study. Therefore, it seems likely that aldosterone facilitates tenascin-C gene expression *in vivo* not through a direct action on cardiac fibroblasts but by actions on other factors secreted by other cells.

There is a growing body of evidence that Ang II/ aldosterone treatment induces inflammation and accumulation of macrophages in perivascular regions in the myocardium [5, 6]. Generally, macrophages are important regulators in inflammation in various tissue and the main source of fibrogenic mediators such as IL-1, TGF-β, and PDGF (reviewed in [38]). In the present study, Ang II infusion caused accumulation of macrophages and upregulation of PDGF-A, -B, PDGF Receptor α and TGF-β1 in mouse hearts. These changes were inhibited by eplerenone, and their extent correlated with the expression level of tenascin-C. In culture, TGF-β1 and PDGF upregulated tenascin-C expression by cardiac fibroblasts. Taken together, it seems likely that aldosterone elicits inflammatory reaction in perivascular regions in Ang II induced hypertensive mouse hearts, which might, in turn, induce tenascin-C synthesis of fibroblasts through partly two signaling pathways mediated by TGFβ and PDGF-A-B/PDGF-receptor α.
Although further studies are necessary to elucidate the complex multi-step molecular pathways involved, induction of tenascin-C by aldosterone in the hypertensive heart might be a key step in perivascular fibrosis and thus a prime target for therapy.

Conclusion

The present results suggest involvement of tenascin-C in hypertensive cardiac fibrosis and that blockade of mineralocorticoid receptor with eplerenone reduces expression of tenascin-C by reducing inflammatory reaction, subsequently resulting in attenuation of perivascular fibrosis.

Acknowledgments

This study was supported by a Grant-in-aid for scientific research (No. 17590725) from the Ministry of Education, Culture Sports, Science and Technology of Japan to K.I.-Y and by a grant for Intractable Disease from the Ministry of Health, Labor and Welfare of Japan to K.I.-Y and M. H. Part of the study was also supported from a grant by Pfizer, Inc.

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Figures

Figure1

Systolic blood pressure (A), body weights (B) for each group of mice. Values are means ± SD. Vehicle, vehicle control mice; Ang II, Ang II-treated mice; Ang II+Ep, Ang II/eplerenone-treated mice; Ep, eplerenone-treated mice; Aldo, aldosterone-treated mice. ***p<0.001 vs. Vehicle control mice.

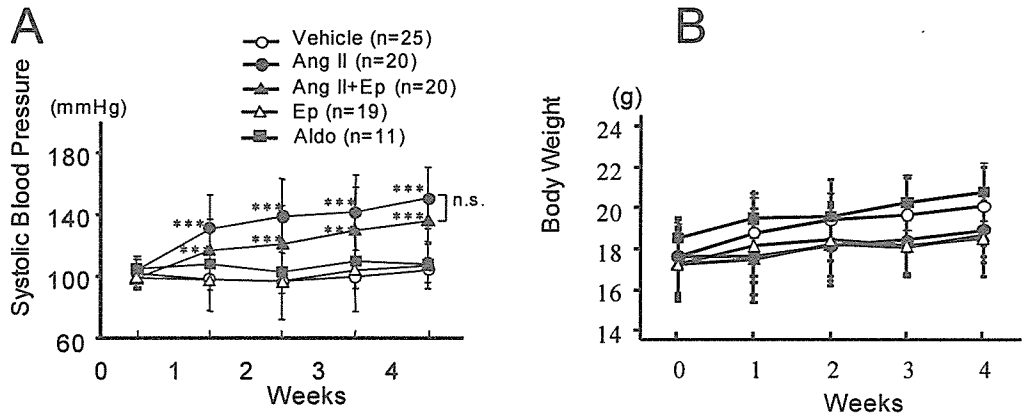


Figure 2

Representative photographs of perivascular areas of myocardial tissue sirius red stained (A) and immunostained for tenascin-C (B), *in situ* hybridization of tenascin-C mRNA in an Ang II-treated mouse (C, D). D is a high power view of the boxed areas in C. Tenascin-C becomes detectable in perivascular region (arrows in B). Interstitial fibroblasts express tenascin-C mRNA (arrows in D). Quantification of collagen volume in perivascular areas (E), and relative mRNA level of collagen type Iα2, IIIα1 and tenascin-C in myocardium (F). Values are means ± SD. Vehicle, vehicle control mice (n=8); Ang II, Ang II-treated mice (n=6); Ang II+Ep, Ang II/eplerenone-treated mice (n=8); Ep, eplerenone-treated mice (n=5); Aldo, aldosterone-treated mice (n=4). *p<0.05, **p<0.01, ***p<0.001 vs. vehicle control group. †p<0.05, †††p<0.001 vs. Ang II-treated group.

