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Four Cases of Kawasaki Syndrome Complicated With Myocarditis

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Background Myocarditis frequently occurs in the acute phase of Kawasaki syndrome (KS), and a few severe cases have been reported. Four cases of myocarditis in KS required additional catecholamine treatment because of severe left ventricular dysfunction (LVD).

Case reports Three cases were relatively older children and 2 cases were complicated with encephalopathy. All 4 developed coronary artery abnormalities during convalescence. There was 1 case of LVD because of prolonged severe inflammation prior to administration of intravenous immunoglobulin (IVIG). The remaining 3 patients had normal values for ejection fraction before the administration of IVIG but decreased values (42–51%) and increased C-reactive protein levels after IVIG administration. These cases demonstrate an association between myocarditis in KS and severe or worsened inflammation.

Conclusions Even with prior normal echocardiography, careful observation of cardiac function may be necessary for patients with KS, especially older children, when inflammation deteriorates after administration of IVIG. (*Circ J* 2006; **70:** 202–205)

Key Words: Echocardiography; Encephalopathy; Kawasaki syndrome; Myocarditis

Myocarditis frequently occurs in the acute phase of Kawasaki syndrome (KS) and may be transient[1,2] but there are a few cases of severe myocarditis[3–8] We present 4 cases of myocarditis in KS that required additional catecholamine treatment for severe left ventricular dysfunction (LVD).

Case Reports (Table 1, Fig 1)

Patient 1 (Fig 1A) A 7-year-old-girl (height 115 cm, body weight 20 kg) was admitted to a general hospital because of 4 days of persistent fever and right cervical adenopathy (white blood cell count (WBC) 22,600/μl, C-reactive protein (CRP) 10 mg/dl). Rash and edema of the hands and feet developed on the 5th day of illness. The echocardiography revealed a normal value of ejection fraction (EF) (69%). On the 8th day, the fever was persisting and she was referred to us. Physical examination revealed a cardiac gallop rhythm, nasal alar breathing, eyelid edema, bilateral conjunctival congestion, strawberry tongue, right cervical adenopathy and edema of the hands and feet. The liver was palpable at 7 cm below the right costal margin. The results of laboratory tests were: WBC 18,700/μl, hemoglobin (Hb) concentration 9.4 g/dl, hematocrit (Hct) 32.4%, platelets 18–10^4/μl, CRP 24 mg/dl, mild liver dysfunction (aspartate aminotransferase (AST) 51 IU/L, alanine aminotransferase (ALT) 81 IU/L), hyponatremia (129 mmol/L), and hypoproteinemia (total protein 4.6 g/dl, albumin 2.0 g/dl). Hypotension became obvious with pulmonary edema and a decreased EF (44%), which were noted on chest X-ray and echocardiography at admission. With a diagnosis of KS with myocarditis, we started treatment with aspirin (30 mg·kg^{-1}·day^{-1}), intravenous immunoglobulin (IVIG: 2 g/kg for 24 h) and dopamine (3 μg·kg^{-1}·min^{-1}). Despite the medication, the hypotension did not improve and sufficient urinary output was not obtained. Dobutamine (3 μg·kg^{-1}·min^{-1}) and diuretics were added and her hypotension and oliguria improved. The fever subsided on the 10th day, but re-emerged the next day. Additional IVIG (2 g/kg for 24 h) was administered and the fever subsided on the 12th day. Giant coronary aneurysms were observed during convalescence.

Patient 2 (Fig 1B) A 6-year-old-girl (height 117 cm, body weight 21 kg) was admitted to Kagoshima Medical Association Hospital because of 3 days of persistent fever and right cervical adenopathy (WBC 30,700/μl, CRP 23 mg/dl). Altered consciousness was observed on the 4th day of illness. Bilateral conjunctival congestion, strawberry tongue and rash developed on the 5th day (WBC 15,800/μl, CRP 23 mg/dl). Echocardiography revealed normal coronary arteries and normal EF (64%). With the diagnosis of KS, IVIG (2 g/kg for 24 h) was started. Because of liver dysfunction, flurbiprofen (4 mg·kg^{-1}·day^{-1}) instead of aspirin was also started. Although the fever subsided on the 6th day, the serum level of CRP increased (26 mg/dl) and EF decreased (48%). Hypotension and oliguria were also observed together with increases in blood urea nitrogen (BUN) (55 mg/dl) and creatinine (1.3 mg/dl). Water limitation, dopamine (2 μg·kg^{-1}·min^{-1}) and diuretics were started. Fever re-emerged and she was referred to us on the 9th day of illness. Her level of consciousness had improved at

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Table 1 Summary of Findings in 4 Cases of KS With Myocarditis

