Case Report

Multiple Giant Aneurysms at Both the Right and Left Coronary Arteries in Incomplete Kawasaki Disease

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Incomplete Kawasaki disease (iKD) is widely accepted as a risk factor for developing coronary artery lesions, partly because of a delay in treatment initiation. However, its association with giant aneurysm (GA) formation has rarely been reported. Here we report a 3-year-old boy with iKD who developed multiple GAs at both the right and left coronary arteries. The boy was admitted to a previous hospital for fever lasting for seven days and conjunctival injection. First, he was treated with antibiotics, but his fever did not resolve. Echocardiography revealed remarkable dilatation of the bilateral coronary arteries. He was transferred to our hospital under the diagnosis of iKD on day 11 of illness. His symptoms improved immediately after the administration of intravenous immunoglobulin, but the diameter of his coronary aneurysms increased. Coronary angiography performed three months after onset revealed multiple GAs at both coronary arteries. An aneurysm at the right coronary artery occluded two years from onset. In case of prolonged fever of unknown origin, it is important to consider incomplete KD and carefully examine echocardiograms, even when there are few major KD symptoms present.

Keywords: coronary artery lesions, giant aneurysm, Kawasaki disease

Introduction

Kawasaki disease (KD) is an acute panvasculitis that can lead to acquired heart disease in children worldwide. The formation of giant aneurysms (GAs) is a serious complication that predisposes patients to ischemic heart diseases and sudden death.

Incomplete KD (iKD) does not reveal the typical manifestations of KD. It comprises 20% of KD cases and carries a risk of forming coronary artery lesions (CALs), probably due to treatment delay.[1, 2)] However, another survey revealed only seven iKD cases with GA formation over a period of 12 years, making the tendency towards GA formation in iKD unclear.[3)]

Here we describe a patient who developed multiple CALs, including GAs, at both the right and left coronary arteries (RCA and LCA, respectively), by day 11 of illness, resulting in complete occlusion at the RCA two years later.

Case

A previously healthy 3-year-old boy developed fever

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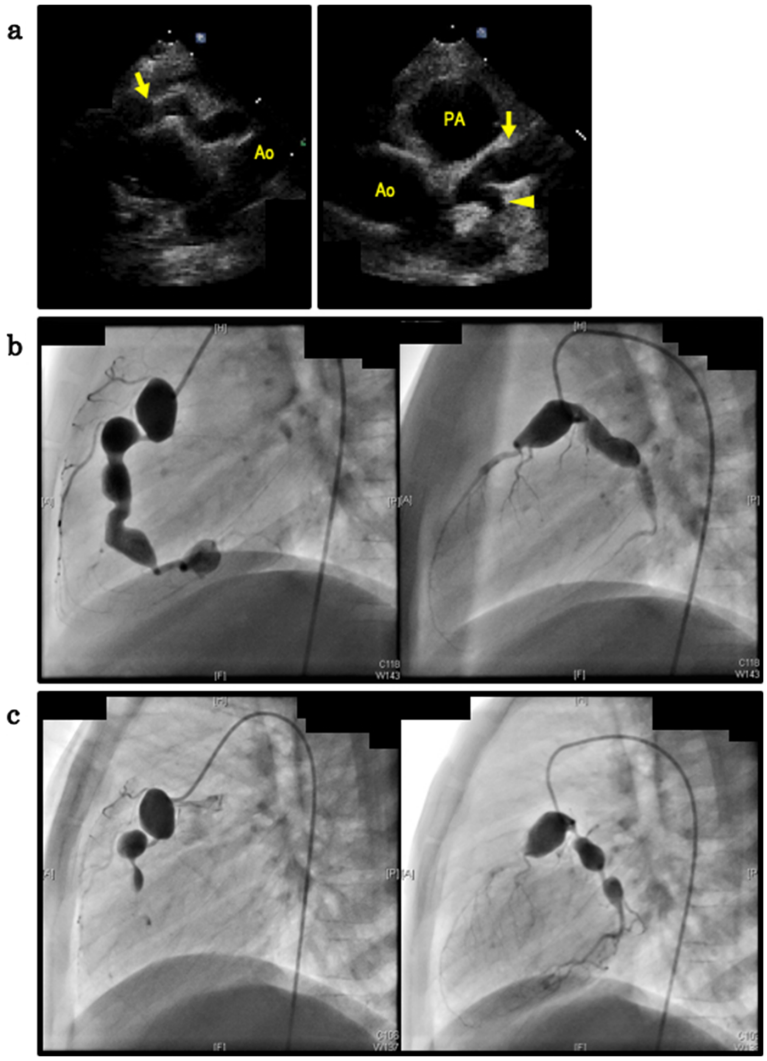

