Poor prognostic cardiac sequelae of possible Kawasaki disease mimicking dilated cardiomyopathy: the importance of extensive and serial cardiac evaluation and the significance of thromboembolic mechanisms

Dilate kardiyomiyopatiyi taklit eden olası Kawasaki hastalığının kötü prognostik kardiyak seyiri: Seri ve kapsamlı kardiyak değerlendirme ve tromboembolik mekanizmaların önemi

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Introduction

Giant coronary artery aneurysm is a serious complication of Kawasaki disease (1). Acute myocardial infarction can occur in some patients with giant coronary artery aneurysms (2), and dilated cardiomyopathy-like manifestations resulting in severe cardiac dysfunction have been rarely reported (3). However, severe cardiac dysfunction due to the cardiac sequelae of Kawasaki disease is sometimes misdiagnosed as idiopathic dilated cardiomyopathy (4). We report a patient who died due to refractory heart failure complicated by ventricular tachyarrhythmia secondary to the cardiac sequelae of possible Kawasaki disease. The patient had been diagnosed as having dilated cardiomyopathy, but long-term anti-platelet therapy had not been instituted. On autopsy, a giant coronary aneurysm that contained a mixture of fresh, organized thrombi was found, which was compatible with the cardiac sequelae of Kawasaki disease. Therefore, extensive and serial cardiac evaluation and long-term antiplatelet treatment are important in young patients with suspected dilated cardiomyopathy.

Case report

A 31-year-old woman, in whom possible idiopathic dilated cardiomyopathy had been diagnosed in another hospital, was admitted to the National Defense Medical College Hospital for the evaluation of epigastralgia. Her past history included a febrile condition of short duration occurring at the age of 10 months. However, the changes in extremities such as erythema of palms and soles, edema of hands and feet, polymorphous exanthema, bilateral bulbar conjunctiva injection without exudates, the changes in lips and oral cavity such as erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae, and cervical lymphadenopathy were not observed nor recorded. However, detailed information about the history at the childhood could not be obtained. At the age of 21 years, premature ventricular contractions were noted on an electrocardiogram (ECG) taken during an annual health examination. At that time, further cardiac evaluation revealed dilation of the left ventricular cavity and decreased left ventricular function without a detectable coronary aneurysm. She had no traditional coronary risk factors. Her family history was not contributory. Since her condition was stable, and she had no symptoms or signs of heart failure, no medications, including antiplatelet and anticoagulant drugs, were prescribed. Possible dilated cardiomyopathy was diagnosed. Since either cardiac magnetic resonance imaging (CMR) or multidetector-row computed tomography (MDCT) was not available at that time, these studies were not performed. According to the medical history, repeated echocardiography revealed no coronary artery aneurysm and coronary angiogram was not performed because of negative exercise treadmill testing and a lack of anginal symptoms and signs. However, detailed reasons why coronary angiogram was not performed were not clear because, at the time of her first admission to our hospital, we could not contact the physician at the other hospital who evaluated this patient because of the long interval between this episode and her last visit to the previous hospital.

The physical examination in the outpatient clinic was unremarkable except for irregular heart rhythm (height 156 cm, body weight 47 kg, blood pressure 84/64 mm Hg, pulse rate 102 beats/min and irregular). Upon admission, her ECG showed frequent premature ventricular contractions with nonsustained vent-

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ricular tachycardia. A QS pattern in leads V1-V4 and ST-segment depression in leads V5-V6 were also found, but no evolving ST-T segment changes indicative of acute myocardial infarction were detected (Fig. 1). However, blood chemistry studies (creatine kinase [CK], 2250 IU/L; CK-MB [CK cardiac fraction], 106 IU/L) were compatible with acute myocardial infarction. Other laboratory data were within normal limits (total cholesterol, 163 mg/dl; triglyceride, 45 mg/dl; HDL-cholesterol, 50 mg/dl; blood glucose, 79 mg/dl; white blood cell, 9900/mm^3; red blood cell, 4.29 x 106/mm^3: platelet, 21.3 x 104/mm^3; CRP, 0.3> mg/dl; negative serologic test for syphilis [STS]; negative test for anti-nuclear antibody; negative for rheumatoid factor; normal profile of serum r-globulin levels).

