

Long-Term Follow-Up of a Patient With Kawasaki Disease and Coronary Aneurysm Associated With Asymptomatic Thrombosis: A Case Report

Hisao MATSUDA, MD
Nobuyuki HASHIMOTO, MD
Kengo SUZUKI, MD
Hidefumi AOYAGI, MD
Yoshihiro AKASHI, MD
Kensuke KAWASAKI, MD
Katsuhiko TSUCHIYA, MD
Atsushi OZAWA, MD
Junzo NAGASHIMA, MD, FJCC
Haruki MUSA, MD, FJCC

Abstract

A 20-year-old male was first diagnosed with Kawasaki disease at age 2 years 9 months. Coronary angiography in the acute phase revealed coronary aneurysms, so chronic antiplatelet therapy was initiated with aspirin and ticlopidine. The patient was asymptomatic and was followed up. Stress myocardial imaging showed asymptomatic myocardial ischemia at age 20 years. Coronary angiography was performed, and revealed 99% occlusion of the right coronary artery and collateral circulation from the left coronary artery. Occlusion was attributed to coronary aneurysm thrombosis. Much remains unknown about the long-term prognosis in patients with coronary aneurysm associated with Kawasaki disease. Asymptomatic children who are followed up sometimes develop ischemic heart disease as young adults. This case highlights the need for long-term follow-up in patients with Kawasaki disease and coronary aneurysms.

J Cardiol 2005 Sep; 46(3): 113–118

Key Words

■Kawasaki disease ■Angiography ■Coronary artery disease
■Exercise tests ■Aneurysms

INTRODUCTION

Kawasaki disease is a systemic inflammatory disorder with a predilection for children aged 4 years and younger. The incidence of Kawasaki disease has continued to increase since the first report in 1967, but the exact etiology remains unclear.

Pathophysiological changes include systemic vasculitis with particular involvement of the coronary arteries. Coronary artery dilation and aneurysm that develop during the acute phase may later regress over time on clinical follow-up. However, other patients continue to display coronary lesions on long-term follow-up, with progression to stenosis

聖マリアンナ医科大学横浜市西部病院 循環器内科: 〒241-0811 横浜市旭区矢指町1197-1

Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, Yokohama City Seibu Hospital, Yokohama

Address for correspondence: MATSUDA H, MD, Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, Yokohama City Seibu Hospital, Yasashi-cho 1197-1, Asahi-ku, Yokohama 241-0811; E-mail: chaom@nifty.com

Manuscript received April 27, 2004; revised August 23, 2004 and March 16, 2005; accepted March 16, 2005

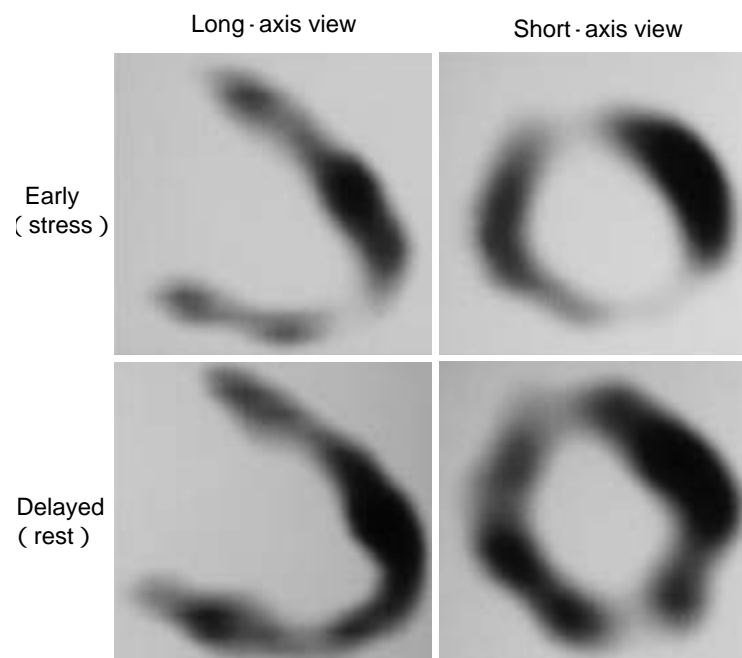


Fig. 1 ^{201}Tl -Cl perfusion single photon emission computed tomography showing decreased uptake in the left ventricular inferior wall during exercise, with redistribution during rest

End point of exercise was leg fatigue and max heart rate was 172 beats/min (86% of target heart rate).