Fig. 1 (a) Echocardiography showing normal left ventricular ejection fraction and slight pericardial effusion, with dilatation of all the coronary arteries, as follows: the right coronary artery (RCA) 9.1 mm (Z score 12; the arrow in left panel), the left anterior descending artery (LAD) 7.7 mm (Z score 8.5; the arrow in right panel), and the left circumflex artery (LCX) 3.1 mm (Z score 3.3; the arrowhead in right panel). Ao, Aorta; PA, Pulmonary artery. (b) Coronary angiography performed three months after presentation showing moniliform GA at the RCA and LAD and remarkable dilatation of the LCX (11 mm, 9.9 mm, and 7.7 mm in diameter, respectively). (c) Coronary angiography performed two years after presentation showing the complete occlusion of the RCA with formation of slight collateral circulation

with abdominal pain. On day 6 of illness, he developed conjunctival injection with an elevated level of C-reactive protein (CRP, 20.9 mg/dL). He was referred to the first hospital and admitted the next day for further examination. Laboratory tests showed leukocytes 13,600/μL (neutrophils 84%), platelets 368,000/μL, erythrocyte sedimentation rate 127 mm/h, albumin 2.95 g/dL, aspartate aminotransferase 50 U/L, alanine aminotransferase 43 U/L, and Na 135 mmol/L. The titer of antinuclear antibody was later found to be 1:80. Because a rapid streptococcal antigen test was positive from a throat swab, a bacterial infection was suspected and he received ampicillin and cefotaxime. On day 9 of illness, he was still febrile and CRP was 11.4 mg/dL. He had no signs of infection on a whole-body computed tomography scan performed on day 10 of illness. On day 11 of illness, echocardiography showed multiple coronary artery dilatations and he was transferred to our hospital.

On admission, he was slightly irritable, not pale, and was febrile at 37.8°C. His blood pressure was 102/42 mmHg, pulse was 110/min without cardiac murmur nor gallop rhythm, and respiratory rate was 20/min with an O_2 saturation of 98% on ambient air. Physical examination revealed mild conjunctival injection and palpable, but not prominent, cervical lymph nodes, although other KD-specific signs were absent. Echocardiography showed the following CALs: RCA 9.1 mm, left anterior descending artery (LAD) 7.7 mm, and left circumflex artery (LCX) 3.1 mm (Fig. 1a). His disease was diagnosed as iKD with multiple CALs. Heparin and warfarin were administered combined with aspirin to keep the international normalized ratio of prothrombin times at approximately 2.0, and the activated partial thromboplastin time between 45 and 75 seconds. The next day, his fever persisted and he was treated with 2 g/kg of intravenous immunoglobulin (IVIG). On day 13 of illness, his symptoms resolved, whereas all the coronary arteries remained markedly dilated in repeated echocardiograms. There were no findings of finger desquamation during the clinical course. The final doses were 0.15 mg/kg/day of warfarin and 5 mg/kg/day of aspirin. The highest levels of interleukin 10 (IL-10) and tumor necrosis factor alpha (TNF-α) were 2.0 pg/mL on day 11 of illness and 12.9 pg/mL on day 7 of illness, respectively, which were within normal range. He was discharged on day 32 of illness.

