Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 44, No. 6, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.01.055

Serum Levels of Interleukin-10 on Admission as a Prognostic Predictor of Human Fulminant Myocarditis

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OBJECTIVES We assessed the significance of serum cytokine levels in patients with fulminant myocarditis.

BACKGROUND Although many investigations have demonstrated the crucial role of cytokines in the development of myocarditis, it remains uncertain whether serum levels of cytokines enable one to predict the prognosis of human myocarditis, especially concerning cardiogenic shock (CS) requiring a mechanical cardiopulmonary support system (MCSS).

METHODS We studied 22 consecutive patients with fulminant myocarditis and compared them with 15 patients with acute myocardial infarction (AMI) requiring MCSS. The patients with myocarditis were classified into three groups: eight patients with CS requiring MCSS on admission (group 1); six patients who unexpectedly lapsed into CS requiring MCSS more than two days after catecholamine had been initiated (group 2); and eight patients without MCSS (group 3). Furthermore, 14 patients with myocarditis requiring MCSS were divided into a fatal group (n = 5) and a survival group (n = 9). Biochemical markers, including serum cytokine levels and hemodynamic variables on admission, were analyzed.

RESULTS Serum levels of interleukin (IL)-10 and tumor necrosis factor-alpha, but not other cytokines, were significantly higher in myocarditis than in AMI. Only serum levels of IL-10 were significantly higher in group 1 and 2 than in group 3 (49.1 ± 37.5/20.7 ± 17.6 pg/ml vs. 2.4 ± 1.1 pg/ml; p = 0.0008/0.0012). Serum IL-10 levels were also significantly higher in the fatal group than in the survival group with myocarditis (74.0 ± 27.0 pg/ml vs. 16.4 ± 8.8 pg/ml; p = 0.003).

CONCLUSIONS Serum IL-10 levels on admission enabled one to predict subsequent CS requiring MCSS and mortality of fulminant myocarditis patients. (J Am Coll Cardiol 2004;44:1292–7) © 2004 by the American College of Cardiology Foundation

McCarthy et al. (1) and Lieberman et al. (2) have presented remarkable reports that the prognosis of patients with fulminant myocarditis, who suffered from cardiac dysfunction and required intensive circulatory supports, is better than that of patients with non-fulminant myocarditis. A monophasic clinical course, that is, prompt recovery upon conclusion of the acute phase often seen in fulminant myocarditis, may contribute to a favorable outcome (3). The

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point to be argued in the aforementioned studies is that most of the included patients with fulminant myocarditis required only high-dose catecholamine without a mechanical cardiopulmonary support system (MCSS). Although the use of MCSS has currently been widespread to maintain hemodynamics in patients with fulminant myocarditis who lapse into cardiogenic shock (CS) without effective response of the administration of high-dose catecholamine (4,5), the prognosis of such patients requiring MCSS is still not satisfactory (6). The fundamental concept to improve survival in patients with fulminant myocarditis with deteriorated hemodynamics despite catecholamine use must be appropriately introduced together with adjustment of MCSS facilitating the recovery from circulatory failure (6). However, there have been no reports concerning the clinical parameters detected in the acute phase to predict whether MCSS is required in cases with fulminant myocarditis.

The significance of cytokines in the pathomechanism of human myocarditis remains uncertain. It has been demonstrated in experimental myocarditis that cytokines such as interleukin (IL)-10, IL-12, tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma play a crucial role in the development of myocarditis (7–12). In addition, some reports have suggested that serum levels of cytokines were elevated in human myocarditis (13,14). These findings imply that cytokines may be a candidate for determining the prognosis in acute myocarditis.

In the present study, we examined whether serum cytokines levels as well as various clinical parameters, including

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Manuscript received July 7, 2003; revised manuscript received December 19, 2003, accepted January 20, 2004.

Abbreviations and Acronyms

AMI = acute myocardial infarction
BNP = brain natriuretic peptide
CS = cardiogenic shock
cTnT = cardiac troponin T
HF = heart failure
IFN = interferon
IL = interleukin
MCSS = mechanical cardiopulmonary support system
TNF = tumor necrosis factor

hemodynamic variables and biochemical laboratory data on admission, enable one to determine the subsequent prognosis in fulminant myocarditis patients.