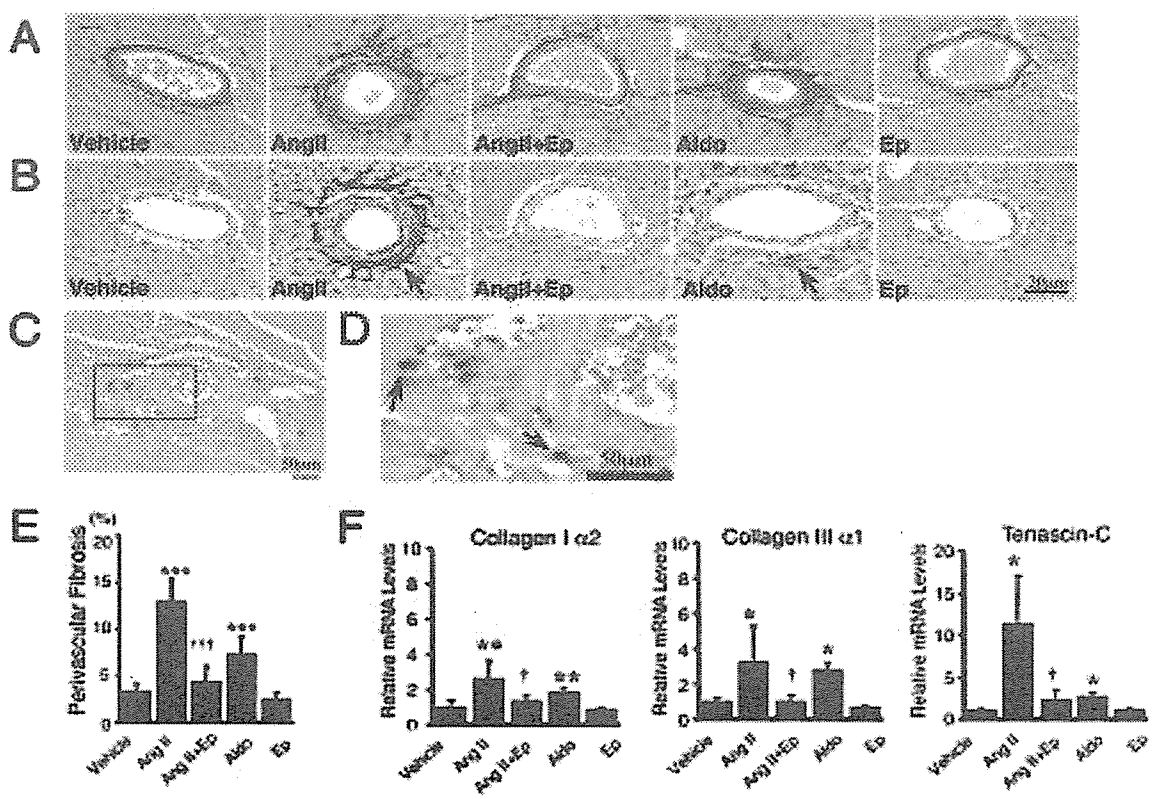


Figure 3
Immunohistochemial analysis of mouse myocardial tissue. Representative photographs of immunostained myocardium and numbers of positively stained cells at perivascular region in each group for Mac 3 (A), PDGF-A (B), PDGF-B(C), PDGF receptor α(D)?, and PDGF receptor β(E)?. Many macrophages, PDGF- A, -B positive cells are seen at perivascular region of Ang II treated mouse (arrows in A,B,C).

