Cardiology in the Young

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Recurrent events of acute coronary syndrome in young adult patients after Kawasaki disease

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Original Article

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Abstract

Objective: I encountered three adult patients with major coronary artery occlusion after Kawasaki disease in childhood, who had developed again acute coronary syndrome of adults in the peripheral branches, such as the 4th segments, the atrioventricular node artery, and the posterior descending artery, of the right coronary artery. *Methods:* I reviewed their clinical course and coronary angiograms. *Results:* Their age at onset of acute coronary syndrome ranged from 29 to 33 years. The male patient with a previous anteroseptal myocardial infarction in children had a symptomatic occlusion of the branch of the 4th posterior descending artery at 32 years of age. Acute coronary syndrome occurred in the area of 4th atrioventricular node artery in two female patients. The collateral arteries from the circumflex artery to the 4th atrioventricular node arteries were not clearly injected. It was suspected that they had developed bilateral giant aneurysms after acute Kawasaki disease. Two patients had an acute myocardial infarction due to thrombotic occlusion in a giant aneurysm of the right coronary artery or the left anterior descending artery, and one patient had an asymptomatic coronary occlusion of the right coronary artery and left anterior descending artery in children. *Conclusion:* Occlusion of peripheral coronary arteries in adulthood can occur in patients with multi-vessel disease caused by Kawasaki disease. Recurrent events of acute coronary syndrome can occur in adults, although its prevalence may be low. Careful follow-up in adults is also needed in this population.

Introduction

During the 1970s and 1980s, the infants with giant aneurysms often had acute myocardial infarction within a year of their initial episode of Kawasaki disease.[1] Such occlusion of coronary arteries is caused by thrombotic occlusion in giant coronary aneurysms of the epi-coronary arteries. Furthermore, most of them had coronary events such as coronary revascularisation in children or adolescents.[2] The occurrence of acute myocardial infarction is a very important factor in outcomes of patients with a history of Kawasaki disease. Coronary artery lesions caused by KD persist long into adulthood, and the number of patients with exceeding 30 years of age has increased. Most patients are asymptomatic many years after childhood onset of KD. However, some patients with multi-vessel disease rarely can have recurrent events of acute coronary syndrome after many years. It is rare that a symptomatic occlusion of the peripheral branches occurs in patients after Kawasaki disease. Here, we report 3 adult patients with thrombotic occlusion of the major coronary arteries as children, who developed recurrent events of acute coronary syndrome due to occlusion of the peripheral coronary arteries as adults.

Patient 1

The first patient had a history of Kawasaki disease at the age of 1 year in 1982 (Table 1, Fig. 1). He had bilateral giant coronary aneurysms, and he had a previous anteroseptal myocardial infarction 5 months after Kawasaki disease. At the age of 5 years, coronary angiograms showed coronary artery aneurysms of the right coronary artery and left anterior descending artery in another hospital. Aspirin was prescribed. He was referred to our hospital at the age of 18 years. Coronary angiograms at the age of 19 years showed dilatation of the right coronary artery and dilatation with localised stenosis in the left anterior descending artery. The left ventricular ejection fraction was 35%. Beta-blocker and angiotensin-converting enzyme inhibitors were added.

At the age of 32 years, he had chest discomfort and respiratory distress at a.m 07:00 hours. He visited an emergency outpatient clinic at a.m 09:00 hours. His height and weight were 178 cm and 70 kg, respectively. A 12-lead electrocardiogram showed ST-T depression in leads V4–V6, and acute myocardial infarction was suspected. Creatine kinase was 72 U/L (normal 62–287), and troponin-T was 0.009 ng/ml (<0.014). High-density lipoprotein and low-density lipoprotein cholesterol levels were 52 (40–96) and 158 mg/dl (<140), respectively. Heparin was administered intravenously, and his condition was continuously observed. His chest

Table 1. Characteristics of patients with acute coronary syndrome caused by Kawasaki disease

