Korean Journal of Pediatrics Vol. 48, No. 8, 2005

□ Case Report □

Giant Coronary and Axillary Aneurysms in an Infant with Kawasaki Disease Associated with Thrombocytopenia

Sei Young Seo, M.D., Jin Hee Oh, M.D., Jong-Hyun Kim, M.D.
Ji-Whan Han, M.D., Kyung-Yil Lee, M.D. and Dae Kyun Koh, M.D.

Department of Pediatrics, College of Medicine, The Catholic University of Korea, Seoul, Korea

Kawasaki disease (KD) is a leading cause of acquired heart disease in children. Yet the etiology of KD is still unknown and diagnosis depends on the exclusion of other diseases and the clinical manifestations meeting the defined criteria. Young infants frequently show atypical clinical courses and are frequently complicated with coronary aneurysms. Some cases show thrombocytopenia, which is known as one of the risk factors for complications with coronary aneurysms. So, a high index of suspicion is the most important factor for the diagnosis of KD in very young infants or adolescents whose clinical courses are equivocal. We report herein on a case of KD in an 80-day-old female infant with fever and seizure with bloody stool; laboratory findings were those of sepsis with disseminated intravascular coagulopathy. In spite of aggressive treatments, fever and thrombocytopenia persisted for two weeks and huge coronary aneurysms developed at the third week in all three major coronary arteries; the diameter of the right one was as large as the aortic annulus. Three months later, huge pulsatile masses developed in both axillas; these were found to be huge axillary aneurysms defined very clearly on multi-detector CT scan. She has been under follow up with antiplatelets and anticoagulation therapy with poor regression of the aneurysms. **(Korean J Pediatr 2005;48:901-906)**

Key Words : Mucocutaneous lymph node syndrome, Infant, Thrombocytopenia, Coronary aneurysm, Axillary aneurysm

Introduction

Kawasaki disease (KD) is a systemic vasculitis and it is currently a leading cause of acquired heart disease in children. Although over thirty seven years have past since the first report of KD in 1967 by Kawasaki[1], the etiology is still unknown and the diagnosis still depends on the clinical manifestations meeting the defined criteria, in addition to excluding any other possible illness. Reports on KD in extreme ages have recently been increasing and these cases have shown atypical clinical presentations[2]. The diagnosis of KD is not so easy in these patients; consequently, the very young infants or patients in late childhood with KD are frequently complicated with coronary aneurysms[3]. Cases of KD have been reported even at as early as the neonatal period[4]. Thrombocytopenia is rarely observed during the acute phase, and this is known for one of the risk factors of coronary arterial aneurysm[5, 6]. There have been a few Korean reports on KD with thrombocytopenia since 1995 by Kim et al[7]. There has been no Korean report of KD with prolonged thrombocytopenia complicated with axillary aneurysm as an extracoronary manifestation also an internationally rare condition. We report herein on a case of KD in a female infant. At 80 days after birth, her initial clinical manifestations were those of severe sepsis with disseminated intravascular coagulopathy (DIC) complicated with giant aneurysms in the coronary arteries and both axillary arteries, and these occurred in spite of our aggressive early treatment with intravenous gammaglobulin and steroids.

접수 : 2005년 4월 18일, 승인 : 2005년 6월 1일
책임저자 : 오진희, 가톨릭대학교 의과대학 소아과학교실
Correspondence : Jin Hee Oh, M.D.
Tel : 031)249-7320 Fax : 031)257-9111
E-mail : Jeany@catholic.ac.kr

Case Report

An 80 day-old-female infant was transferred to our hospital with the chief complaints of bloody stool and seizure