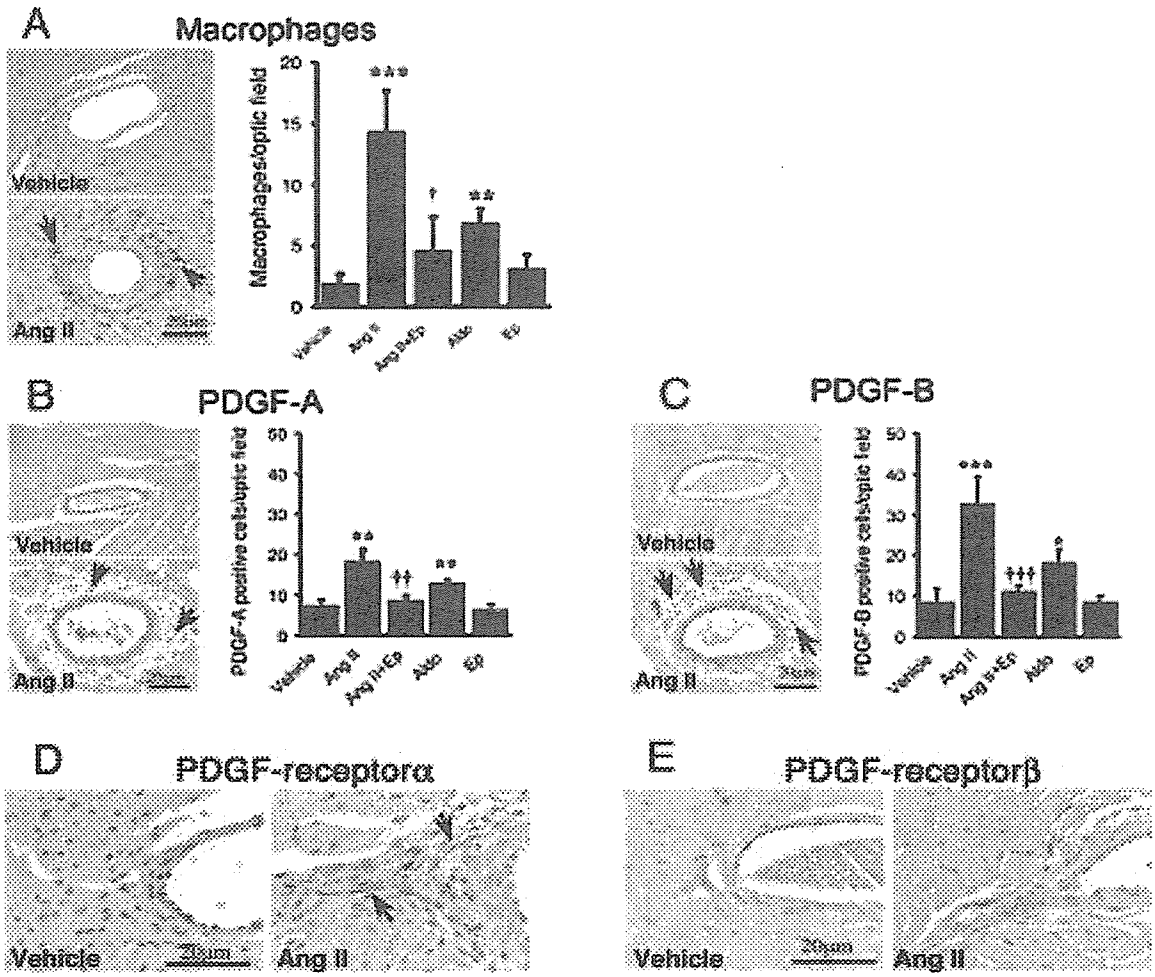


Figure 4
Quantitative RT-PCR analysis of proinflammatory/profibrotic mediators in mouse myocardium. Expression of TGF-β1 was? increased in Ang II and aldosterone treated mice and eplerenone significantly reduced this upregulation. No significant change of mRNA level of IL-1β was observed in any groups. Values are means ± SD. Vehicle, Vehicle control mice (n=10); Ang II, Ang II-treated mice (n=3); Ang II+Ep, Ang II/eplerenone-treated mice (n=5); Ep, eplerenone-treated mice (n=3); Aldo, aldosterone-treated mice (n=3). *p<0.05 vs. Vehicle control group, †p<0.05 vs. Ang II-treated group.