METHODS

Subjects. Twenty-two consecutive patients admitted to Kitasato University Hospital during 1995 to 2001, classified as fulminant myocarditis according to the criteria of Lieberman et al. (2), were included in this study. All of the patients were diagnosed as having active myocarditis histopathologically either from endomyocardial biopsy or autopsy according to the Dallas criteria (15). Table 1 shows the individual baseline data of patients with fulminant myocarditis included in this study. A viral study was performed in nine patients by measurement of neutralizing antibody titers in a paired sample. Three patients were positive for Coxsackievirus B3. Histologic examination demonstrated that only one (5%) or two patients (9%) were diagnosed as having giant cell myocarditis or eosinophilic myocarditis, respectively, whereas the rest of the patients (86%) were diagnosed as having lymphocytic myocarditis. All of the patients suffered from flu-like symptoms one to two weeks before the distinct onset of cardiac symptoms and received treatment with high-dose catecholamine immediately after hospital admission owing to circulatory failure.

Based on the clinical course, the present study population of patients with fulminant myocarditis was classified into three groups as follows: eight patients who had already lapsed into CS and required MCSS with high-dose catecholamine on admission (group 1); six patients who unexpectedly lapsed into CS requiring MCSS more than two days after high-dose catecholamine had been initiated (group 2); and eight patients who required only high-dose catecholamine but not MCSS (group 3). In addition, patients requiring MCSS were divided into a fatal group (n = 5) and a survival group (n = 9). Non-survivors died from refractory heart failure (HF) or fatal arrhythmia, whereas all of the survivors could be discharged with improvement of cardiac symptoms. The MCSS was introduced according to the therapeutic guidelines from the Scientific Committee of the Japanese Circulation Society (6). Briefly, if the patient did not recover from circulatory failure despite the administration of enough cardiotonic or vasodepressor drugs and the subsequent use of an intra-aortic balloon pump, percutaneous cardiopulmonary support was introduced.

Control subjects were 15 consecutive patients with acute myocardial infarction (AMI) without ventricular rupture, who required MCSS for CS during the disease course. There were 5 non-survivors, who died from CS, and 10 survivors.

Blood sampling and biochemical assays. Blood samples were taken from the radial artery before any therapies on admission. Serum was immediately separated from the blood element by centrifugation at 400 × *g* for 10 min. Aliquots were stored at −80°C until assay. Intra-assay and inter-assay coefficients of variation were <10%.

Levels of serum cardiac troponin T (cTnT) were measured using the third-generation Enzyme cTnT assay (Roche, Indianapolis, Indiana). High-sensitivity assays for C-reactive protein were performed according to methods described by the manufacturer (Behring Diagnostic, Westwood, Massachusetts), and plasma brain natriuretic peptide (BNP) levels were measured with a specific immunoradiometric assay for human BNP (Shionoria, Osaka, Japan). Serum levels of IL-10, IL-12, TNF-alpha, and IFN-gamma were measured according to the methods of the manufacturer of the enzyme-linked immunoabsorbent assay (BioSource, Camarillo, California). The normal upper limit of the assay was as follows: 2 pg/ml for IL-10; 106 pg/ml for IL-12; 3.1 pg/ml for TNF-alpha; and 20 pg/ml for IFN-gamma.

Hemodynamic measurements. Hemodynamic variables, including heart rate, systolic blood pressure, cardiac output, pulmonary capillary wedge pressure, central venous pressure, and venous saturation, were measured together with blood gas analysis using direct pressure monitoring from the radial artery and the Swan-Ganz catheter technique on admission before any therapies were undertaken.

Statistical analysis. Data were statistically analyzed by use of the software program StatView J-5.0 (Abacus Concepts, Berkeley, California). Comparisons of several clinical parameters and serum levels of cytokine between the fulminant myocarditis group and the AMI group, as well as among the subgroups of fulminant myocarditis, were performed with the Mann-Whitney *U* test. Each value is shown as the mean ± SD. We judged that values showed a statistically significant difference at $p < 0.05$.