	Patient no.			
	1	*2*	*3*	*4*
Age (years)/sex	*7/F*	*6/F*	*2/M*	*7/M*
Findings of heart failure	*Hypotension (65/42 mmHg), hepatomegaly, gallop rhythm, oliguria*	*Hypotension (72/60 mmHg), hepatomegaly, oliguria*	*Weight gain*	*Hypotension (74/54 mmHg), gallop rhythm*
Infusion volume (ml·kg^{-1}·day^{-1})	*70*	*40*	*50*	*40*
CTR (%)	*65*	*52*	*54*	*60*
ECG findings	*Flat T in $V_{4,5}$*	*Negative T in V_{4-6}*	*Flat T in V_{4-6}*	*Normal*
EF/FS (%)	*44/18*	*48/23*	*51/25*	*42/16*
%LVEDD	*115*	*112*	*103*	*113*
Pericardial effusion	+	–	+	+
MR/TR	+/+	+/+	+/+	+/–
Encephalopathy	–	+	–	+
CK (IU/L)	*57*	*671*	*30*	*1,186*
CK-MB (IU/L)		*16*		*13*
CAA at convalescence	*Giant aneurysm*	*Dilatation*	*Moderate aneurysm*	*Small aneurysm*

Infusion volume per day included intravenous immunoglobulin; CTR, cardiothoracic ratio; ECG, electrocardiogram; EF, ejection fraction; FS, fractional shortening; %LVEDD, percent of predicted left ventricular end-diastolic dimension; MR, mitral regurgitation; TR, tricuspid regurgitation; CK, creatine kinase; CAA, coronary artery abnormalities.

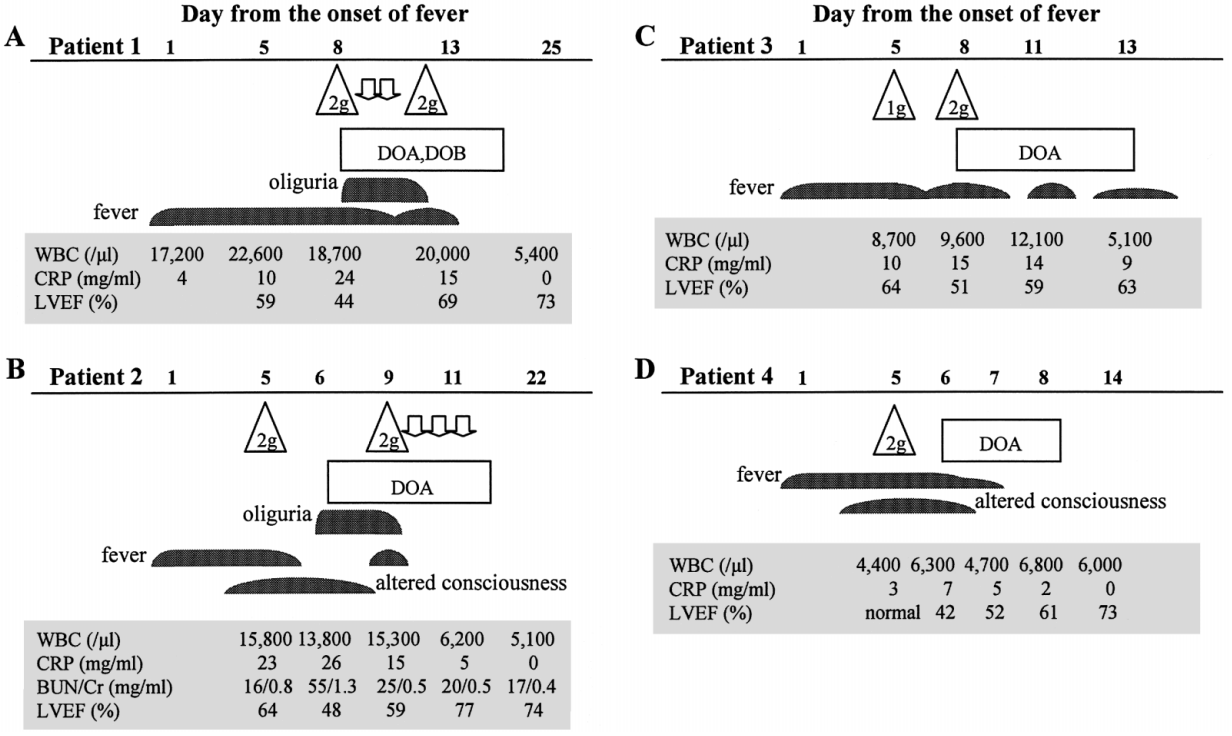

Fig 1. Clinical course of (A) patient 1, (B) patient 2, (C) patient 3, and (D) patient 4. DOA, dopamine; DOB, dobutamine; WBC, white blood cell; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; BUN, blood urinary nitrogen; Cr, creatinine; △, intravenous immuno-globulin; ⇩, albumin.

