Cardiac Sarcoidosis Underlies Idiopathic Dilated Cardiomyopathy — Importance of Mediastinal Lymphadenopathy in Differential Diagnosis —

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

Methods and Results Thoracic computed tomography (CT) was retrospectively analyzed in detail with special reference to lymph node swelling (LNS) in the mediastinum of 8 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 7 (88%) of them and in only 1 (5%) of the 20 controls. There was a significant difference in the incidence of LNS in the 2 groups (p=0.00005).

Conclusion Evaluation of mediastinal lymphadenopathy by CT is an easy and valuable initial screening method for distinguishing cardiac sarcoidosis from idiopathic DCM. (Circ J 2007; 71: 1937–1941)

Key Words: Cardiac sarcoidosis; Computed tomography; Mediastinal lymphadenopathy

Left ventriculoplasty (LVP), the so-called Batista procedure, has been recently introduced for the treatment of patients with dilated cardiomyopathy (DCM) with refractory congestive heart failure.1-2 Thus far, in our experience of 110 patients who underwent LVP, 8 (7%) have been diagnosed with cardiac sarcoidosis as a result of histological examination of the resected myocardium (unpublished data). Those 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 may be primarily related to difficulties in the diagnosis. This finding is considered crucial because appropriate therapy with immunosuppressive agents can be initiated if a early diagnosis is achieved.

Bilateral hilar lymphadenopathy (BHL), chiefly comprising the hilar, interlobar and lobar lymph nodes (LNs), has a classic 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 radiography on presentation.3 In particular, the paucity of radiographic findings in cardiac sarcoidosis is 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.”3,6 On the other hand, in a pathological study of 320 cases of sarcoidosis diagnosed at autopsy, mediastinal lymphadenopathy was reported in more than 80% of the patients with cardiac involvement.7 It is thought that chest radiography cannot detect mediastinal lymphadenopathy because the LNs are often buried deep in the mediastinum. Thus, we conducted a detailed analysis of thoracic computed tomography (CT) in cardiac sarcoidosis patients with special reference to LN swelling (LNS) in the mediastinum.

Methods

Study Population
Eight patients (4 men, 4 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 retrospective-

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ly compared the clinical features of these 8 cardiac sarcoi-
dosis patients and their preoperative thoracic CTs with
those of 20 age-matched consecutive idiopathic DCM pa-
tients who underwent LVP during the same period. The
clinical characteristics of the DCM and cardiac sarcoidosis
patients are shown in Table 1. Written informed consent was
given by all patients and the study protocol was approved
by the institutional review board.

Clinical Information
Age, gender, systolic and diastolic blood pressures
(mmHg), heart rate (beats/min) and New York Heart Asso-
ciation functional class were evaluated as the essential in-
formation. Left ventricular end-diastolic diameter (LVDD),
end-systolic diameter (LVDs), and left ventricular ejection
fraction (LVEF) were measured by standard echocardiogra-
phy. The existence of complete atrioventricular block and
ventricular tachycardia was evaluated by the 24-h ambula-
tory electrocardiogram monitoring.

Biochemical Analysis
Plasma B-type natriuretic protein concentrations were
measured using a specific immunoradiometric commercial
assay kit (Shionogi, Osaka, Japan). Serum angiotensin-
converting enzyme (ACE) levels were measured by the
Kasahara method.

Thoracic CT and LN Map Definitions
All the preoperative thoracic CTs were interpreted by an
experienced radiologist (Y.O.) and a cardiovascular physi-
cian (H.S.), who reached a consensus unaware of the clini-
cal findings. The LN map definitions were in accordance
with the report by Mountain and Dresler. In the present
study, significant lymphadenopathy was determined by ob-
serving LNs with minor axial diameters of more than 1 cm.