Patient	1	2	3
Age at acute coronary syndrome (years)	32	29	33
Gender	Male	Female	Female
Culprit lesion	Posterior descending artery	Atrioventricular node artery	Atrioventricular node artery
Location	Inferior	Inferior	Inferior
Left ventricular ejection fraction (%)	35	44	55
Coronary artery lesions	RCA dilatation, LAD dilatation with localised stenosis	RCA segmental stenosis, LAD occlusion, LCA aneurysm	RCA segmental stenosis, LAD occlusion
Age at the onset of KD (years)	1	4	1
Previous myocardial infarction			
Age	1 year 5 months	4 years, 5 years	
Location	Anteroseptal	Inferior, anteroseptal	
Age at coronary artery bypass grafting (years)		5, 28	19
Medication in the late period	Aspirin,	Coumadin, Aspirin	Aspirin
	Carvedilol	Carvedilol	Carvedilol
	ACEI	ACEI	

RCA, right coronary artery; LAD, left anterior descending artery; LCA, left coronary artery; ACEI, angiotensin-converting enzyme inhibitor.

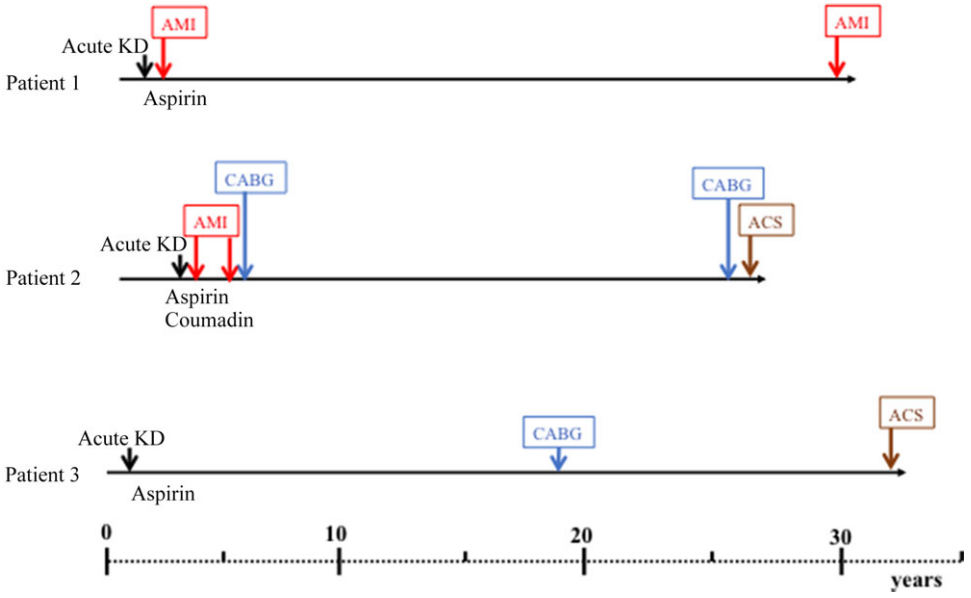

Figure 1. Clinical course and cardiac events with ageing in each patient. KD, Kawasaki disease, AMI = acute myocardial infarction, ACS = acute coronary syndrome, CABG = coronary artery bypass grafting.

discomfort disappeared at a.m 11:00. Coronary angiograms at 14:00 hours showed 99% stenosis of the branch of the 4th posterior descending (Fig. 2). Spontaneous recanalisation of the branch of the 4th posterior descending was suspected. At 18:00 hours, creatine kinase and creatine kinase-MB concentration were 1,151 U/L and 163 U/L (<12), respectively. The next day, troponin-T was 1.710 ng/ml. On ^{99m}Tc myocardial perfusion imaging, hypoperfusion of the inferior wall of the left ventricle, in addition to previous severe hypoperfusion of the anteroseptal wall at the apex, was seen (Fig. 3). CT angiogram 8 years after this episode showed the patency of the branch of the 4th posterior descending.