attack. She was treated with antibiotics for three days at a local clinic because of her fever. She looked acutely ill at presentation and she showed bilateral conjunctival injections and red lips. Mild erythematous change at the BCG inoculation site was suspected. The initial laboratory findings showed the following results : hemoglobin 6.8 g/dL, WBC 9,140/mm^3 (segment neutrophils 60%, lymphocytes 15 %, stab-neutrophils 18% and metamyelocytes 3%), platelets 16,000/mm^3, total protein/albumin 3.7/2.5 g/dL, CRP 14 mg/dL, PT/PTT 17.9/55.1 sec and FDP positive, serum ferritin 504 ng/mL (Table 1). She received antibiotics and a transfusion of packed red blood cells under the clinical impression of sepsis with disseminated intravascular coagulopathy. The culture of the cerebrospinal fluid examination was sterile. On the 4th day, rash developed over the whole body. She was studied with echocardiography to rule out KD. We found increased perivascular echogenicity around the coronary arteries and trivial mitral regurgitation. The diameters of the right coronary artery (RCA) and the left main coronary artery (LMCA) were 2 mm. Her laboratory findings were Hb 11.9 g/dL, WBC 13,380/mm^3 (segment neutrophils 79% and stab-neutrophils 11%), platelet 24,000/mm^3 and CRP 7.9 mg/dL. We then administered intravenous gamma globulin (IVIG) (2 gram/kg/day) and aspirin. Her fever was sustained and she got second dose of IVIG (2 gram/kg/day) 3 days after first dose of IVIG, but, remittent fevers were sustained for two weeks in spite of adding oral prednisolone (2 mg/kg/day). The thrombocytopenia continued for 12 days after the onset of fever, and at that time, the diameter of LMCA was 2.37 mm, the left anterior descending artery (LADA) diameter 2.5 mm and the RCA diameter 2.2 mm. With methylprednisolone pulse therapy (30 mg/kg/day for four times every other day) defeverescence was achieved and her platelet counts started to increase, and this happened at the same time as the rapid coronary arterial dilatation. At that time, the platelets were 297,000/mm^3, the total protein/albumin was 6.0/2.9 g/dL and the CRP was 5 mg/dL; a fusiform aneurysm (4.4 mm) in the LAD and in the RCA (6.9 mm) were then found in the echocardiography. We added dipyridamol

Table 1. Summary of the Patient's Results of the Studies, the Clinical Course and Therapy during the Admission

Days of hospitalization	HD 1	2	4	7	9	11	13	16	19	22	40	3 months
Days of febrile illness	FD 4	5	7	10	12	14	17	19	22	25	37	
Fever	+	+	+	+	+	+	−	+	−	−	−	−
Clinical findings other than fever*	3	2	2	2	2	Desquamation	−	−	−	−	−	−
Platelets counts (/mm^3)	16,000	34,000	24,000		32,000	88,000	297,000		549,000	886,000	399,000	
Hemoglobin (gram/dL)	6.8	Transfusion	11.9		10.8	11	9.6		9	8.6	9	
WBC (/mm^3)	9,140		13,380		12,000	16,800	22,700		2,400	13,250	7,710	
Stab neutrophils (%)	18		11		2		6		8			
CRP (mg/dL)	14		7.9		10.3		5		10.5	11.6	0.87	
FDP	+		+		+							
Echocardiography												
RCA (mm)			Trivial mitral regurgitation		2.2			6.9	10 (giant)	11.4		???
LAD (mm)					2.5			4.4	5.3	6.5		
IVIG (2 g/kg/d)			(2 g/kg)	(2 g/kg)								
Prednisolone (2 mg/kg)†					⇒	⇒	⇒	⇒				
Solumedrol (30 mg/kg)‡									⇒	⇒		
Aspirin and dipyridamol			high dose	⇒	⇒	⇒	Low dose	⇒	⇒	⇒	⇒	⇒
Warfarin								⇒	⇒	⇒	⇒	⇒
RBC scan										Checked		
Tl-scan											Checked	
MD-CT												Checked

* Clinical findings other than fever for the diagnosis of KD : bilateral bulbar conjunctival injection, changes in the mucosa of oropharynx, edema and/or erythema of the hands and feet, polymorphous rash, cervical adenopathy
† Oral administration of prednisolone daily for 8 days
‡ Pulses of intravenous methylprednisolone every other day for 4 administrations