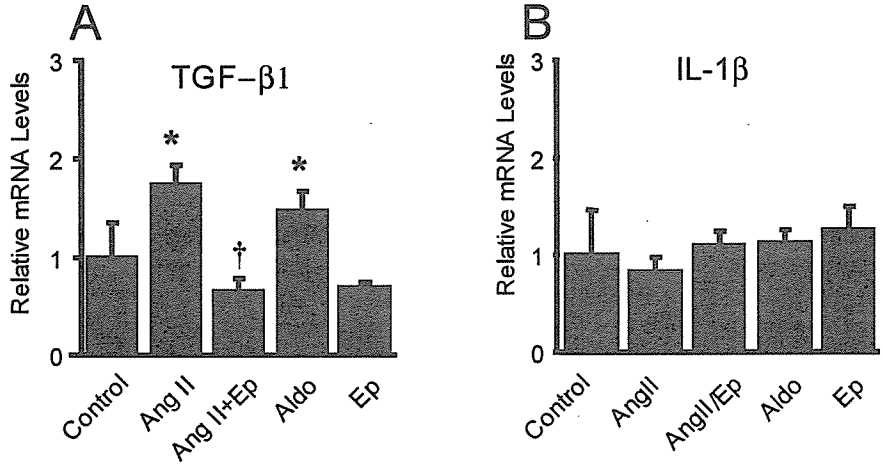
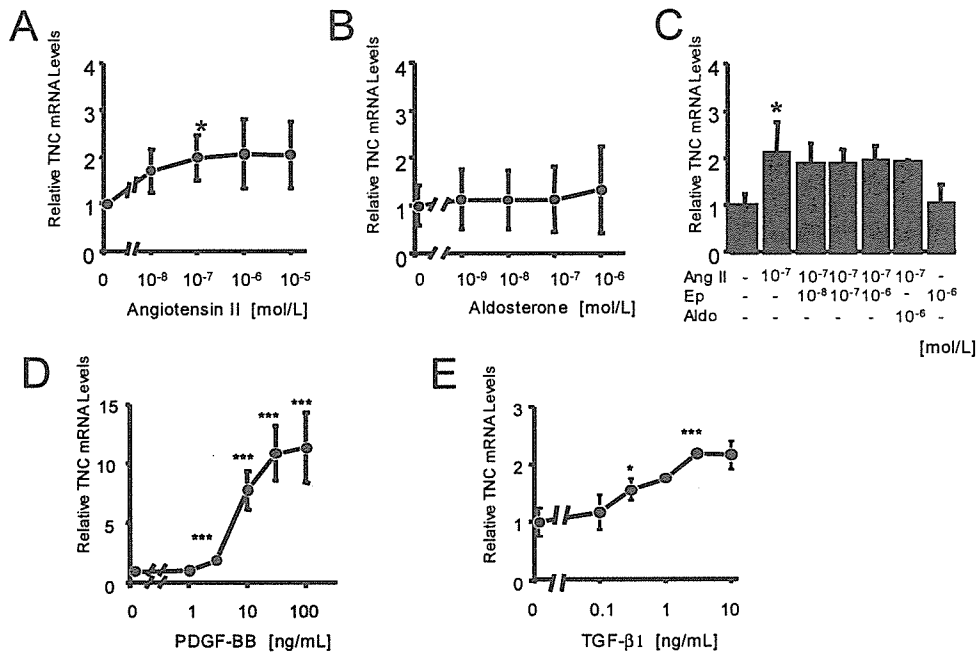


Figure 5

Direct effects of Ang II, aldosterone and proinflammatory/profibrotic mediators on cultured cardiac fibroblasts. Six hours after addition of Ang II (0 to 10^{-5} mol/L) or aldosterone (0 to 10^{-6} mol/L), total RNA was extracted and relative tenascin-C mRNA levels were quantified using real-time RT-PCR. Tenascin-C mRNA levels in cardiac fibroblasts treated with Ang II were increased (A), but not with aldosterone (B). Combined effects of eplerenone (0, 10^{-8}, 10^{-7}, 10^{-6} mol/L) on Ang II (10^{-7} mol/L) induced tenascin-C expression in cardiac fibroblasts were not observed (C). PDGF markedly upregulated the mRNA for tenascin-C(D). TGF-β1 also significantly increased tenascin-C expression. Ang II, AngiotensinII-treated (E); Ep, eplerenone-treated; Aldo, Aldosterone; TNC, tenascin-C; *p<0.05 vs. no substance. Values are means ± SD. *p<0.05, ***p<0.001 vs. no substance, TNC, tenascin-C.