A resting thallium scintigraphic study revealed a diffuse perfusion defect, especially marked perfusion defect seen in the inferior and anteroseptal and lateral wall, and global deterioration of left ventricular wall motion (Fig. 2). A coronary angiogram showed large calcified coronary artery aneurysms in the left main trunk (8 mm x 13 mm) and in the proximal portion of the right coronary artery (13 mm x 14 mm) (Fig. 3). The right coronary artery was occluded. The left coronary artery other than the left main trunk showed no significant stenosis. Left ventriculography revealed diffuse hypokinesis, and the global left ventricular ejection fraction was 10%. She was treated conservatively with aspirin, isosorbide dinitrate, β-blocker, angiotensin-converting enzyme inhibitor and diuretics. As her clinical course was stable, she was discharged after three weeks of hospitalization. Her physical condition of activity was between class III and IV of New York Heart Association definition. After discharge, her daily activities were not limited by any cardiac symptoms and she could go out from her home with the assistance of her family so that she was not listed of heart transplantation at this moment. However, five months later, ventricular tachyarrhythmia developed and this aggravated heart failure. She was readmitted due to acute left ventricular failure. She died as a result of refractory heart failure complicated by refractory ventricular tachyarrhythmia despite intensive treatment.

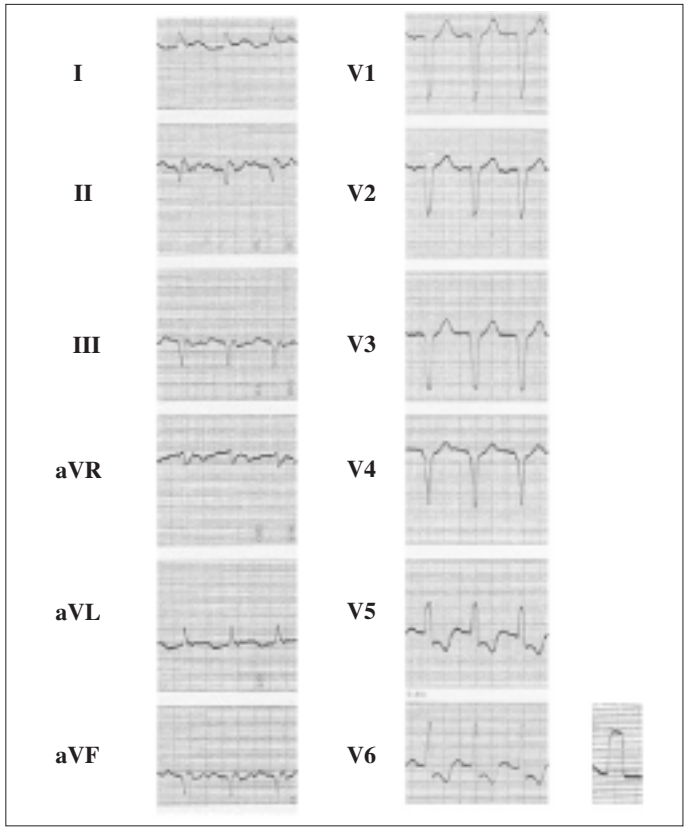

Figure 1. 12-lead electrocardiogram on admission. Sinus tachycardia, a QS pattern in leads V1-V4 and ST-segment depression in leads V5-V6 are observed

Autopsy revealed calcified coronary aneurysm (10 mm x 15 mm) in the left main trunk of the coronary artery and two complex aneurysms (one 15 mm x 17 mm and the other 12 mm x 15 mm) in the proximal right coronary artery. The right coronary artery was occluded at the proximal portion of the second aneurysm, whereas the left coronary artery was patent without significant atherosclerotic changes except in the main trunk. Microscopic examination revealed luminal expansion of each aneurysmal lesion. Transverse section of coronary aneurysm revealed that coronary vessel wall maintained the wall integrity and the distinct presence of three layer of a vessel wall containing intima, media and adventitia, which excluded the presence of pseudoaneurysm. Fresh, organized thrombi were recognized in all the aneurysms. The heart weighed 440 g, and both ventricles were dilated (Figure 4). Extensive necrosis and fibrosis in the left ventricle were seen in the inferior, the anterolateral and the anteroseptal walls. Microscopic findings were compatible with acute myocardial infarction with old myocardial scars.