referral. Neither cardiac murmur nor gallop rhythm was heard by auscultation. She had bilateral conjunctival congestion, red and fissured lips, strawberry tongue and right cervical adenopathy. The edge of the liver was palpable below the right costal margin. The results of laboratory tests were: WBC 16,400/μl, Hb concentration 9.0 g/dl, Hct 27.5%, platelets 23×10^4/μl, CRP 20 mg/dl, BUN 24.7 mg/dl, creatinine 0.5 mg/dl, total protein 7.3 g/dl, and albumin 2.6 g/dl. After administration of IVIG (2 g/kg for 24 h), the fever subsided and the EF normalized rapidly. Mild dilatation of the coronary arteries was observed during convalescence.

Patient 3 (Fig 1C) A 2-year-old-boy (height 89 cm, body weight 13 kg) was admitted to Izumi City Hospital because of 5 days of persistent fever, rash, strawberry tongue, bilateral conjunctival congestion, cervical adenopathy and edema of the hands and feet (WBC 8,700/μl, CRP 10 mg/dl). Echocardiography revealed a normal EF (64%). With the diagnosis of KS, aspirin (30 mg·kg^{-1}·day^{-1}) and IVIG (1 g/kg for 24 h) were started. The fever

Table 2 Reported Cases of Myocarditis in Kawasaki Syndrome

Author	Year of report	Age (years)/sex	Day of initial IVIG	Day of lowest EF	Lowest EF or FS (%)	CRP (mg/dl)	Treatment	CAA
Suzuki et al[3]	1986	9/F	–	7	EF 54	5+	Aspirin	None
Nakatsu et al[4]	1987	4/M	5	6	EF 47	19	Aspirin, IVIG	Giant aneurysm
Senzaki et al[5]	1994	8/M	–	5 or 6	EF 40	26	Flurbiprofen	Moderate aneurysm
Shinohara et al[6]	1999	4/M	NR	4	FS 20	NR	IVIG	Giant aneurysm
Shinohara et al[6]	1999	6/M	NR	6	FS 25	NR	IVIG	NR
Kato et al[7]	2000	12/F	6	5	EF 47	15	Aspirin, IVIG	Moderate aneurysm
Kitano et al[8]	2004	2/F	5	6	FS 19	5	Aspirin, IVIG	None

IVIG, intravenous immuno-globulin; EF, ejection fraction; FS, fractional shortening; CRP, C-reactive protein; CAA, coronary artery abnormalities; NR, not reported.

subsided on the 6th day, but it re-emerged with an increased CRP level (15 mg/dl), weight gain of 450 g, and a decreased EF (51%) on the 8th day. Dopamine (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and additional IVIG (2 g/kg for 24 h) were started and the fever subsided on the 10th day. However, the fever re-emerged and he was referred us on the 11th day of illness. Neither cardiac murmur nor gallop rhythm was heard by auscultation. He had bilateral conjunctival congestion, red and fissured lips and edema of the hands and feet. The results of laboratory tests were: WBC 12,100/μl, Hb concentration 9.8 g/dl, Hct 29.8%, platelets $35\times10^4/\mu l$, CRP 14 mg/dl, AST 53 IU/L, ALT 50 IU/L. We stopped the antibiotic that had been administered prior to referral, and his fever began to subside gradually. The EF had improved by the 11th day. Moderate coronary aneurysm was observed during convalescence.

Patient 4 (Fig 1D) A 7-year-old-boy (height 122 cm, body weight 28 kg) was admitted to Saiseikai Sendai Hospital because of 3 days of persistent fever, right cervical adenopathy, bilateral conjunctival congestion, erythema of the oropharynx and altered consciousness. Neither cardiac murmur nor gallop rhythm was heard by auscultation at admission. The results of laboratory tests were: WBC 4,480/μl, Hb concentration 12.4 g/dl, Hct 35.9%, platelets $21\times10^4/\mu l$, and CRP 3 mg/dl. Echocardiography revealed normal coronary arteries and normal left ventricular (LV) wall motion. Electroencephalography (EEG) revealed generalized slow waves (5–7 Hz) and computed tomography scan was normal. Cerebrospinal fluid examination demonstrated a cell count of 17/3, protein level of 20 mg/dl, and glucose level of 53 mg/dl. With the diagnosis of KS, aspirin (30 $mg \cdot kg^{-1} \cdot day^{-1}$) and IVIG (1 g/kg for 24 h) were started on the 5th day. Although his fever began to subside the next day, the CRP level increased (7 mg/dl) and the EF decreased (42%), together with the development of hypotension and gallop rhythm. Dopamine (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was used to control the acute heart failure. The fever subsided and his level of consciousness improved on the 7th day and the EF improved on the 8th day. The slow waves on EEG improved during convalescence and there was a small coronary aneurysm.