Patient 2

The second patient had a history of acute Kawasaki disease at the age of 4 years and bilateral giant aneurysms. Four months after

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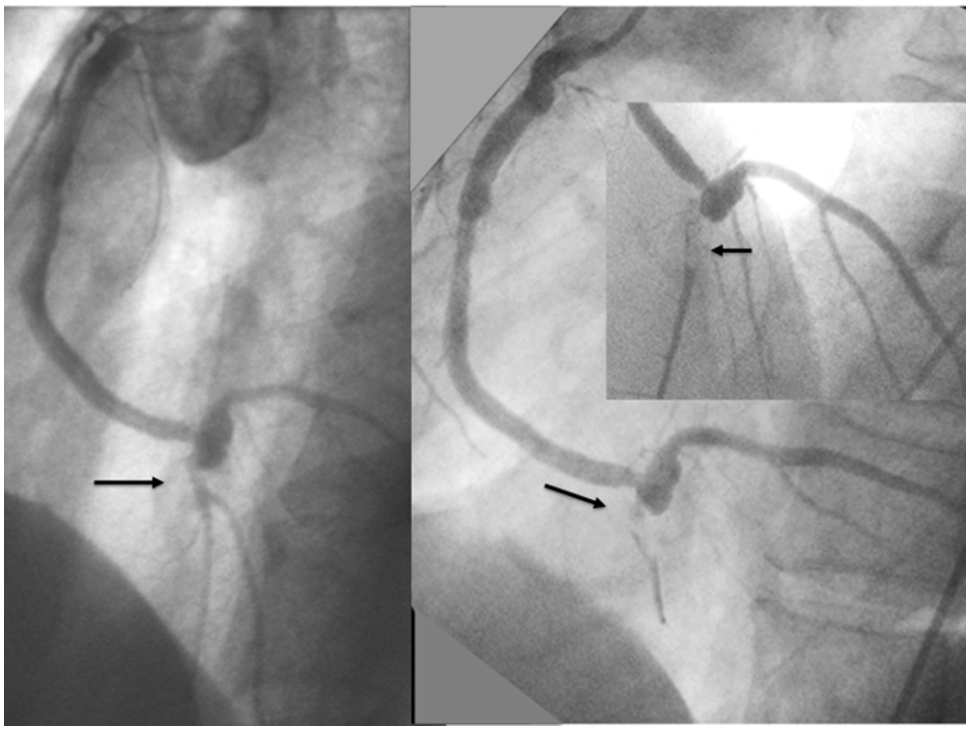

Figure 2. The right coronary angiograms at the age of 19 years and 32 years (Patient 1). Left, 19 years old. Right, 32 years old. Coronary angiograms 99% stenosis of the 4th posterior descending.

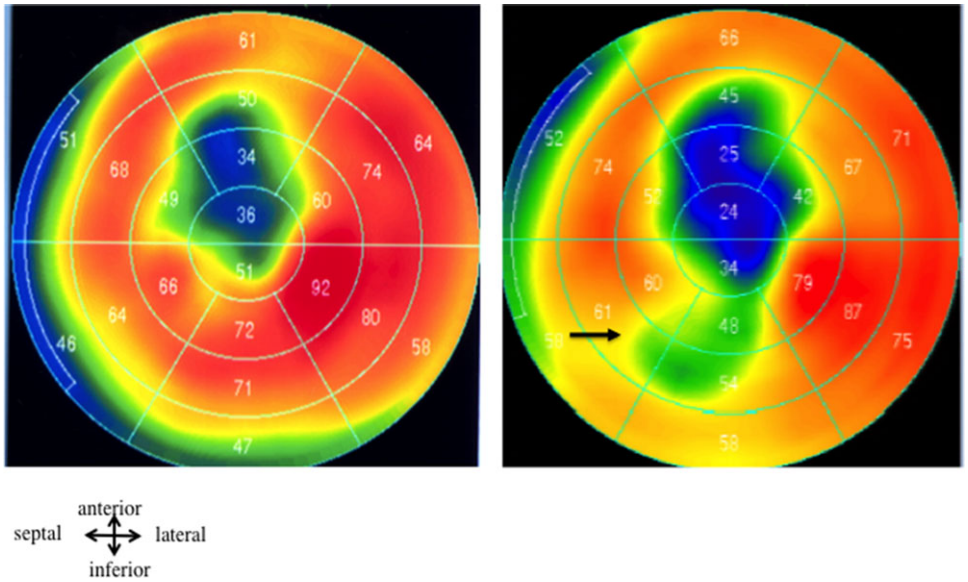

Figure 3. ^{99m}Tc myocardial perfusion imaging at the ages of 19 years and 32 years (Patient 1). Left, 19 years old. Right, 32 years old. Hypoperfusion of the inferior wall of the left ventricle in addition to previous severe hypoperfusion of the anteroseptal wall at the apex was seen.