Cardiac sarcoidosis underlies idiopathic dilated cardiomyopathy: Importance of mediastinal lymphadenopathy in differential diagnosis

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Total 14pages, 2 tables, 1 figure

Abstract:

Background: Cardiac sarcoidosis is frequently overlooked or misdiagnosed as idiopathic dilated cardiomyopathy (DCM), primarily because of difficulties in its diagnosis. This is crucial because appropriate therapy with immunosuppressive agents can be initiated if a proper diagnosis is achieved earlier.

Methods and Results: We analyzed computed tomography (CT) in detail with special reference to lymph node swelling (LNS) in the mediastinum. We conducted a retrospective examination of thoracic CTs of eight patients diagnosed with idiopathic DCM who underwent left ventriculoplasty (LVP), and were later proven to have active cardiac sarcoidosis by histological evaluation of the resected myocardium. Twenty age-matched patients with idiopathic DCM who also underwent LVP served as controls. On conventional chest radiographs, none of the cardiac sarcoidosis patients exhibited lymph node involvement, including bilateral hilar lymphadenopathy. However, CT demonstrated significant mediastinal LNS in seven (88%) of the eight cardiac sarcoidosis patients and in only one (5%) of the 20 idiopathic DCM patients. There was a significant difference between the incidence of LNS in the cardiac sarcoidosis and idiopathic DCM patients ($p = 0.00005$).

Conclusion: The evaluation of mediastinal lymphadenopathy by CT is an easy and valuable initial screening method to distinguish cardiac sarcoidosis from idiopathic DCM.

(197 words)

Key Words: Cardiac sarcoidosis; Mediastinal lymphadenopathy; Computed tomography

Acknowledgments:

This study was supported in part by grants from the Ministry of Health, Labor, and Welfare of Japan.

Text:

Recently, left ventriculoplasty (LVP), the so-called Batista procedure, has been introduced for the treatment of patients with idiopathic dilated cardiomyopathy (DCM) with refractory congestive heart failure.[1, 2] Thus far, of the 110 patients who underwent LVP, 8 (7%) were diagnosed with cardiac sarcoidosis as a result of histological examination of the resected myocardium (unpublished data). These patients were initially diagnosed with idiopathic DCM and referred for surgery during end-stage severe heart failure. The frequency of overlooking cardiac sarcoidosis is unexpectedly high, and this may primarily be due to difficulties in the diagnosis. This finding is considered crucial because appropriate therapy with immunosuppressive agents can be initiated if a proper diagnosis is achieved earlier.[3]

Bilateral hilar lymphadenopathy (BHL), chiefly composed of the hilar, interlobar and lobar lymph nodes, has a classical radiographic appearance in patients with sarcoidosis. Although the chest radiograph is helpful in establishing the radiographic stage of sarcoidosis, 5–15% of sarcoidosis patients have normal chest radiographic appearances at presentation.[4] In particular, the paucity of radiographic findings in cardiac sarcoidosis has been well known in patients for whom the disease was discovered at autopsy or by endomyocardial biopsy, and this has led some authors to refer to cardiac sarcoidosis as an "all or none process." [5, 6] On the other hand, in a pathological study of 320 sarcoidosis cases at autopsy, mediastinal lymphadenopathy was reported in more than 80% of the patients with cardiac involvement.[7] It is supposed that chest radiographs cannot detect mediastinal lymphadenopathy because these lymph nodes are often buried deep in the mediastinum.

epithelioid granulomas. One patient revealed accumulation of ^{67}Ga in the heart. Cardiac sarcoidosis was characterized by a high incidence of advanced atrioventricular block as reported previously.[8]

Thoracic computed tomography and lymph node map definitions

All the preoperative thoracic CTs were interpreted by an experienced radiologist (Y.O.) and a cardiovascular physician (H.S.), who reached a consensus unaware of the clinical findings. The lymph node map definitions were in accordance with the report by Mountain and Dresler.[9] In the present study, the significant lymphadenopathy was determined by observing lymph nodes with minor axial diameters of more than 1 cm.

Statistical analysis

The difference between the occurrences of mediastinal LNS in the patients with cardiac sarcoidosis as compared with those with idiopathic DCM was analyzed by Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

None of the eight patients with cardiac sarcoidosis or the 20 patients with idiopathic DCM included in this study presented with BHL on conventional chest radiographs. On the other hand, significant mediastinal lymphadenopathies were observed in seven of the eight (88%) cardiac sarcoidosis patients. The distribution of the swollen lymph nodes is shown in Table 2. All the

Thus, we conducted a detailed analysis of thoracic computed tomography (CT) in cardiac sarcoidosis patients with special reference to lymph node swelling (LNS) in the mediastinum.