Discussion

This case demonstrates that extensive and serial cardiac evaluation and long-term antiplatelet treatment are important in young patients with suspected dilated cardiomyopathy even though no coronary artery changes on echocardiography are found. Especially, the technology on CMR and MDCT has recently showed a great advance. These new modalities should be applied to a case similar to this patient.

Autopsy findings in this patient suggest that the widespread extensive myocardial necrosis occurred due to repeated distal coronary thromboemboli arising from the thrombi in the coronary aneurysms, and could have caused left ventricular dysfunction.

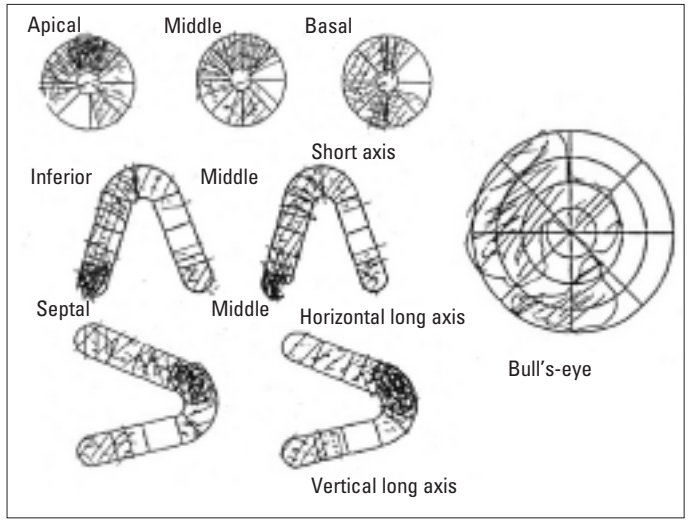

Figure 2. A resting thallium scintigraphic study. Inferior and anteroseptal fixed defects indicating extensive necrosis are noted.

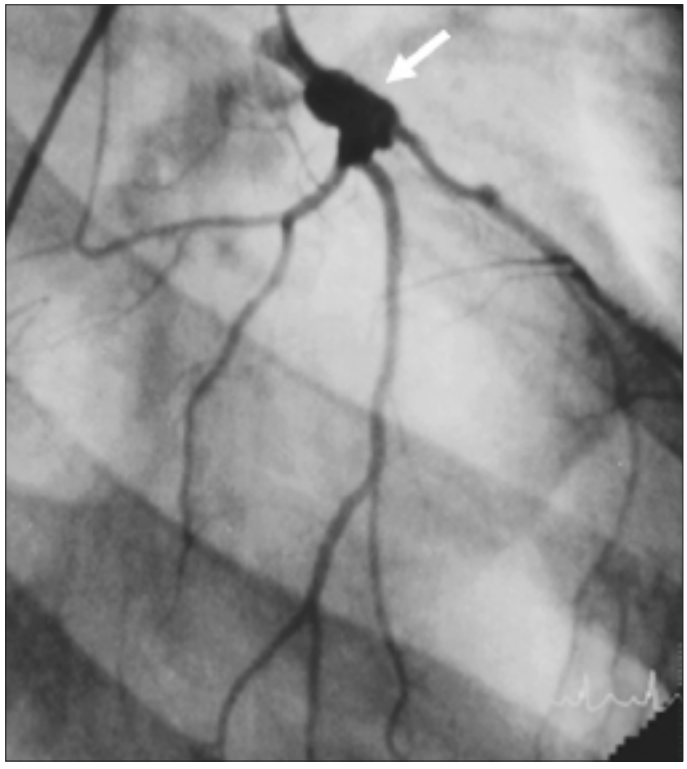

Figure 3-1. Coronary angiogram (left coronary artery). Coronary angiogram shows giant aneurysm in the left main trunk of the coronary artery. Open arrow indicates aneurysm. Picture was taken at left anterior oblique view.