RESULTS

Mortality of cases with fulminant myocarditis. The mortality of group 1 (4 of 8; 50%) was higher than that of group 2 (1 of 6; 17%). All patients in group 3 survived with improvement of cardiac symptoms during the disease course (Table 1).

Table 1. Individual Baseline Information of Patients With Fulminant Myocarditis on Admission

Case	Age	Gender	Day	Hist	CS on AD	IABP	PCPS	SBP (mm Hg)	CI (min/m^2)	PCWP (mm Hg)	SvO_2 %	CVP (mm Hg)	cTnT (ng/ml)	BNP (pg/ml)	CRP (μg/dl)	IL-10 (pg/ml)	IL-12 (pg/ml)	TNF-α (pg/ml)	Virus	Outcome
1	83	M	4	L	+	on AD	on AD	72	0.9	20	52	14	2.82	520	11,100	70.9	87.9	22.0	n.e.	Fatal
2	77	M	10	L	+	on AD	on AD	70	1.2	22	58	15	4.08	680	17,000	42.3	260.0	55.2	CVB3	Fatal
3	36	F	4	G	+	on AD	on AD	70	1.2	18	58	10	2.42	780	7,395	90.4	280.0	23.8	n.e.	Fatal
4	55	F	8	L	−	p AD	p AD	112	1.9	14	74	8	0.44	160	9,779	56.2	140.0	26.8	CVB3	Fatal
5	60	F	12	L	+	on AD	on AD	80	0.7	28	56	16	4.69	600	11,500	110.0	120.0	54.3	n.e.	Fatal
6	46	M	6	L	+	on AD	on AD	72	1.0	33	56	15	3.99	430	3,500	6.6	7.8	22.3	−	Survival
7	62	M	5	L	−	p AD	p AD	100	1.9	12	77	9	0.66	300	2,390	16.1	11.0	34.2	CVB3	Survival
8	45	M	3	L	−	p AD	p AD	100	2.1	16	78	14	1.97	296	6,777	13.2	28.3	44.2	n.e.	Survival
9	32	M	14	L	−	p AD	p AD	110	1.1	13	60	12	2.6	362	2,225	10.1	25.1	20.7	n.e.	Survival
10	45	F	6	L	+	on AD	on AD	72	1.3	22	58	16	2.32	820	1,350	19.7	174.2	17.2	−	Survival
11	51	M	7	L	+	on AD	on AD	70	0.7	20	58	15	2.82	800	12,000	37.6	191.9	16.2	n.e.	Survival
12	23	M	8	L	−	p AD	p AD	112	2.2	11	77	10	2.57	270	22,124	16.1	19.6	18.6	n.e.	Survival
13	38	F	6	L	−	p AD	p AD	90	2.4	12	78	7	1.1	96	561	12.3	14.9	16.1	n.e.	Survival
14	41	F	3	L	+	on AD	p AD	80	1.2	20	58	13	0.9	123	3,450	15.5	36.2	20.1	n.e.	Survival
15	43	M	12	L	−	−	−	110	1.8	10	70	5	2.38	300	359	2.1	16.0	8.6	n.e.	Survival
16	77	M	10	L	−	−	−	96	2.3	12	78	6	1.29	88	8,156	4.1	22.1	64.2	−	Survival
17	29	F	8	L	+	−	−	80	1.5	15	60	10	1.86	320	7,752	3.1	102.0	60.3	n.e.	Survival
18	17	M	11	L	−	−	−	110	3.6	6	80	3	0.96	50.6	1,531	1.3	87.3	26.5	−	Survival
19	74	M	8	L	−	−	−	152	2.9	7	78	3	0.19	120	309	0.6	20.2	10.2	n.e.	Survival
20	83	F	11	E	−	−	−	100	2.2	12	74	8	1.19	130	5,316	2.6	60.6	35.6	−	Survival
21	33	M	20	E	+	−	−	90	1.2	16	62	13	1.03	270	2,564	2.7	34.0	20.6	n.e.	Survival
22	36	M	5	L	−	−	−	118	3.6	10	76	6	1.11	131	3,201	2.9	56.0	23.3	−	Survival