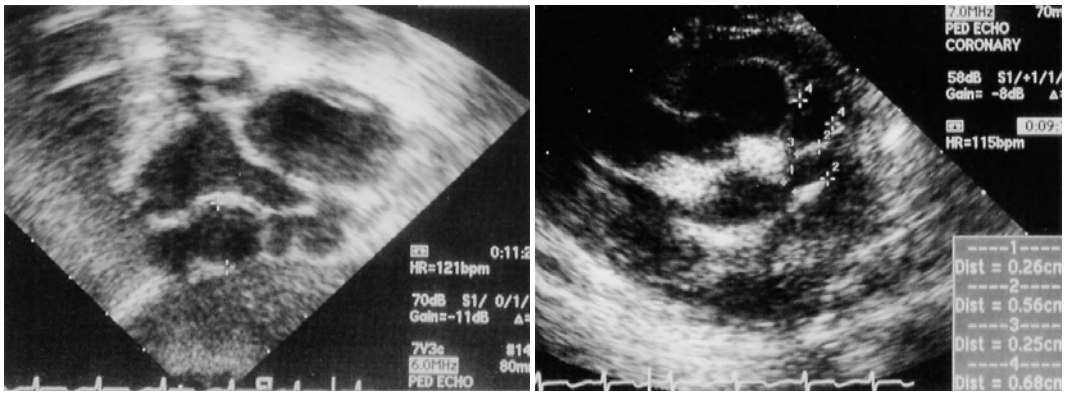

Fig. 1. The echocardiographic findings at the 18th day of admission show a giant aneurysm at the right coronary artery that was as large as the aortic annulus, and fusiform aneurysm in left coronary arteries are also shown.

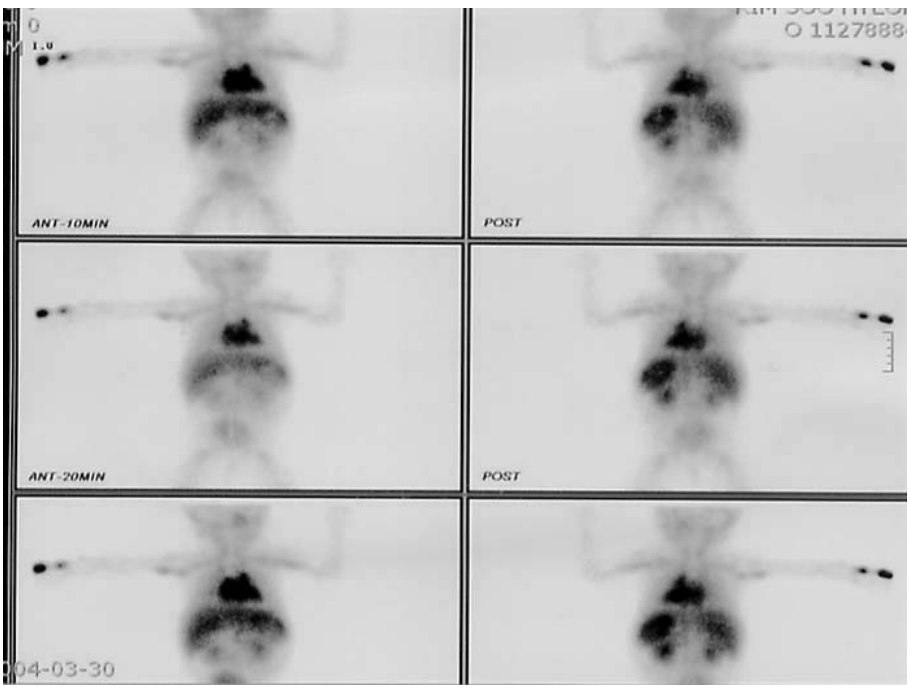

Fig. 2. Axillary aneurysms are suspected on the RBC scan at 20 days after admission.

andwarfarin to treat any possible coronary thrombosis. At the 3rd week the RCA was very tortuous with diffuse beaded appearance; the RCA diameter was 10 mm and that of the aorta was 11.2 mm, and the LAD diameter was 5.3 mm (Fig. 1). Twenty five days after the onset of fever, her platelet count was 806,000/mm^3 and the CRP was 11.6 mg/dL. She was checked with a Tc-99m RBC radionuclide scan at 20 days to search for extracardiac aneurysms, and dilatations were suspected in both axillary arteries (Fig. 2). The patient was finally discharged with aspirin, dipyridamol and warfarin. Echocardiography after discharge showed a diffuse giant aneurysm in the RCA (11 mm in diameter) and there was no evidence of ischemia suspected on the laboratory tests, the ECG and the Thallium-201 adenosine SPECT. Three months later, huge pulsatile masses developed in both axillas (Fig. 3A). These were found to be huge axillary aneurysms on multi-detector CT (MDCT) scan in which the aneurysmal configuration was defined very clearly (Fig. 3B). She has been under follow up care for 12 months with no evidence of thrombosis in the coronary and axillary arteries but, shows poor regression of the aneurysms in the study with echocardiography.