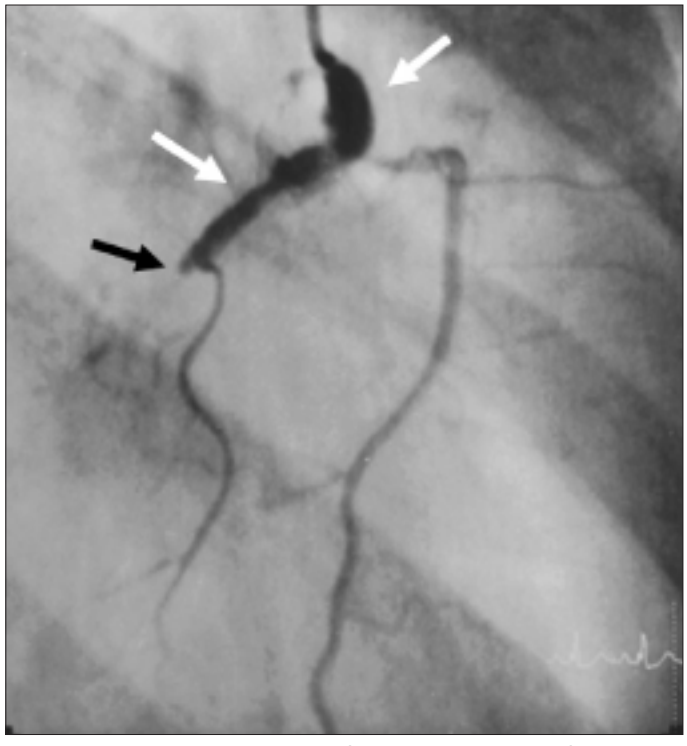

Figure 3-2. Coronary angiogram (right coronary artery). Coronary angiogram shows complex giant aneurysm in the proximal portion of the right coronary artery. Total occlusion in the aneurysmal lesion is observed. Open arrow indicates aneurysm and closed arrow indicates total occlusion of proximal portion of the right coronary artery. Picture was taken at left anterior oblique view.

These findings were interpreted as possible Kawasaki disease with end stage arteritis (5). A coronary angiogram had not been done at the time of the patient's first abnormal ECG since no aneurysms were detected on echocardiography. Thus, the cardiac sequelae of possible Kawasaki disease were not diagnosed until the development of acute myocardial infarction and uncompensated heart failure.

Since relatively long interval between a febrile episode in infant and the diagnosis of coronary aneurysm existed in this case, we considered the possible Kawasaki disease for the etiology of coronary aneurysm even if there were no convincing symptoms, signs and laboratory findings supporting that this patient had Kawasaki disease. Generally, aneurysm of the coronary artery can be congenital or can be secondarily caused by atherosclerosis, inflammatory or infectious disease (Kawasaki disease, Takayasu disease, systemic lupus erythematosis or polyarteritis nodosa, endocarditis, syphilis), connective tissue diseases (Marfan's syndrome or Ehlers-Danlos syndrome), metastatic tumors, or blunt trauma to the chest. Among them, atherosclerotic coronary artery aneurysm is the most common form of the aneurysms (6). However, this patient did not have any traditional coronary risk factors. And physical signs and laboratory findings denied the most of the etiology described above except Kawasaki disease and polyarteritis nodosa. Atypical course of both Kawasaki disease and polyarteritis nodosa is possible. Acute inflammatory phase was a very long distance from the discovery of cardiac sequelae of these diseases so that we considered the atypical form of Kawasaki disease is more likely than the atypical course of juvenile form of polyarteritis nodosa. However, the latter can not completely be excluded from the etiology of the coronary artery aneurysm in this patient. Another possibility is that the other febrile episodes in childhood or in the later life of this patient were overlooked and missed to be reported. Since some missed information on the childhood could not be precisely obtained in this patient, definitive diagnosis for Kawasaki disease was difficult. However, multiple coronary aneurysms, calcificati-