BNP = brain natriuretic peptide; CI = cardiac index; CRP = C-reactive protein; CS = cardiogenic shock; cTnT = cardiac troponin T; CVB3 = coxsacklevirus B3; CVP = central venous pressure; Day = duration since flu-like symptoms until admission; E = eosinophilic myocarditis; G = giant cell myocarditis; Hist = histology; IABP = intra-aortic balloon pump; IL = interleukin; L = lymphocytic myocarditis; n.e. = not examined; on AD = on admission; p AD = post admission; PCPS = percutaneous cardiopulmonary support; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; SvO_2 = mixed venous saturation; TNF-α = tumor necrosis factor-alpha; − = negative; + = positive.

Table 2. Baseline Characteristics of Fulminant Myocarditis and Acute Myocardial Infarction on Admission

	FMC (n = 14)	AMI (n = 15)	p Value
Age (yrs)	50 ± 17	55 ± 25	NS
Male:female	8:6	13:2	NS
HR (/min)	73 ± 33	99 ± 36	NS
SBP (mm Hg)	86 ± 17	83 ± 24	NS
CI (l/min/m^2)	1.4 ± 0.6	1.2 ± 0.5	NS
PCWP (mm Hg)	18.0 ± 6.0	14.1 ± 5.9	NS
CVP (mm Hg)	12.4 ± 3.0	10.0 ± 4.1	NS
SvO_2 (%)	64.1 ± 10.0	59.2 ± 14.0	NS
Base excess (mEq/l)	−2.9 ± 5.2	−3.4 ± 6.6	NS
Plasma BNP (pg/ml)	410 ± 246	268 ± 338	NS
Serum CRP (μg/dl)	6,466 ± 5,103	2,147 ± 2,897	0.047
Serum Cr (mg/dl)	1.1 ± 0.1	1.3 ± 0.4	NS
Serum IL-10 (pg/ml)	37.0 ± 33.0	13.7 ± 11.4	0.025
Serum TNF-α (pg/ml)	28.0 ± 13.6	8.3 ± 4.6	0.00014

Values are mean ± SEM or number of patients.

AMI = acute myocardial infarction that similarly required mechanical circulatory support; Cr = creatinine; FMC = fulminant myocarditis that lapsed into cardiogenic shock requiring mechanical circulatory support; HR = heart rate; other abbreviations as in Table 1.

Comparison of biochemical markers, including circulating cytokines levels and hemodynamic variables on admission, between fulminant myocarditis and AMI. Serum levels of IL-10 and TNF-alpha in all patients with fulminant myocarditis increased above the normal upper limit on admission, but elevation of serum levels of IL-12 was observed in only 27% of patients (6 of 22) (Table 1). Serum IFN-gamma levels were within the normal range in all patients. This tendency was also observed in patients with AMI (data not shown).

Serum levels of IL-10 and TNF-alpha were significantly higher in patients with fulminant myocarditis requiring MCSS during the acute phase than in patients with AMI similarly requiring MCSS (IL-10: 37.0 ± 33.0 pg/ml vs. 13.7 ± 11.4 pg/ml, p = 0.025; TNF-alpha: 28.0 ± 13.6 pg/ml vs. 8.3 ± 4.6 pg/ml, p = 0.00014). There were no significant differences in hemodynamic variables, including plasma levels of BNP, between the two groups (Table 2).

Comparison of biochemical markers, including circulating cytokines levels and hemodynamic variables on admission, among the subgroups of fulminant myocarditis. Circulating levels of BNP and cTnT were significantly higher in group 1 than levels in groups 2 and 3 parallel with the severity of circulatory failure. Serum levels of IL-10, but not other parameters, on admission were significantly higher not only in group 1 but also in group 2 than levels in group 3 (49.1 ± 37.5/20.7 ± 17.6 pg/ml vs. 2.4 ± 1.1 pg/ml; p = 0.0008/0.0012) (Table 3).