Methods

Study population

Eight patients (four men and four women; mean age 54 ± 6 years) underwent LVP or mitral valvuloplasty between September 1997 and January 2006 at Shonan Kamakura General Hospital, Hayama Heart Center, or Osaka Medical College Hospital, Japan, following the diagnosis of idiopathic DCM. These patients were first diagnosed with active cardiac sarcoidosis postoperatively following histological examination of the resected myocardium. We retrospectively compared the clinical features of these eight cardiac sarcoidosis patients and their preoperative thoracic CTs with those of 20 age-matched consecutive idiopathic DCM patients who underwent LVP during the same period. Clinical characteristics of the cardiac sarcoidosis patients are shown in Table 1. None of the cardiac sarcoidosis patients suffered from pulmonary tuberculosis, malignancy, or other inflammatory disease. All the cardiac sarcoidosis patients had severe left ventricular dilatation with poor contraction. The mean left ventricular end-diastolic dimension was 74.0 ± 10.4 mm and the mean left ventricular ejection fraction was 23.1 ± 7.7%. The plasma concentrations of angiotensin-converting enzyme (ACE), which were measured in five patients, were not significantly elevated (mean: 15.6 ± 3.1 IU/L; normal range: 8.3–21.4 IU/L). Two patients had undergone endomyocardial biopsies; however, no findings proved cardiac sarcoidosis such as non-caseating

sarcoidosis patients, except one (No. 8), had swelling of the lower paratracheal lymph nodes (#4). A representative case (No. 7) is described hereinafter. In the 20 patients with confirmed idiopathic DCM, only one patient exhibited mediastinal LNS of unknown etiology. There was a significant difference between the occurrence of LNS in the patients with cardiac sarcoidosis as compared with those with idiopathic DCM ($p = 0.00005$). When limited to end-stage DCM or DCM-like patients, the sensitivity of examination of mediastinal lymphadenopathy on CT for detecting cardiac sarcoidosis was 87.5% and the specificity was 95.0%. In addition, the positive and negative predictive values were 87.5% and 95.0%, respectively. For the distribution of the swollen lymph nodes, the incidence of lower paratracheal, subaortic, and paraaortic LNS (#4, #5, and #6, respectively) was quite high in the patients with cardiac sarcoidosis.

Representative Case (No. 7)

A 44-year-old man with complaint of dyspnea on exertion since October 2005 was admitted to our hospital. He had previously been implanted with a permanent cardiac pacemaker for complete atrioventricular block in 1993. A chest radiograph revealed severe cardiomegaly (cardiothoracic ratio, 54%), but BHL was not definite (Figure 1A). Echocardiography showed dilatation of the left ventricle with diffusely reduced wall motion (left ventricular diastolic dimension/left ventricular systolic dimension = 80 mm/71 mm, fractional shortening = 9.8%). Severe mitral regurgitation was noted. ^{67}Ga scintigraphy did not demonstrate abnormal uptake neither in the hilar and mediastinal lymph nodes nor in the heart. The plasma concentration of ACE

was not elevated (15.8 IU/L). Coronary angiography showed no organic stenosis in his coronary arteries, and left ventriculography revealed diffuse hypokinesis with severe mitral regurgitation (Sellers classification grade 3). Endomyocardial biopsy of the right ventricular septum did not show the typical findings of sarcoidosis. He underwent LVP (septal anterior ventricular exclusion; SAVE) and mitral annuloplasty for refractory congestive heart failure. Histological examination of intraoperative biopsy specimens revealed that non-caseating epithelioid granuloma with Langhans giant cells was evident, thus, definite diagnosis of cardiac sarcoidosis was obtained. The preoperative thoracic CT of this patient revealed marked mediastinal lymphadenopathy (Figure 1B–D), but BHL was not definite.