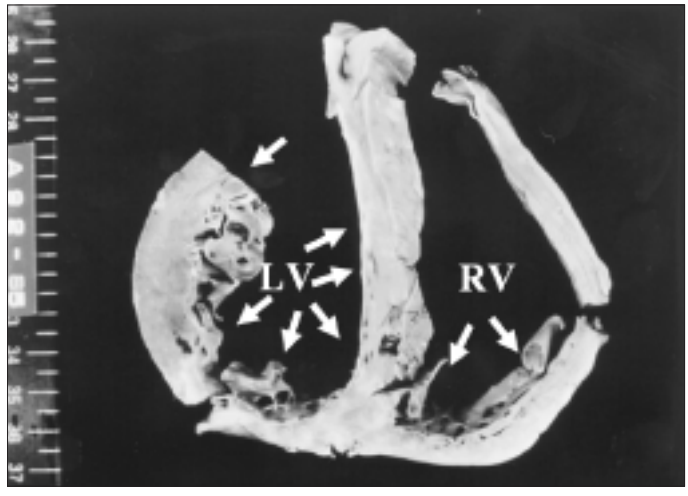

Figure 4. Autopsy findings. Cross-sectional view of the heart is shown. Left ventricle (left side) and right ventricle (right side) are extremely dilated. Extensive scars were noted in both ventricular walls. Extensive necrosis and fibrosis in the left ventricle were seen in the inferior, the anterolateral and the anteroseptal walls. These findings were in accordance with the findings of a resting thallium scintigraphic study (Fig. 2).

LV- left ventricular cavity, RV- right ventricular cavity, arrow indicates the scar tissues.

ons, stenoses and complete obstruction of coronary artery in a young woman like this patient are feasible for diagnosing Kawasaki disease. In addition, it is reported (7) that the fourth stage of Kawasaki disease lasts for years and that during this period the described coronary pathology may cause slow left ventricular dilatation, systolic dysfunction and progression to cardiac insufficiency. These findings support the possible Kawasaki disease in this patient.

The recent guideline for treating Kawasaki disease indicates that periodic assessment and counseling about known cardiovascular risk factors every five years is recommended even if patients show no coronary artery changes on echocardiography at any stage of their illness (7). If Kawasaki disease had been considered under differential diagnosis for the etiology of this patient's heart failure before she visited to our hospital, more extensive and serial (or periodical) evaluation for detecting coronary aneurysms should have been performed. This advice, which was indeed overlooked in this case, is in agreement with our observations. According to the literature, children with giant aneurysms (maximum diameters > 8 mm) have the worst prognosis (1). In those patients with giant aneurysms, thrombosis is promoted by the combination of sluggish blood flow within the aneurysm and stenotic lesions around the origin of the aneurysm (8). These reports concur with the autopsy findings in our case.

A diagnosis of the cardiac sequelae of Kawasaki disease can be missed in cases of atypical Kawasaki disease. The reported incidence of dilated cardiomyopathy-like left ventricular dysfunction is about 1%-5% (9) in patients with cardiac sequelae of Kawasaki disease. Though the reported diagnostic accuracy of transthoracic echocardiography for detecting cardiac sequelae of Kawasaki disease is excellent, it is not perfect. Since coronary artery visualization by transthoracic echocardiography becomes progressively more difficult as children grow up, new imaging modalities, such as CMR and/or MDCT, should be considered for the diagnosis and follow-up (10) of young patients with suspected dilated cardiomyopathy and negative echocardiography findings. As a matter of fact, this patient was first evaluated by echocardiography at the age of 21 years; it is likely that transthoracic echocardiography might not be precise enough to detect coronary aneurysm.

It is also important to consider antiplatelet medications in young patients with heart failure. Although routine use of antiplatelet agents for the treatment of heart failure is not supported (11), low dose aspirin is effective in preventing cardiac events in patients with coronary artery disease and in those with cardiac sequelae of Kawasaki disease. Thus, the prescription of low dose aspirin should be considered in young patients with heart failure, such as in this case. In addition, for the patients with giant aneurysms, the most common anti-thrombotic regimen is low-dose aspirin together with warfarin, maintaining an international normalized ratio (INR) of 2.0 to 2.5 (7).

At a later stage some patients with Kawasaki disease can develop dilated cardiomyopathy-like cardiac dysfunction secondary to repeated coronary thromboemboli arising from a giant coronary aneurysm. The cardiac sequelae of Kawasaki disease are sometimes difficult to identify in the chronic stage. Therefore, new imaging modalities, such as CMR, MDCT and/or diagnostic coronary angiography, as well as antiplatelet therapy, should be utilized in patients in whom Kawasaki disease is suspected, especially in those who have both dilated cardiomyopathy-like ventricular dysfunction and a history of febrile illness in childhood.

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