Kawasaki disease, she had an inferior myocardial infarction. At the age of 5 years, intracoronary thrombolysis was performed for thrombus of a giant aneurysm at the bifurcation of the left coronary artery. After that, she then underwent coronary artery bypass grafting to the left anterior descending artery. However, the left internal thoracic artery graft was occluded after the operation, because of competition between native artery flow and the graft flow. She was put on warfarin and aspirin. She underwent re-coronary artery bypass grafting at the age of 28 years. The left ventricular ejection fraction was 44%. The right internal thoracic artery graft was anastomosed to the left anterior descending artery, and it was also anastomosed to the diagonal branch and 4th atrioventricular node artery with a radial artery graft. Coronary angiograms one year later showed that the grafts were patent, and warfarin was stopped.

At the age of 29 years, she developed chest discomfort and the pain of her left shoulder at 19:00. She visited a hospital on the next morning, because of persistent chest discomfort and headache. Her

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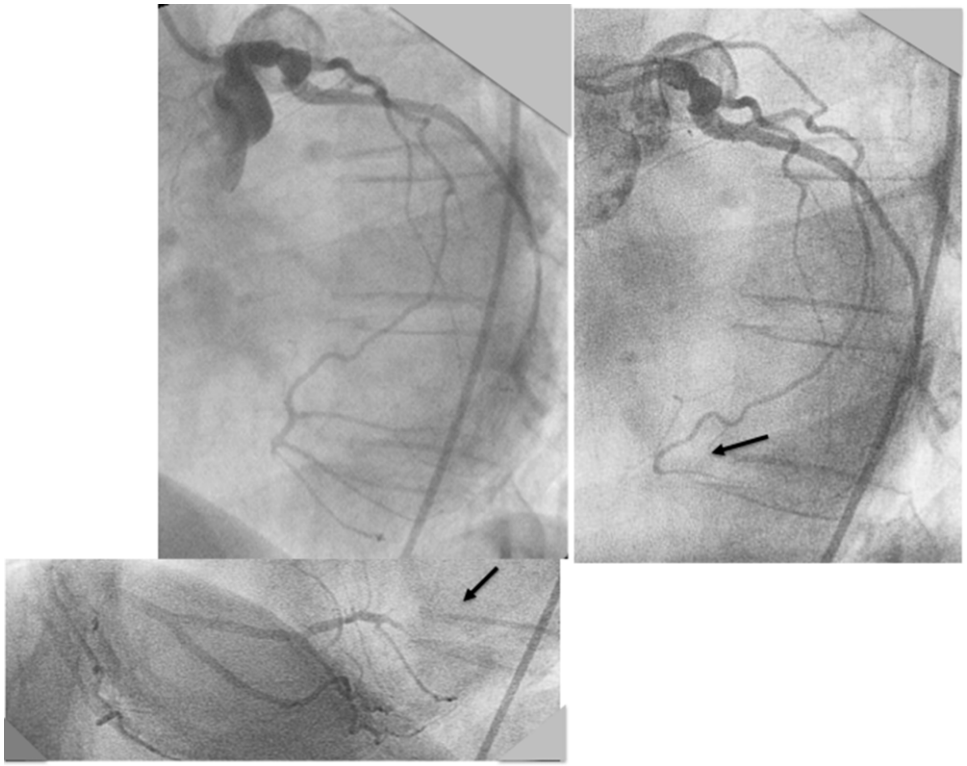

Figure 4. The left coronary angiograms at the age of 28 years and 29 years (Patient 2). Left upper: The left coronary angiogram at 28 years old. Left lower: The right coronary angiogram at 28 years old. Right: The left coronary angiogram at 29 years old. On coronary angiograms, the collateral arteries to the 4th atrioventricular node artery were not clearly injected through the left circumflex artery.