Upper row: Early image. Lower row: Four hours delayed image.

and thrombosis. This mandates periodic monitoring in all patients with exercise stress testing and echocardiography. Much remains unknown about the long-term prognosis of Kawasaki arteritis, but myocardial infarction in young patients is now being reported in association with coronary artery lesions due to Kawasaki disease.

Here we report the follow-up of a patient who remained clinically asymptomatic with no abnormalities on regular follow-up, but who later developed thrombotic occlusion of a coronary aneurysm 17 years after the first diagnosis of Kawasaki disease.

CASE REPORT

The patient developed Kawasaki disease in 1984 (age 3 years). Coronary angiography (CAG) during the acute phase revealed giant aneurysms at the origins of the left and right coronary arteries, so antiplatelet therapy with aspirin and ticlopidine was prescribed. The patient was referred for evaluation and follow-up in the department of pediatrics of our institute in 1990 (age 9 years). The patient had remained asymptomatic, and periodic stress electrocardiography showed no abnormalities. CAG revealed giant aneurysms and calcification at the

origins of the left and right coronary arteries in 1995 (age 13 years). Distal flow in the left and right coronary arteries was satisfactory. Antiplatelet therapy was continued with aspirin, 0.4g/day and ticlopidine, 40 mg/day.

The patient was transferred for follow-up to the Department of Cardiovascular Disease at age 20 years. He remained clinically asymptomatic. Stress thallium myocardial imaging was performed in December 2001. Stress electrocardiography showed no significant ischemia, but myocardial single photon emission computed tomography identified decreased uptake in the left ventricular inferior wall during exercise, with redistribution during rest (Fig. 1). The patient was admitted to the hospital for further evaluation of coronary artery sequelae on April 4, 2002.

On admission, his height was 161cm; weight, 62.5kg; blood pressure, 100/62 mmHg; and pulse rate, 90 beats/min and regular. Physical examination revealed clear lung fields, no extra heart sounds or murmurs, and no abnormal abdominal findings. Neurological examination was normal. Biochemical studies yielded normal results. Chest radiography showed clear lung fields, with a cardiothoracic ratio of 33% (Fig. 2). Results from rest-

ing electrocardiography were normal.

CAG was performed on April 4, 2002, and showed a giant aneurysm measuring about 10mm in diameter at the origin of the left coronary artery. The left anterior descending and circumflex branches displayed direct branching from the aneurysm. The left coronary artery showed no evidence of thrombus formation or stenosis, and distal coronary flow was satisfactory. A giant aneurysm was also present at the origin of the right coronary artery, with thrombus formation and outflow stenosis. Thrombolysis in Myocardial Infarction (TIMI) grade 1 flow into the distal coronary artery was noted. Collateral channels were present from the left coronary artery to the right coronary artery (Fig. 3). Left ventricular wall motion was normal.

Revascularization of the right coronary artery by coronary intervention was considered, but was complicated by the presence of the giant aneurysm at the origin. In addition, coronary artery bypass surgery was not indicated at the time due to the absence of myocardial ischemia in the region of the left coronary artery. However, because of possible acute coronary obstruction due to thrombus formation in the aneurysm, anticoagulant therapy (war-

farin, 4mg/day) was added to the antiplatelet therapy (aspirin, 0.4g/day), and the patient was scheduled for outpatient follow-up.



Fig. 2 Chest radiograph showing clear lung fields, and a cardiothoracic ratio of 33%