Discussion

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology.[10] Cardiac sarcoidosis is a fatal disease in which common causes of death are refractory heart failure, ventricular arrhythmias, and high degree atrioventricular block.[6] Sudden death can occur at any stage of sarcoidosis, but is much more common in cases of severe myocardial involvement.[11] Therefore, an early diagnosis of cardiac sarcoidosis is important for developing a treatment strategy and clinical outcome. However, the diagnosis of cardiac sarcoidosis is often difficult, particularly in patients with no evidence of other organ involvement, such as BHL, and/or lung, eye, or skin manifestations. A significant number of cases of myocardial sarcoidosis are discovered at autopsy and are never suspected antemortem.[12] Donsky *et al.* reported a patient who underwent heart

transplantation for presumed idiopathic DCM. On further examination, the explanted heart was found to have significant sarcoid involvement.[13] Endomyocardial biopsy frequently fails to detect sarcoid granulomas because of their random distribution.[14] Uemura *et al.* reported that non-caseating epithelioid granulomas were discovered by endomyocardial biopsies in only 19% of the patients in whom cardiac sarcoidosis was strongly suspected.[15] Consequently, most patients without histological diagnoses are treated as idiopathic DCM.

Electrocardiography and echocardiography are commonly used to detect cardiac involvement in sarcoidosis patients.[16, 17] However, early diagnosis of cardiac involvement and differentiation between cardiac sarcoidosis and idiopathic DCM are difficult. Although ^{201}Tl scintigraphy is also used to detect cardiac involvement in patients with sarcoidosis, it may be a sensitive but nonspecific method for the detection of active cardiac sarcoidosis, because ^{201}Tl scintigraphy detects myocardial injury with or without active inflammation.[18] ^{67}Ga scintigraphy is a well-known imaging method for diagnosing and assessing disease activity of cardiac sarcoidosis; however, it appeared to offer lower sensitivity.[18]

In the present study, none of the cardiac sarcoidosis patients exhibited lymph node involvement, including BHL on conventional chest radiographs. However, thoracic CT demonstrated significant mediastinal LNS in seven of the eight cardiac sarcoidosis patients, while only one of the 20 idiopathic DCM patients exhibited mediastinal LNS.

Although cardiac lymphatic drainage in humans is not completely understood, principal lymphatics may drain from the ventricular muscle and pass to the upper mediastinum via the

cardiac lymph nodes.[19] BHL on the chest radiographs is mainly composed of the hilar, interlobar and lobar lymph nodes (#10, #11, and #12, respectively), which receive drainage from the lung and bronchial regions. Thus, upper mediastinal LNS without apparent BHL may be caused primarily by inflammation of cardiac origin. Indeed, the incidence of lower paratracheal, subaortic, and paraaortic LNS (#4, #5, and #6, respectively) was quite high in the patients with cardiac sarcoidosis (Table 1).

One patient with cardiac sarcoidosis did not show definite mediastinal lymphadenopathy, which may be related to the fact that the degree of inflammation found by histological examination was mild in this case. One idiopathic DCM patient had swelling of the lower paratracheal lymph nodes (#4). Malignancy, pulmonary tuberculosis, and other inflammatory diseases including sarcoidosis are possible causes of lymphadenopathy; however, the etiology is unknown at present in this case. In fact, the frequency of mediastinal lymphadenopathy in the general population is not sufficiently clear, and there may be environmental causes such as air pollution and smoking.

To our knowledge, this may be the first report describing the details of mediastinal lymphadenopathy observed on thoracic CT of DCM-like patients with histologically proven cardiac sarcoidosis. Recently, non-invasive techniques such as ^{201}Tl, ^{67}Ga, ^{123}I-metaiodobenzyl-guanidine scintigraphy,[20] magnetic resonance imaging, and positron emission tomography[21-23] have been revealed to be useful for the identification and assessment of disease activity in cardiac sarcoidosis. In addition to these modalities, the examination of mediastinal lymphadenopathy on CT could be an easy, cost-effective, and valuable initial screening method for distinguishing cardiac sarcoidosis

from idiopathic DCM, particularly when there is no definite involvement of other organ(s).