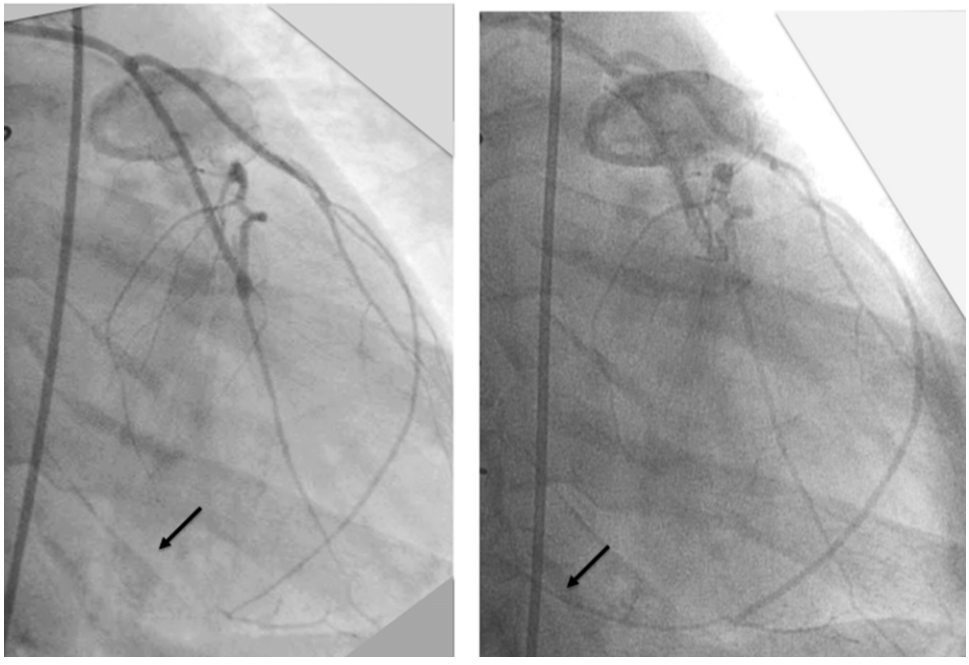

Figure 5. The right thoracic internal arteriograms at the age of 28 years and 29 years (Patient 2). Left: 28 years old. The right internal thoracic artery graft was anastomosed to the left anterior descending artery, and it was also anastomosed to the diagonal branch and 4th atrioventricular node artery with a radial artery graft. Right: 29 years old. The 4th atrioventricular node artery was vaguely detected through the radial artery graft.

height and weight were 159 cm and 59 kg, respectively. A 12-lead electrocardiogram showed a flat T in lead I and a negative T wave in lead aVL. Acute coronary syndrome was suspected. Creatine kinase was 30 U/L and troponin-T was 0.006 ng/ml. High-density lipoprotein and low-density lipoprotein cholesterol levels were 60 and 80 mg/dl, respectively. On coronary angiograms, the collateral arteries to the 4th atrioventricular node artery were not clearly injected through the left circumflex artery. However, the 4th atrioventricular node artery was vaguely detected through the radial artery graft (Figs. 4 and 5).

Patient 3

The third patient had a history of Kawasaki disease at the age of 1 year and 6 months and was treated with aspirin for acute Kawasaki disease. She underwent selective coronary angiograms 5 months

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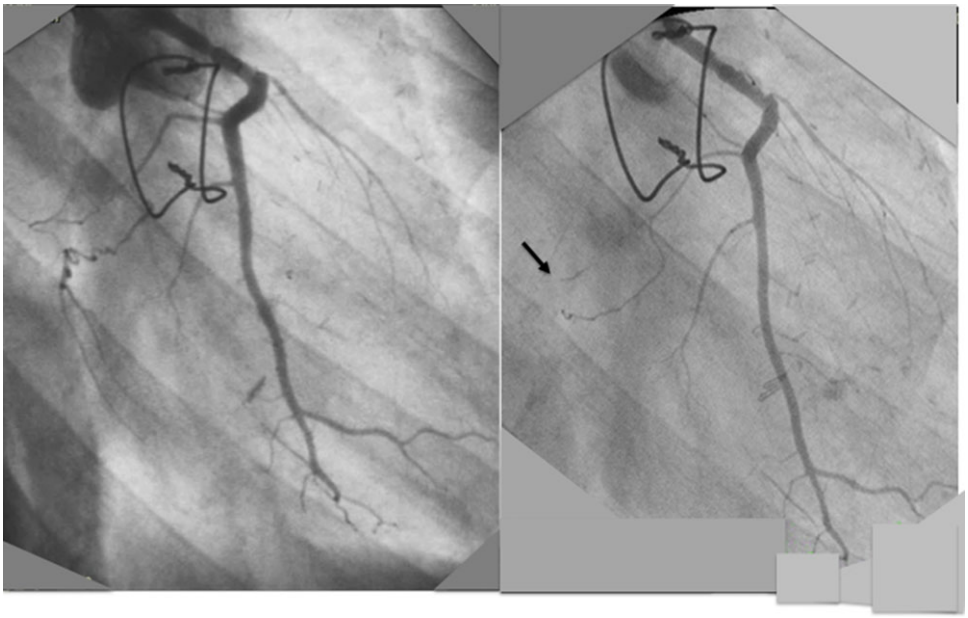