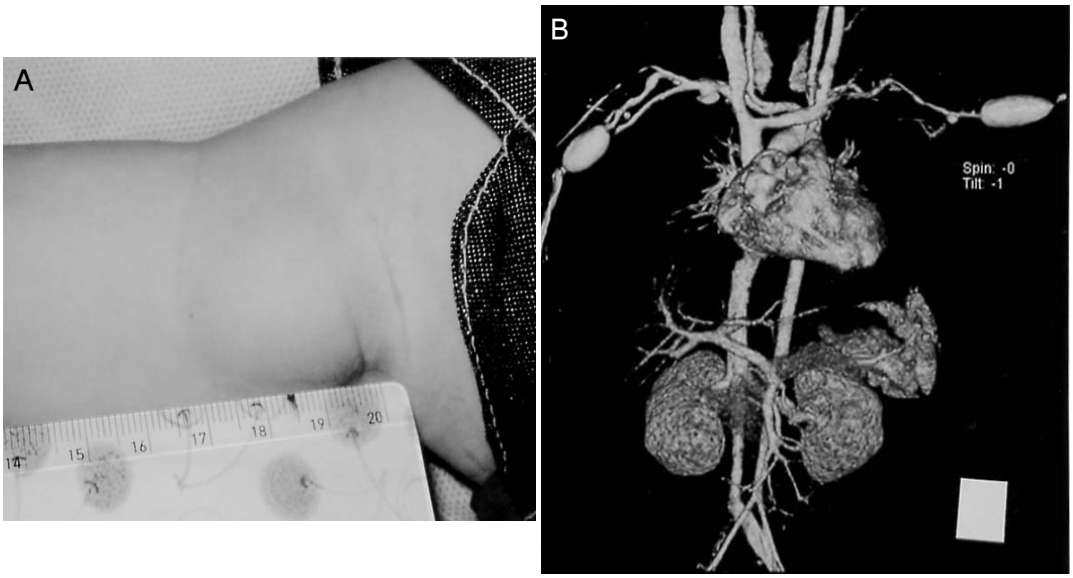

Fig. 3. (A) Pulsatile axillary mass at the right axilla is shown. **(B)** Multi-detector computed tomogram clearly shows axillary arterial aneurysms.

Discussion

The reports on cases of KD at extremes of age have increased these days, and these cases frequently show cardiac complications[3]. Patients with KD, and especially for patients younger than 3 months and older than 5 years, they more frequently show coronary complications than those patients who are at the usual age for the KD illness. This is believed to happen because it is difficult to differentiate a septic condition resulting from other acute diseases from KD. Our patient was younger than 3 months after birth and looked as if suffering from a sepsis caused by a certain microorganism. Although she showed erythema at the BCG site and red lips when admitted, she looked critically ill and, furthermore, the severe anemia and thrombocytopenia, and laboratory findings of DIC for two weeks made it very difficult to make a diagnosis of KD. Although she met the incomplete diagnostic criteria for KD, we examined her with echocardiography on the fourth day of admission because of the erythema over the BCG site, which is known as one of the strong diagnostic clues for infantile KD[8, 9]. The echocardiography showed trivial mitral regurgitation and increased perivascular echogenicity around the coronary arteries, so we started IVIG and high dose aspirin.