Further investigation from the viewpoint of mortality was undertaken, and it was discovered that serum levels of IL-10, but not TNF-alpha, were extremely higher in the fatal group than levels in the survival group of fulminant myocarditis (74.0 ± 27.0 pg/ml vs. 16.4 ± 8.8 pg/ml; p = 0.003) (Fig. 1A). Furthermore, serum IL-10 levels were also higher in four non-survivors than in four survivors only in group 1 (74.8 ± 28.9 pg/ml vs. 19.9 ± 13.0 pg/ml; p = 0.01) (Table 1).

Table 3. Baseline Characteristics in Subgroups of Fulminant Myocarditis on Admission

	Group 1 (n = 8)	Group 2 (n = 6)	Group 3 (n = 8)
Age (yrs)	54 ± 17	43 ± 15	49 ± 25
Day	7 ± 3	7 ± 4	11 ± 4
Heart rate (/min)	74 ± 22	76 ± 33	77 ± 31
SBP (mm Hg)	73 ± 4	104 ± 9†	106 ± 23†
CI (l/min/m^2)	1.0 ± 0.2	2.1 ± 0.2†	2.4 ± 0.9†
PCWP (mm Hg)	23 ± 5	13 ± 2†	11 ± 4†
CVP (mm Hg)	14 ± 2	10 ± 3†	7 ± 3†
SvO_2 (%)	57 ± 2	74 ± 7†	72 ± 8†
Base excess (mEq/l)	−6.6 ± 2.7	1.9 ± 3.0†	0.8 ± 3.0†
Serum cTnT (ng/ml)	3.01 ± 1.21	1.56 ± 0.95*	1.25 ± 0.65*
Serum CRP (μg/dl)	8,412 ± 5,386	3,649 ± 3,112	3,872 ± 3,601
Plasma BNP (pg/ml)	594 ± 236	247 ± 99†	176 ± 104†
Serum Cr (mg/dl)	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.2
Serum IL-10 (pg/ml)	49.1 ± 37.5	20.7 ± 17.6‡	2.4 ± 1.1†
Serum TNF-α (pg/ml)	28.9 ± 16.2	26.8 ± 10.7	31.2 ± 21.1

Values are mean ± SEM. Group 1: fulminant myocarditis that had already lapsed into cardiogenic shock (CS) requiring mechanical cardiopulmonary support system (MCSS) with high-dose catecholamine (HCA) on admission; Group 2: fulminant myocarditis that unexpectedly lapsed into CS requiring MCSS more than two days after HCA had started on admission to the hospital; Group 3: fulminant myocarditis that required only HCA but not MCSS. *p < 0.05, †p < 0.01 versus Group 1; ‡p = 0.0012 versus Group 3.

cTnT = cardiac troponin T; Day = duration from flulike symptoms. Other abbreviations as in Tables 1 and 2.

DISCUSSION

Several reports have discussed the predictive clinical parameters for the prognosis of acute myocarditis as a whole (13). In this study, we focused on useful markers for the prediction of fulmination requiring MCSS, because the prognosis of patients with fulminant myocarditis requiring MCSS is still unfavorable (6). In fact, patients in groups 1 and 2, who lapsed into severe HF requiring MCSS during the acute phase, showed a much higher mortality rate than patients in group 3 without MCSS. In other words, these results suggested that the severity of HF could be a factor determining the subsequent prognosis of fulminant myocarditis.

The prognosis of fulminant myocarditis in our study population was poorer than that in the study of McCarthy et al. (1): only 7% with fulminant myocarditis died during hospitalization in McCarthy's study, whereas 23% with fulminant myocarditis died in ours (Table 1). Why was there such a large difference in the prognosis? We can easily show that 64% of patients required MCSS in the present study, whereas only 13% did in the McCarthy et al. (1) study. That is, differences in patient populations regarding the severity of cardiac dysfunction and circulatory failure will lead to differences in prognosis in the two studies.