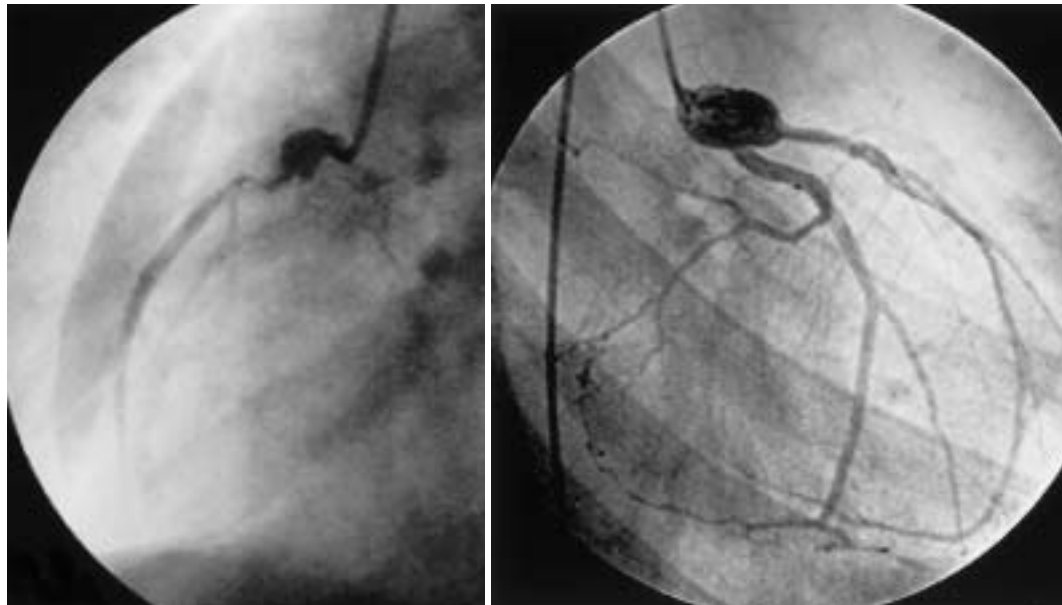


Fig. 3 Coronary angiograms in 2002 showing giant aneurysms and calcifications at the origins of the left and right coronary arteries (at age 20 years)

Distal flow in the left coronary artery was satisfactory. Right coronary artery shows thrombus formation and outflow stenosis, and Thrombolysis in Myocardial Infarction grade 1 flow into the distal coronary artery. Collateral channels were present from the left coronary artery to the right coronary artery.

Left: Right coronary artery (left anterior oblique view)

Right: Left coronary artery (right anterior oblique view)

DISCUSSION

Recently, the number of adults with Kawasaki disease and coronary aneurysm seen by cardiologists has been increasing. In general, these patients are closely monitored during childhood due to the risk of ischemic heart disease. However, after long periods of asymptomatic follow-up, monitoring for ischemic heart disease often tends to be relaxed. In our patient, the coronary artery aneurysms were patent at 10 years after disease onset, but occlusion due to thrombosis was noted after 17 years. This case suggests the need for caution in long-term follow-up of Kawasaki disease and coronary aneurysms. Patients displaying a satisfactory clinical course during childhood should still be considered at high risk for development of ischemic heart disease in adulthood.

Kawasaki arteritis is a type of panarteritis that begins by edematous dissection of the outer tunica media, progressing to involvement of the outer intima to the inner intima and infiltration of inflammatory cells from the adventitia. Blood vessels have reduced resistance to arterial pressure, resulting in aneurysm formation¹⁾. Coronary aneurysms were common in patients with Kawasaki disease prior to the availability of intravenous infusion of gamma globulin (IVGG), and are still seen in cases of Kawasaki disease refractory to IVGG treatment. The coronary aneurysms remain large^{2,3)}.

Follow-up of 594 patients with Kawasaki disease over an average of 13.6 years found coronary aneurysms during the acute phase in about 25% of patients (about 50% of aneurysms tended to regress), ischemic heart disease in 4.7%, and death in 0.8%⁴⁾. In addition, patients without coronary aneurysms on CAG during the acute phase had no subsequent development of cardiovascular lesions. Moreover, patients with giant aneurysms later display a high rate of progression to ischemic heart disease. This finding is attributed to the severe turbulence and stagnation of blood flow within the aneurysm, leading to thrombus formation. Evaluation of coronary aneurysms in 43 patients using a flow wire found increased stagnation of blood flow and thrombus formation as aneurysm size increased⁵⁾.

About 16% of patients with coronary aneurysms during the acute phase suffer obstruction, and in 78% of these patients, the obstruction is confirmed by CAG within 2 years after disease onset. The

obstruction is often first detected on follow-up CAG in clinically asymptomatic patients. Many of these patients display recanalized vessels and development of collateral channels. However, ischemic heart disease or sudden death can occur during adulthood^{6,7)}. Kawasaki arteritis has also been suggested as a risk factor for acceleration of arteriosclerosis^{8,9)}.

