin, should prompt the inclusion of AKD in the differential diagnosis. We did not include multisystem inflammatory syndrome in the differential diagnosis because both cases were hospitalized before the beginning of the coronavirus disease 2019 pandemic. EBV infection is also reported to be a severity factor for KD. Case 1 showed a past-infection pattern, but we did not examine this point in the second case. It is important to include EBV infection in the differential diagnosis of KD (6).

CAL begins to form 7 days after the onset of pediatric KD (7). AKD is usually complicated with cardiac comorbidities, such as CAL, pericarditis, or myocarditis, rather than pediatric KD, because of a delayed diagnosis (2). In our cases, when the patients were diagnosed with AKD at eight to nine days from the onset, which is earlier than on average (2, 3), they had already shown CAL and myocarditis at that time. It is necessary to clarify whether there are risk factors of AKD that exacerbate cardiac complications other than the duration of vasculitis. After initial IVIG treatment, the clinical course of both of our cases was clearly different. In Case 1, repeated IVIG was effective in controlling inflammation and coronary aneurysm development. His clinical course was similar to that of pediatric KD cases that were refractory to first-line IVIG. In contrast, in Case 2, we chose PEx to avoid volume overload with second-line IVIG because myocarditis-induced heart failure was critically aggravated. Myocarditis is one of the most serious cardiac complications of KD, other than coronary artery aneurysms. KD-myocarditis is usually treated according to the ordinal KD, i.e. IVIG plus ASA or methylprednisolone pulse therapy (8). We used different doses of ASA in both cases because there is no consensus concerning the dose of ASA to be used in adult cases, with some using high doses (3) and others low doses (5). Therefore, Case 1 was treated with a low to intermediate dose of ASA, while Case 2 received an intermediate dose in response to the severity. IVIG-refractory AKD-myocarditis with an improved cardiac function is treated with infliximab (9). However, our Case 2 still showed progressive heart failure due to AKD-myocarditis. We believe that PEx is effective for the fulminant form of AKD-myocarditis as well as pediatric KD with CAL (10). To our knowledge, this is the first case report to describe the effectiveness of PEx for AKD. For the long-term course, we plan to perform coronary CT during outpatient follow-up because it is difficult to identify mid- or distal CAL with TTE alone.

In conclusion, we encountered two distinct cases of AKD. It is important to diagnose patients with KD as early as possible and to select the most appropriate treatment for each patient.

The authors state that they have no Conflict of Interest (COI).

References

1. Kawasaki T. Pediatric acute febrile mucocutaneous lymph node syndrome with characteristic desquamation of fingers and toes: my clinical observation of fifty cases. Pediatr Infect Dis J **21**: 1-18, 2002.
2. Fraison JB, Sève P, Dauphin C, et al. Kawasaki disease in adults: observations in France and literature review. Autoimmun Rev **15**: 242-249, 2016.
3. Gomard-Mennesson E, Landron C, Dauphin C, et al. Kawasaki disease in adults: report of 10 cases. Medicine (Baltimore) **89**: 149-158, 2010.
4. McCrindle BW, Rowley AH, Newburger JW, et al.; the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation **135**: e927-e999, 2017.
5. Sève P, Stankovic K, Smail A, Durand DV, Marchand G, Broussolle C. Adult Kawasaki Disease: report of two cases and literature review. Semin Arthritis Rheum **34**: 785-792, 2005.
6. Maggio MC, Fabiano C, Corsello G. Kawasaki disease triggered by EBV virus in a child with Familial Mediterranean Fever. Ital J Pediatr **45**: 129, 2019.
7. Ichida F, Fatica NS, Engle MA, et al. Coronary artery involvement in Kawasaki syndrome in Manhattan, New York: risk factors and role of aspirin. Pediatrics **80**: 828-835, 1987.
8. Sato T, Somura J, Maruo Y. Steroid pulse therapy for Kawasaki disease complicated with myocarditis. Indian Pediatr **53**: 1015-

1016, 2016.

9. Kawaguchi T, Rikitake Y, Tsuruda T, et al. Infliximab as an alternative therapy for refractory adult onset Kawasaki disease: a case report. Medicine (Baltimore) **97**: e12720, 2018.

10. Noguchi S, Saito J, Kudo T, Hashiba E, Hirota K. Safety and efficacy of plasma exchange therapy for Kawasaki disease in children in intensive care unit: case series. JA Clin Rep **4**: 25, 2018.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).

© 2022 The Japanese Society of Internal Medicine