Higher levels of BNP and cTnT in group 1 with high mortality suggested that BNP and cTnT, as markers for severity of HF and myocardial damage, respectively, might be useful prognostic markers for fulminant myocarditis. On the other hand, circulating levels of C-reactive protein, a

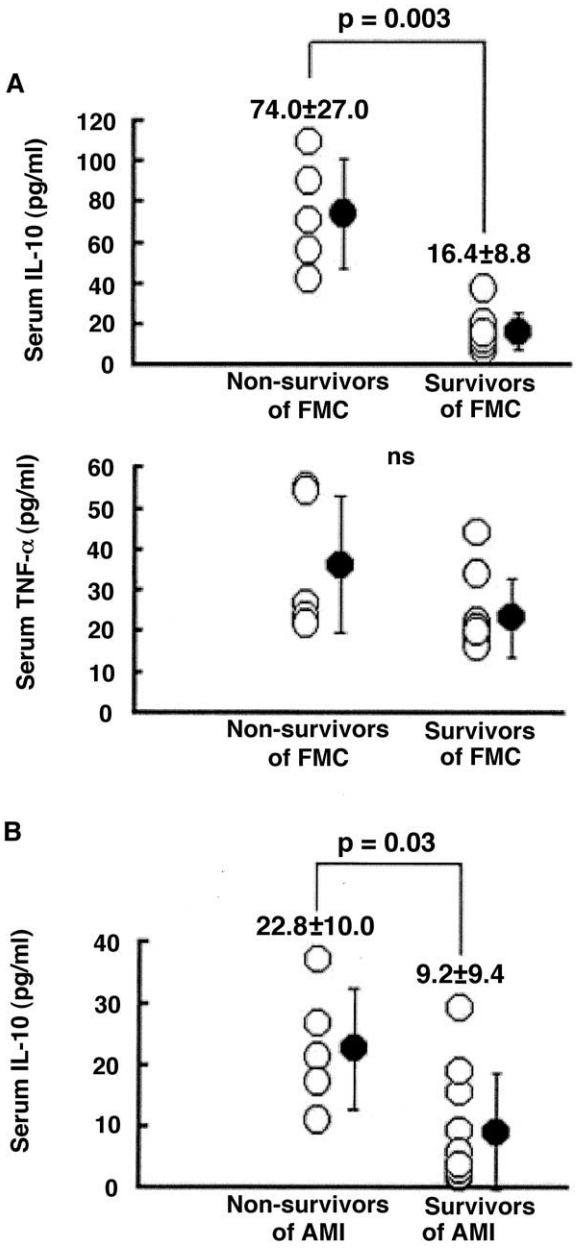

Figure 1. **(A)** Comparison of serum levels of interleukin (IL)-10 and tumor necrosis factor (TNF)-alpha on admission between non-survivors and survivors in fulminant myocarditis. Serum levels of IL-10, but not TNF-alpha, on admission increased considerably in five non-survivors when compared with levels in nine survivors of fulminant myocarditis with cardiogenic shock requiring mechanical circulatory support. **(B)** Comparison of serum levels of IL-10 on admission between non-survivors and survivors in acute myocardial infarction. Serum levels of IL-10 on admission slightly increased in 5 non-survivors when compared with levels in 10 survivors of acute myocardial infarction with cardiogenic shock requiring mechanical circulatory support. **Solid bars** and **closed circles** = mean ± SEM; **Open circles** = data of subjects in the present study. AMI = acute myocardial infarction; FMC = fulminant myocarditis.

representative marker for the systemic inflammation, may not be available to predict higher mortality in view of the result that some survivors of group 1 revealed a rather mild elevation of C-reactive protein on admission and the elevation of C-reactive protein on admission could not distinguish Group 1 from the other groups (Table 1).