As demonstrated in the present case, long-term follow-up of Kawasaki disease using exercise stress electrocardiography and echocardiography is insufficient, as obstruction at the site of coronary aneurysm may be present even with negative findings. Interest has recently focused on the utility of evaluating coronary aneurysms using noninvasive studies such as multislice spiral computed tomography, magnetic resonance coronary angiography¹⁰⁻¹²⁾, and transesophageal echocardiography¹³⁾. However, these studies are available in only a limited number of medical centers, and are not widely used at present because of the poorer resolution than CAG. Evaluation by stress myocardial scintigraphy remains highly useful, and based on the results, CAG should be performed as necessary.

Giant coronary aneurysms are an indication for treatment with antiplatelet and anticoagulant drugs. However, anticoagulant therapy is more difficult to control in children, so many of these patients who are clinically asymptomatic are maintained on chronic antiplatelet therapy. This case suggests that even in patients with no changes during antiplatelet therapy in childhood, concomitant treatment with anticoagulants should be considered when the patient reaches adulthood.

The present patient developed giant aneurysms at the origins of the left and right coronary arteries during the acute phase, but CAG at 10 years after disease onset revealed no changes, and antiplatelet therapy was continued. However, 17 years after disease onset, thrombosis was present in the giant aneurysm at the origin of the right coronary artery. This suggests that even in patients with no changes during antiplatelet therapy in childhood, concomitant treatment with anticoagulants should be considered when the patient reaches adulthood.

No comprehensive reports have yet investigated the treatment or prognosis in patients with Kawasaki disease who reach adulthood, and this remains an area for future investigation. Predicting the long-term prognosis for development of myocardial infarction or sudden death is difficult,

and patients with giant aneurysms should continue to undergo follow-up CAG as adults. Several studies have now reported effective treatment¹⁴⁾ by coronary intervention¹⁵⁾ and coronary artery bypass surgery¹⁶⁻¹⁸⁾. Correct selection of therapy in each individual patient is essential to provide the most effective treatment.

The present case of thrombosed coronary aneurysm occurred in a patient with Kawasaki disease who remained clinically asymptomatic during

long-term follow-up. Most children with Kawasaki disease and coronary aneurysms remain asymptomatic during pediatric follow-up and are eventually transferred to care by adult cardiology departments. However, many of these patients may later develop ischemic heart disease. Cardiologists should keep this in mind and perform coronary angiography when necessary. Continued evaluation of coronary lesions and optimal selection of therapy is essential in these patients.

要 約

無症候性血栓性閉塞を認めた川崎病冠動脈瘤の長期観察の1例

松田 央郎 橋本 信行 鈴木 健吾 青柳 秀史 明石 嘉浩
川崎 健介 土屋 勝彦 小澤 敦 長嶋 淳三 武者 春樹

症例は20歳，男性．2歳9ヵ月のときに川崎病を発症した．急性期に施行した冠動脈造影で冠動脈瘤が認められ，アスピリンとチクロピジンの抗血小板療法を継続した．自覚症状は認められず，経過観察したが，発症より17年が経過した20歳時に負荷心筋シンチグラフィで無症候性心筋虚血が認められ冠動脈造影を行った．右冠動脈は99%閉塞しており，左冠動脈からの側副血行が認められた．冠動脈瘤内血栓による閉塞と考えた．川崎病冠動脈瘤の長期予後は不明な点が多い．小児期は無症状で経過し，若年成人で虚血性心疾患を発症する症例がみられ，巨大冠動脈瘤を有する川崎病は定期的な長期フォローアップが重要であると考えられた．