Figure 6. The left coronary angiograms at the age of 18 years and 33 years (Patient 3). Left: 18 years old. Right: 33 years old.

after acute Kawasaki disease in another hospital. Coronary angiograms showed occlusion of the right coronary artery and aneurysms of the left anterior descending artery and the left circumflex. She was referred to our hospital at the age of 8 years. Coronary angiograms showed segmental stenosis of the right coronary artery and occlusion of the left anterior descending artery. The left anterior descending artery was retrogradely injected through the right coronary artery, and the collateral arteries to the 4th atrioventricular node artery were injected from the circumflex. At the age of 18 years, ST-T depression was seen in leads II, III, aVF, and V4–6 on the treadmill test. She had been asymptomatic after acute Kawasaki disease. She underwent a coronary artery bypass grafting to the left anterior descending artery with a left internal thoracic artery graft at the age of 19 years. The left ventricular ejection fraction was 55%. She took aspirin, and she delivered three times vaginally without complications. At the age of 32 years, she was prescribed carvedilol, because of premature ventricular contractions.

At the age of 33 years, she developed chest pain at a.m 06:30 hours. She visited a hospital that morning, because of persistent chest discomfort. A 12-lead electrocardiogram showed negative T waves in lead V2–4 in the emergency department. Heparin was continuously administered intravenously. After a while, the changes on the electrocardiogram improved. Creatine kinase was 30 U/L, and trop-T was negative. On CT angiogram, the collateral arteries from the circumflex to the 4th atrioventricular node artery were not clearly injected. Coronary angiograms the next day showed that the collateral arteries were few and vague (Fig. 6). MRI showed a partial late gadolinium enhancement of the inferior wall of the left ventricle. It was not detected in the previous examination.

Discussion

The causes of acute coronary syndrome are different between coronary artery lesions caused by Kawasaki disease in children and ischaemic heart disease due to atherosclerosis in adults. Usually, the cause of acute coronary syndrome due to atherosclerosis is induced by plaque rapture.[3] On the other hand, coronary artery lesions caused by Kawasaki disease can lead to myocardial involvement that is caused by occlusion of coronary arteries, most of which are induced by giant aneurysms.[2] The occlusion can be symptomatic or asymptomatic. Thrombus formation of coronary arteries after Kawasaki disease can occur when three factors of Virchow are present: endothelial dysfunction, stasis within giant aneurysms, and hypercoagulability. The endothelial cells in giant coronary aneurysms are injured after severe acute vasculitis. Furthermore, blood flow in giant aneurysms is stasis. Grande NG et al reported that endothelial cell dysfunction is most likely related to the hemodynamic parameters of decreased wall sheer stress and increased particle residence time within aneurysm.[4] An activation of the coagulation fibrinolytic system continues within 1 year after acute Kawasaki disease. In particular, a coronary artery occlusion is likely to occur within 6 months after the onset of Kawasaki disease.[1] In the 1980s, antithrombotic therapy with Warfarin and antiplatelet therapy was not widespread in patients with giant aneurysms. Therefore, many patients with giant aneurysms often had acute myocardial infarctions immediately after Kawasaki disease at those days. Antithrombotic therapy with Warfarin and antiplatelets agents is useful in the prevention of acute myocardial infarction within 6 months after acute Kawasaki disease. Anticoagulation therapy and antiatherosclerotic therapy are mandatory in adult patients after giant aneurysms. Acute coronary syndrome involving the major coronary arteries occurs rarely in adults more than 20 years after Kawasaki disease.[5,6] It would not be clarified that a usefulness of antithrombotic therapy with Warfarin and antiplatelets agents in adults whose giant aneurysms had already occluded in their children, because the prevalence of their cardiac events is very low.