The present study showed that serum levels of IL-10 and TNF-alpha, but not always IL-12 and IFN-gamma, on admission increased above the normal upper limit in patients with myocarditis as well as with AMI. Furthermore, serum IL-10 and TNF-alpha levels were significantly higher in patients with myocarditis than those levels in hemodynamically equivalent patients with AMI. These data imply that pathomechanistic factors other than HF, which are found in myocarditis but not in AMI, must contribute to the differing serum levels of these cytokines in the two diseases, although previous reports demonstrated that serum IL-10 and TNF-alpha levels increased in patients with HF when compared with levels in normal subjects (16,17). Among various biomarkers, only serum IL-10 levels on admission could distinguish group 2 from group 3. This suggested that the increase of IL-10 could predict the appearance of severe CS requiring MCSS at an earlier stage in fulminant myocarditis. In addition, the extremely higher IL-10 levels in fatal cases when compared with survivors among patients with fulminant myocarditis requiring MCSS (Fig. 1A), and the slightly higher IL-10 levels among patients with AMI (Fig. 1B), suggested that serum level of IL-10 on admission could also be a powerful predictor of mortality in such a case with fulminant myocarditis, but not in AMI similarly requiring MCSS. Interestingly, the serum IL-10 levels were also significantly lower in survivors than levels in non-survivors only among group 1 patients (Table 1), suggesting that a lower IL-10 level is a possible marker for better prognosis of survival even in limited cases with fulminant myocarditis with poor prognosis. Furthermore, the serum level of IL-10 in one non-survivor of group 2 was as high as levels in non-survivors of group 1 (Table 1). These findings might provide evidence to demonstrate that serum IL-10 levels on admission reflect not only the severity of HF but also the outcome concerning mortality.

It has been reported that the inhibition of natural killer cells results in increased virus titers in the heart through delayed virus clearance (18). Interleukin-10 inhibits the production of IFN-gamma in natural killer cells, which has been demonstrated in association with susceptibility to *Trypanosoma cruzi*-induced myocarditis (19,20). In addition, it has been shown that IL-10 is transcribed in the myocardium parallel with viral replication in the acute and chronic stages of experimental Coxsackievirus B3 viral myocarditis (8,9). These findings suggest that the expression of myocardial IL-10 may reflect the persistence of active myocardial viral infection and play a crucial role in the development of viral myocarditis. Interestingly, a closely correlated expression of virus and IL-10 in the acute stage of murine viral myocarditis was also found in a spleen-regulating, systemically immune response similar to that in the heart (9). Hofmann et al. also reported that IL-10 expression in human peripheral monocytes was strongly and persistently induced by Coxsackievirus B3 infection despite only slight production of other proinflammatory cytokines

such as TNF-alpha, IL-1, and IL-6 (21). This may suggest that an extreme elevation of serum levels of IL-10, rather than TNF-alpha, on admission in human myocarditis can reflect subsequent myocardial inflammation, which leads to future deterioration from the disease, through delayed clearance of the virus. On the other hand, some reports using experimental models have demonstrated a protective role of IL-10 in the development of acute myocarditis (11–13). This mechanism was explained by its suppressive effect against excessive immune response to viral infection or a subsequent autoimmune response leading to myocardial injury. Extreme elevation of serum levels of IL-10 may paradoxically reflect severe myocardial inflammation and damage, which it is unable to modulate.

We could not completely confirm these hypotheses in all cases reported here because of unproven direct viral infection. If myocardial IL-10 reflects active viral infection, the viral antigen or genome might be identified in the myocardial biopsy specimen using immunohistochemistry or reverse transcriptase-polymerase chain reaction (22). Unfortunately, there is no adequate form of myocardial material, including frozen tissue, for these purposes. This is a limitation of the present study concerning a retrospective investigation. However, prodrome, histologic findings, and elevation of virus titers (Table 1) could support the possibility that subjects of myocarditis included here were affected by viral infection.

CONCLUSIONS

The extreme elevation of serum levels of IL-10 on admission, which may reflect future progression of myocardial inflammation in addition to cardiac dysfunction, enables one to determine not only the occurrence of CS requiring mechanical circulatory support but also the mortality in patients with fulminant myocarditis.

Acknowledgments

The authors thank Ms. Toshie Hashizume, Chiaki Notoya, and Kazumi Nakazato for their excellent technical assistance.

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