Thrombocytopenia in the acute phase is known as one of the potent risk factors for the coronary complications seen in KD[5, 10]. Our patient showed thrombocytopenia coincident with her fever for 12 days in spite of two doses of IVIG (2 gram/kg/day each) 3 days apart and the oral prednisolone therapy, and these treatments led to a transient defeverescence. After the intravenous methylprednisolone pulse therapy, definite defeverescence was achieved, and at that moment the thrombocytosis started, and this was coincident with the dilatation of the coronary arteries. That means that the acute phase of KD in this patient was a little longer than that has been reported before, and it was not successfully treated with IVIG and steroids. The children who are unresponsive to the conventional treatment present a challenge. The levels of tumor necrosis factor-alpha and many other cytokines are known to peak during the acute and subacute phase of KD, especially in those children who develop coronary artery aneurysms[11]. Diverse modalities of immune modulation therapy including methylprednisolone and cyclophosphamide are currently being used to treat refractory KD[12].

During the prolonged thrombocytopenia and the intermittent fever, dilatations of coronary arteries were just mild to 2 mm in diameter, and we should take into consideration of more strict definition of coronary dilatation in regards to the body surface area of the infant[13, 14]. Huge coronary aneurysms were finally developed at the third week in all three major coronary arteries and the diameter of the right one was as large as that of the aortic annulus. Usually coronary arterial aneurysms in KD occur in 25% of un-

treated cases and in about 4% of patients who are treated with IVIG and high dose aspirin. Weiss et al. reported a 3-year-old male with KD and giant coronary artery aneurysms who was unresponsive to multiple doses of IVIG and methylprednisolone, and then treated with infliximab[15]. They reported that the first dose of treatment with infliximab made him defeverescent and his laboratory measures improved.

Extracardiac lesions have been usually found incidentally on the angiogram or the abdominal sonogram during the chronic phase. It's been reported that 1.6% to 2.2% of the KD patients show aneurysms in the axillary, iliac and renal arteries[16]. There has been a report on a case with severe extracardiac aneurysm that resulted in gangrene[17]. We tried to search for extracoronary arterial lesions with a RBC scan initially at the 3rd week in her acute phase, but the image was poor. Three months later, huge pulsatile masses developed in patient's axilla and these corresponded to the lesions suspected on the scan. They were found to be axillary aneurysms on the MDCT.

MDCT can be a good alternative diagnostic modality for the detection of cardiac and extracardiac KD complications. MDCT has advantages in that it is a non-invasive modality that can be checked during the acute phase with a briefer running time than sonogram (it requires only a few seconds), but there are disadvantages of poor resolution in the case of patients with tachycardia or arrhythmia, and there is hazard of exposure to radiation. Its diagnostic specificity is known for over 90%. Sohn et al. reported that it may be able to replace conventional angiography for follow up cases with coronary artery disease in the future[18].

Brenner et al.[19] reported three fatal KD cases of 3 month or 5 month old patients having multiple aneurysms in their coronary arteries and extracoronary arterial aneurysm with peripheral gangrene, and these patients died following a myocardial infarction, despite multiple doses of IVIG and high dose aspirin and steroids. The patient we report herein treated with dipyridamol and warfarin from the point that the diameter of RCA was 6.9 mm, and there has been no evidence of thrombosis or ischemia on the laboratory findings and the thallium-201 dipyridamol scan till now for 1 year.

Because the patient is a very young infant, sometimes she suffers from coagulopathy due to warfarin therapy and pain with frequent blood sampling to maintain the International Normalized Ratio (INR) of the prothrombin time. Her chief complaints of bloody stool and seizure attack at the time of admisson are suspected to be very rare extracardiac complications of KD[20]. Young infants frequently show atypical clinical courses and the cases are frequently complicated with coronary aneurysms; so, a high index of suspicion is the most important factor for the diagnosis, and early intervention with aggressive treatment in acute phase of KD is recommended.

한 글 요 약

혈소판 감소증이 지속된 영아 가와사끼병 환아에서 발생한 거대관상동맥류와 액와동맥류

가톨릭대학교 의과대학 소아과학교실

서세영 · 오진희 · 김종현 · 한지환 · 이경일 · 고대균

가와사끼병은 소아 연령에서 발병하는 급성 전신성 혈관염으로 현재 소아 후천성 심질환의 가장 흔한 원인이다. 아직 원인 불명이고 진단도 여전히 임상 증상에 의존하고 있는데, 최근 비호발 연령의 환자 및 비전형적 가와사끼병의 증례 보고와 이들에서 빈발하는 관상 동맥 합병증의 보고가 증가되고 있다. 관상동맥 합병증의 위험 인자 중 하나인 지속적 발열과 혈소판 감소증은 매우 어린 영아에서 간혹 초기 감별 진단을 어렵게 만든다. 저자들은 패혈증으로 전원된 3개월 여아에서 초기에 정맥글로불린과 스테로이드 등의 약제로 치료하였으나 빈혈, 혈소판 감소증과 발열이 지속되다 거대 관상 동맥류와 액와 동맥류를 합병한 1례를 보고하는 바이다.