However, it is very rare such as an infarction of the limited area caused by peripheral coronary arteries in this adult population Atherosclerotic factors affect the coronary arteries after Kawasaki disease. Various coronary risk factors are added with ageing. Although smoking was also a risk factor for acute coronary syndrome in this population, all three patients were no smokers.[7] Although the first patient had an increase of low-density lipoprotein cholesterol levels, the later two patients had had no atherosclerotic risk factors. Statins for decrease of low-density

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lipoprotein cholesterol levels would be needed. Involvement of the coronary arterial wall continues after the appearance of coronary artery aneurysms due to acute Kawasaki disease vasculitis.[8,9] Furthermore, the progressive stenosis also leads to coronary artery occlusion. Although coronary artery occlusion of the major coronary arteries is often found, acute coronary syndrome due to occlusion of peripheral coronary arteries is rare. It depends on the distribution of coronary aneurysms in the acute phase of Kawasaki disease. Three patients in the present report had typical coronary artery occlusion of major coronary arteries in children, and they had chest pain due to coronary artery occlusion in peripheral branches such as the 4th posterior descending and 4th atrio-ventricular node artery. They may be some differences in the cause and mechanism of coronary artery occlusion between the major coronary arteries and peripheral coronary arteries.

Especially, in the later two female patients, it was suspected that the 4th atrioventricular node artery segments injected retrogradely through the left circumflex became to the culprit lesions of acute coronary syndrome. It is questionable whether the collateral arteries occlude or not. In two patients, their myocardial enzyme and serum biomarkers were not elevated, although they had chest pain with their electrocardiographic changes. With respect to the appearance of pain due to coronary artery occlusion, it may also be a difference between children and adult. Further, it may be also a sex difference between male and female in micro-coronary circulation. In patients with giant aneurysms after Kawasaki disease, persistent coronary aneurysms and the affected coronary arteries after Kawasaki disease can also lead to further myocardial involvement in adult.

The degree of myocardial involvement with symptomatic coronary artery occlusion is severer than that with asymptomatic coronary artery occlusion. The left ventricular ejection fraction is usually decreased in most patients with symptomatic coronary artery occlusion. Their late gadolinium enhancement on MRI indicating myocardial fibrosis was found to be transmural.[10] On the other hand, the left ventricular ejection fraction in most patients with asymptomatic coronary artery occlusion is preserved, because the late enhancement due to asymptomatic occlusion is within 50% of the myocardial wall. Generally, coronary artery aneurysms in Kawasaki disease develop in the proximal portion of the epi-coronary arteries. Therefore, occlusion of coronary aneurysms in the major coronary arteries is widespread in the myocardial wall of the left ventricle. These were characteristics of acute myocardial infarction in children after Kawasaki disease.

The possibility of recurrent cardiac events in patients with giant aneurysms of multi-vessels was considered to be high in their life.[2,11,12] In fact, the prevalence of cardiac events in this population remains unknown, and it must be clarified in the future. All three patients in this report had persistent coronary artery aneurysms and stenotic lesions after Kawasaki disease. Although they had had giant aneurysms in children, there had been already no giant aneurysms in adults. Even if giant coronary aneurysms regress, involvements of its coronary artery wall persisted in the site of regressed aneurysms. The endothelial dysfunction of involved coronary arteries may induce recurrent events with ageing in this population. There are probably many such patients, now in their forties and fifties, at risk, and the cause of cardiac events in this group and its prevention are important issues. Symptoms caused by Kawasaki disease are rare, and evidence of ischaemia is often not present until an adulthood actual cardiac event occurs. Patients with giant aneurysms and families of patients at potential risk of cardiac complications in their long life should be educated about careful follow-up.

Conclusion

Recurrent events of acute coronary syndrome in adults can occur in patients with multi-vessel disease caused by Kawasaki disease. Occlusion of peripheral coronary artery vessels can occur in adults. Careful follow-up in adults is also needed in this population.

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Competing interests. The author states that I have no conflict of interest.

Ethical approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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