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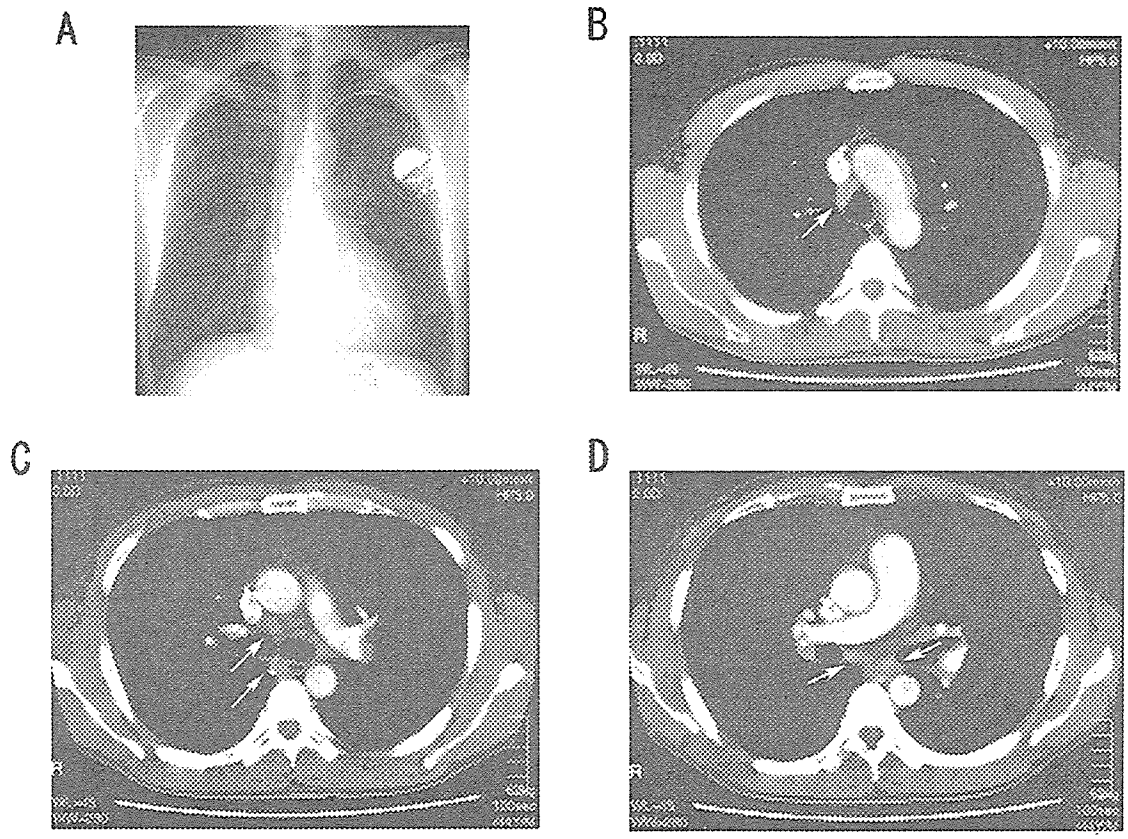

Figure Legend

Figure 1

(A) Chest radiograph of case No. 7. Cardiomegaly was observed, but BHL was not definite.

(B–D) Enhanced computed tomography from the same patient. Marked lymph node swelling of the lower paratracheal (arrows in panel B and C) and subcarinal (arrows in panel D) regions was evident.

Table.1 Clinical characteristics of cardiac sarcoidosis patients as a result of histological examination of the resected myocardium.

CASE	Age	Gender	Mode of detection	Date of operation	Symptom at onset	LVDd (mm)	LVEF (%)	ACE (U/L)	Myocardial biopsy	Cardiac uptake at Ga schintigraphy	Histroy of cardiac problem
1	60	M	LVP	1997.9.1	DOE	88	24	ND	ND	ND	MVP (MR) at the time of onset
2	63	M	LVP	1999.7.6	DOE	85	21	ND	ND	ND	PMI (Ⅲ° AVB) 6 years after onset
3	51	F	LVP	1999.7.30	DOE	62	29	18.2	Negative	ND	LV aneurysm at the time of onset
4	51	F	LVP	2001.10.2	Palpitation	68	35	12.9	ND	(+)	LV aneurysm at the time of onset
5	49	F	MVPL	2002.7.29	DOE	66	24	19.1	ND	(-)	(-)
6	55	M	MVPL	2004.4.28	DOE	69	26	15.1	ND	ND	LV aneurysm at the time of onset
7	44	M	LVP	2006.1.18	DOE	81	11	10.0	Negative	(-)	PMI(Ⅲ°AVB)
8	59	F	LVP	1999.10.12	DOE	68	18	ND	ND	ND	PMI (Ⅲ° AVB) 1 year after onset

LVP: Left ventriculoplasty, MVPL: Mitral valvuloplasty, DOE: Dyspnea on exertion, LVDd: Left ventricular end-diastolic dimension, LVEF: Left ventricular ejection fraction, ND: not done, PMI: Permanent pacemaker implantation, AVB: Atrioventricular block, LV: Left ventricular