Coronary angiography performed three months after presentation showed moniliform GAs at the RCA and LAD and remarkable dilatation of the LCX (11 mm, 9.9 mm, and 7.7 mm in diameter, respectively; Fig. 1b). Although he was consecutively treated with warfarin and aspirin without any clinical symptoms and without any cardiovascular event, angiography two years after presentation revealed a completely occluded RCA with formation of slight collateral circulation (Fig. 1c). He has been carefully followed by regular exercise testing, echocardiography, cardiac MRI studies, and catheterization, with tight control of warfarin. If he were to have ischemia, stent insertion would be considered, but so far there has been no evidence of ischemia.

Discussion

This case suggests that iKD is not really a "mild" form of KD because multiple CALs including GAs were formed by day 11 of illness, even though the patient presented with only fever and conjunctival injection. Autopsy cases revealed that panvasculitis in entire coronary arterial walls and plasmotomy of internal elastic membranes can occur on day 10 of KD and aneurysm formation on day 12 of KD.[4] Our patient did not have any previous history of KD nor signs or symptoms of systemic inflammation, such as unidentified fever and arthritis; this suggested that CAL formation occurred during the present episode and was due to KD. Although a recent report has shown that the median day of CAL formation is day 11 in KD patients who finally developed GA, developing multiple CALs including GAs by day 11 of illness in our case should be considered as an accelerated and more severe clinical course.[3] A similar case report described a 12-week-old infant with fever and rash who developed multiple giant aneurysms by day 11 of illness.[5] It is widely accepted that KD patients at younger than 12 months old mostly tend to have the incomplete form and they have been reported to be at risk of developing CALs.[2] The course at a typical age like this case is rare and is considered worth reporting.

In Japan, high risk factors of GA formation were thought to exist in patients who required additional IVIG without the use of steroids and those who received steroid administration regardless of the additional use of IVIG, but not in patients with iKD itself.[6] It is also believed that more intensive treatment for IVIG-refractory KD seems effective to prevent GA complications. In fact, new strategies against refractory KD such as steroid-combined initial IVIG and a rescue therapy with infliximab (a monoclonal antibody against TNF-α) have been presented.[7–9] However, in as many as 16% of patients who finally developed GA, CALs had already been formed before the initial IVIG was started.[3] Therefore, we propose that efforts for earlier diagnosis and treatment are required, and that even a lower risk score or lack of typical symptoms does not mean that iKD should be considered as a mild form.

Interestingly, cytokine levels of IL-10 and TNF-α were not elevated in this case. However, because we could measure cytokine levels only after seven days from the onset, it does not deny the possibility that these cytokines had been elevated during the earlier days of the illness.

We believe it is difficult to evoke KD in the case of atypical symptoms and decrease in inflammatory markers after antibiotic treatments. Even if the algorithm in

the 2017 AHA statement were applied, the diagnosis and treatment of iKD could not have been made in the acute phase before the transfer, considering the few principal clinical features.[10] The reference clauses in the newly revised Japanese diagnostic criteria could have urged paying attention to hypoalbuminemia, but the diagnosis might still have been difficult. In addition, multiple CALs including GAs can develop by day 11 of illness.

In this case, the detection of CALs by echocardiography and the remarkable effectiveness of IVIG led to the final diagnosis of iKD. We believe this case emphasizes the importance of performing echocardiography and administrating IVIG for the diagnosis of iKD and they are expected to be performed earlier in case of prolonged fever of unknown origin when iKD cannot be excluded.

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Conflicts of Interest

All the authors have no conflict of interest.

Author Contributions

Satoshi Yoshimura drafted the manuscript; Hiroshi Ono, Hiroshi Masuda, Sayaka Fukuda, and Hiroshi Katsumori attended to patient management; Tohru Kobayashi, Hitoshi Kato, Jun Abe and Akira Ishiguro contributed to analysis and interpretation of data and assisted in the preparation of the manuscript; All the authors read and approved the final manuscript.

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