References

1) Kawasaki T. Acute febrile mucocutaneous lymph node syndrome with lymphoid involvement with specific desquamation of fingers and toes in children. Jpn J Allergy 1967;16:178-222.
2) Rosenfeld EA, Corydon KE, Sculman ST. Kawasaki disease in infants less than one year of age. J Pediatr 1995;126:524-9.
3) Newburger JW, Taubert KA, Shulman ST, Rowley AH, Gewitz MH, Takahashi M, et al. Are patients at extremes of age at increased risk for coronary artery involvement in Kawasaki disease? [abstract] Pediatr Res 2003;53:153-7.
4) Tsuchida S, Yamanaka T, Tsuchida R, Nakamura Y, Yashiro M, Yanagawa H. Epidemiology of infant Kawasaki disease with a report of the youngest neonatal case ever reported in Japan. Acta Paediatr 1996;85:995-7.
5) Niwa K, Aotsuka H, Hamada H, Uchishiba M, Terai M, Niimi H. Thrombocytopenia : a risk factor for acute myocardial infarction during the acute phase of Kawasaki disease. Coron Artery Dis 1995;6:857-64.
6) Stanley TV, Grimwood K. Classical Kawasaki disease in a

neonate. Arch Dis Child Fetal Neonatal Ed 2002;86:135-6.
7) Kim HS, Hong YM, Lee SJ. Three cases of Kawasaki disease associated with thrombocytopenia. J Korean Pediatr Soc 1995;38:1686-9.
8) Lee SJ, Kim SJ, Kim HS, Sohn S. Clinical characteristics of Kawasaki disease in infants younger than 3 months of age. J Korean Pediatr Soc 2003;46:591-6.
9) Genizi J, Miron D, Spiegel R, Fink D, Horowitz Y. Kawasaki disease in very young infants : high prevalence of atypical presentation and coronary arteries. Clin Pediatr 2003;42:263-7.
10) Nofech-Mozes Y, Garty BZ. Thrombocytopenia in Kawasaki disease : a risk factor for the development of coronary artery aneurysms. Pediatr Hematol Oncol 2003;20:597-601.
11) Lin CY, Lin CC, Hwang B, Chiang BN. Cytokines predict coronary aneurysm formation in Kawasaki disease patients. Eur J Pediatr 1993;152:309-12.
12) Wallace C, French J, Kahn S, Sherry D. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. Pediatrics 2000;105:E78.
13) Kurotobi S, Nagai T, Kawakami N, Sano T. Coronary diameter in normal infants, children and patients with Kawasaki disease. Pediatr Int 2002;44:1-4.
14) Tan TH, Wong KY, Cheng TK, Heng JT. Coronary normograms and coronary-aorta index : Objective determinants of coronary artery dilatation. Pediatr Cardiol 2003;24:328-35.
15) Weiss JE, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as a novel therapy for refractory Kawasaki disease. J Rheumatol 2004;31:808-10.
16) Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow up study of 594 patients. Circulation 1996;94:1379-85.
17) Tomita S, Chung K, Mas M, Gidding S, Shulman ST. Peripheral gangrene associated with Kawasaki disease. Clin Infect Dis 1992;14:121-6.
18) Sohn S, Kim HS, Lee SW. Multidetector row computed tomography for follow up of patients with coronary aneurysms due to Kawasaki disease. Pediatr Cardiol 2004;25:35-9.
19) Brenner JL, Jadavji T, Pinto A, Trevenen C, Patton D. Severe Kawasaki disease in infants : two fatal cases. Can J Cardiol 2000;16:1017-23.
20) Tizard ET. Complications of Kawasaki disease. Curr Pediatr 2005;15:62-8.