J Cardiol 2005 Sep; 46(3): 113 - 118

References

- 1) Suzuki J: Etiology of coronary artery lesions of Kawasaki disease. *Ann Rev Cardiol* 2002; **2002**: 75 - 80
- 2) Terai M, Honda T, Yasukawa K, Higashi K, Hamada H, Kohno Y: Prognostic impact of vascular leakage in acute Kawasaki disease. *Circulation* 2003; **108**: 325 - 330
- 3) Salice P, Pietrogrande MC, Barbier P, Ghiglia S, Laicini E, Fesslova V: Cardiovascular abnormalities in Kawasaki disease: An Italian prospective study. *Cardiologia* 1998; **43**: 1367 - 1374 (in Italian with Eng abstr)
- 4) Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R: Long-term consequences of Kawasaki disease: A 10-to 21-year follow-up study of 594 patients. *Circulation* 1996; **94**: 1379 - 1385
- 5) Kuramochi Y, Ohkubo T, Takechi N, Fukumi D, Uchikoba Y, Ogawa S: Hemodynamic factors of thrombus formation in coronary aneurysms associated with Kawasaki disease. *Pediatr Int* 2000; **42**: 470 - 475
- 6) Sugiura T, Suzuki K, Sugiura T, Suzuki K, Okato T, Ito Y, Ito S, Suzuki T: A case report of young adult acute myocardial infarction with Kawasaki disease. *Jpn J Interv Cardiol* 2003; **18**: 279 - 283
- 7) Satoh S, Inou T: Ischemic heart disease 31 years after possible Kawasaki disease. *Jpn Circ J* 1996; **60**: 805 - 808
- 8) Suzuki A, Miyagawa-Tomita S, Nakazawa M, Yutani C: Remodeling of artery lesions due to Kawasaki disease: Comparison of arteriographic and immunohistochemical findings. *Jpn Heart J* 2000; **41**: 245 - 256
- 9) Iemura M, Ishii M, Sugimura T, Akagi T, Kato H: Long term consequences of regressed coronary aneurysms after Kawasaki disease: Vascular wall morphology and function. *Heart* 2000; **83**: 307 - 311
- 10) Inaba R: Screening and follow up of coronary lesion with Kawasaki disease in adulthood: About the utility of magnetic resonance coronary angiography. *Progress in Medicine* 2002; **22**: 1619 - 1623 (in Jpn with Eng abstr)
- 11) Flacke S, Setser RM, Barger P, Wickline SA, Lorenz CH: Coronary aneurysms in Kawasaki disease detected by magnetic resonance coronary angiography. *Circulation* 2000; **101**: 156 - 157
- 12) Greil GF, Stuber M, Botnar RM, Kissinger KV, Geva T, Newburger JW, Manning WJ, Powell AJ: Coronary magnetic resonance angiography in adolescents and young adults with Kawasaki disease. *Circulation* 2002; **105**: 908 - 911
- 13) Habon T, Toth K, Keltai M, Lengyel M, Palik I: An adult case of Kawasaki disease with multiplex coronary aneurysms and myocardial infarction: The role of transesophageal echocardiography. *Clin Cardiol* 1998; **21**:

- 529 - 532
- 14) Kato H, Baba K, Harada K, Hamaoka T, Gato H, Tsuda E, Uemura S, Saji T, Akagi S, Ishii M, Ogawa S, Echigo S, Yamaguchi T, Ueno T: A guide for coronary intervention for coronary sequela of Kawasaki disease. *Shinzo* 2002; **34**: 587 - 593 (in Japanese)
- 15) Ueno T, Kai H, Ikeda H, Ichiki K, Hashino T, Imaizumi T: Coronary stent deployment in a young adult with Kawasaki disease and recurrent myocardial infarction. *Clin Cardiol* 1999; **22**: 147 - 149
- 16) Tanaka H, Narisawa T, Hirano J, Suzuki T, Asano F, Ebato B, Takeyama Y, Takaba T: Coronary artery bypass grafting for coronary aneurysms due to Kawasaki disease. *Ann Thorac Cardiovasc Surg* 2001; **7**: 307 - 310
- 17) Rahmatullah SI, Khan IA, Nair VM, Vasavada BC, Sacchi TJ: Bifurcating aneurysm of the left main coronary artery involving left anterior descending and left circumflex arteries: A case report. *Angiology* 1999; **50**: 417 - 420
- 18) Hayashida N, Tayama E, Teshima H, Kawara T, Aoyagi S: Coronary artery bypass grafting in an adult case with Kawasaki disease. *Ann Thorac Cardiovasc Surg* 2002; **8**: 47 - 50