Flat or negative T waves in leads V_{4-6} were observed on the electrocardigrams of patients 1–3, and became positive during convalescence. Mitral and tricuspid regurgitation observed during the acute phase disappeared in all patients during convalescence.

Discussion

These 4 cases of myocarditis in association with KS showed severe LVD. Three patients were older (7, 6, 7 years old) than typical cases of KS and 2 cases were complicated with encephalopathy. All 4 cases showed coronary artery abnormalities during convalescence. Patient 1 had LVD on the 8th day of illness because of severe prolonged inflammation. The remaining 3 cases had normal values of EF before administration of IVIG, but showed decreased values with increased levels of CRP after IVIG. The LV wall motion in all cases improved rapidly with administration of a small dosage of catecholamine.

Myocarditis is present in at least 50% of patients with KS;[2] so mild LVD is not rare. Shinohara et al reported decreased values of the shortening fraction of the left ventricle (≤0.28) in 8 of 107 patients (7.7%)[6] and Adrian et al reported a higher incidence of patients with LVD.[9] In that study, the average shortening fraction of 25 patients with KS prior to treatment was 28.5±6.0%, which was significantly lower than age-matched controls (p=0.0001), and of these 25 patients, 14 (56%) were diagnosed with abnormal contractility (mean-2SD). After treatment with IVIG, their shortening fraction increased significantly within 24 h. Those findings indicated that clinical or subclinical LVD may exist during the acute phase of KS and improved with IVIG treatment. The therapeutic effects of IVIG in KS (normalization of acute-phase reactant and reducing the prevalence of coronary disease)[2] are well known and in addition, IVIG improves myocardial function in patients with acute KS.[10] A variety of cytokines, including gamma interferon, tumor necrosis factor alpha, interleukin-1 and -6, are elevated in the sera of patients with acute KS[2] and may contribute to cardiac myocyte contractile dysfunction.[11] IVIG therapy decreases the levels of these cytokines and thus improves myocardial function. On the other hand, adverse effects of IVIG, such as rigors, pruritus, hypotension, urticaria, and nausea, are also well known,[12] and IVIG treatment may also increase blood viscosity which has been associated with cardiovascular thromboembolism,[13,14] and may impair capillary blood flow.[15] With the volume effect of IVIG, blood viscosity may be a potential risk factor for cardiac output. As the therapeutic effect of IVIG in KS is greater than its adverse effects, clinical or subclinical LVD may improve after IVIG. However, of the present patients showed normal values of EF at admission but decreased values after IVIG administration, as well as increased levels of CRP, and LVD emerged. We consider that the deterioration of inflammation and LVD are related to IVIG administration.

Shinohara et al reported that the age of patients with LVD tended to be higher (45±21 months) than those without (28±24 months)[6] and this tendency has been observed in patients with myocarditis reported previously (Table 2)[3–5,7,8] and also in the present report; 9 of 11 patients with myocar-

ditis were 4 years of age or older.

Two of the present cases were complicated with encephalopathy. Takagi et al examined 5 KS patients complicated with encephalopathy and reported that significantly longer CRP positive duration and significantly higher incidence of coronary artery abnormalities were observed in these patients compared with those without encephalopathy.[16] They concluded that the encephalopathy of KS is the result of vasculitis of microvessels (small arteries, arterioles, capillaries, and venules). Thus, the development of encephalopathy in patients with KS indicates severe vasculitis. The myocarditis in KS is also related to severe vasculitis, so careful observation of LV function may be necessary in patients with KS when they have altered levels of consciousness.

Viral myocarditis is considered to be the result of injury to the myocardium by direct infiltration of the virus, as well as the cellular and humoral immune response.[17] However, the myocarditis in KS is characterized by infiltration of inflammatory cells from the coronary arteries to the interstitial myocardium, and myocardial necrosis is infrequently observed, which might explain the rapid clinical improvement of the present cases.

Conclusions

We report 4 cases of myocarditis with severe LVD in the acute phase of KS. LVD in all cases improved rapidly after treatment with a small dosage of catecholamine. Even with prior normal echocardiography, careful observation of cardiac function may be necessary for patients with KS, especially older children, when inflammation deteriorates after administration of IVIG.

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