Table 1 Clinical Characteristics of Patients With Dilated Cardiomyopathy and Cardiac Sarcoidosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dilated cardiomyopathy (n=20)</th>
<th>Cardiac sarcoidosis (n=8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.7±10.6</td>
<td>54.0±6.4</td>
<td>NS</td>
</tr>
<tr>
<td>Men</td>
<td>18 (90%)</td>
<td>4 (50%)</td>
<td>0.024</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+2</td>
<td>3 (15%)</td>
<td>1 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>3+4</td>
<td>17 (85%)</td>
<td>7 (88%)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>97±13</td>
<td>97±6</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>62±10</td>
<td>62±9</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83±9</td>
<td>86±9</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>14 (70%)</td>
<td>4 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium channel antagonists</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>ß-blockers</td>
<td>11 (55%)</td>
<td>5 (63%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>20 (100%)</td>
<td>8 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>14 (70%)</td>
<td>6 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete atrioventricular block</td>
<td>1 (5%)</td>
<td>4 (50%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>16 (80%)</td>
<td>3 (38%)</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>84.2±8.3</td>
<td>73.4±6.8</td>
<td>0.006</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>74.1±7.2</td>
<td>63.1±11.3</td>
<td>0.005</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>20.7±6.2</td>
<td>23.5±7.2</td>
<td>NS</td>
</tr>
<tr>
<td>Interventricular septum thickness (mm)</td>
<td>8.8±1.5</td>
<td>9.1±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior wall thickness of the left ventricle (mm)</td>
<td>9.2±2.0</td>
<td>9.6±2.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV aneurysm</td>
<td>0 (0%)</td>
<td>3 (38%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/ml)</td>
<td>788±526</td>
<td>715±450</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history</td>
<td>8 (40%)</td>
<td>3 (38%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means±SDs or numbers (%).
NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme-inhibitors; ARB, angiotensin II receptor blockers; LV, left ventricular; EF, ejection fraction.

Table 2 Clinical Characteristics of Cardiac Sarcoidosis Patients as a Result of Histological Examination of the Resected Myocardium

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

Dd, end-diastolic dimension; ACE, angiotensin-converting enzyme; LVP, left ventriculoplasty; DOE, dyspnea on exertion; ND, not done; MVPL, mitral valvulo-
plasty; MR, mitral regurgitation; PMI, permanent pacemaker implantation; AVB, atrioventricular block. Other abbreviations see in Table 1.
Statistical Analysis

Data are expressed as means ± SD for continuous variables, and as numbers (percentages) for categorical variables. Comparison between 2 groups was performed by Fisher’s exact test or the unpaired Student’s t-test. A p-value of <0.05 was considered statistically significant.

Results

Clinical Information

Between the DCM and cardiac sarcoidosis groups, statistical differences were observed in gender, existence of complete atrioventricular block, LVDd and LVDs, and left ventricular (LV) aneurysm (Table 1). There was no significant statistical difference in the smoking history. None of the cardiac sarcoidosis patients suffered from pulmonary tuberculosis, malignancy, or other inflammatory disease. Some of the clinical characteristics of the cardiac sarcoidosis patients are summarized in Table 2. The plasma concentrations of ACE were not significantly elevated (mean: 15.6±3.1 IU/L; normal range: 8.3–21.4 IU/L), measured in 5 cardiac sarcoidosis patients. Two cardiac sarcoidosis patients had undergone endomyocardial biopsies; however, no findings proved cardiac sarcoidosis, such as non-caseating epithelioid granulomas. One of 3 patients who had undergone 67Ga scintigraphy revealed abnormal accumulation in the heart.

The prognosis of the patients whose information could be obtained was as follows. During a mean follow-up of 43 months after surgery, 5 (63%) of the 8 patients with cardiac sarcoidosis died, compared with 11 (58%) of 19 DCM patients during a mean follow-up of 40 months.
Thoracic CT and the Distribution of Swollen LNs

None of the patients with either cardiac sarcoidosis or idiopathic DCM presented with BHL on conventional chest radiographs. However, significant mediastinal lymphadenopathies (minor axial diameters >1 cm) were observed in 7 (88%) cardiac sarcoidosis patients. The distribution of the swollen LNs is shown in Table 3. All the sarcoidosis patients, except 1 (No. 8), had swelling of the lower paratracheal LNs (#4). A representative case (No. 7) is described below. In the 20 patients with confirmed idiopathic DCM, only 1 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). In this study, the sensitivity of examination of mediastinal lymphadenopathy on thoracic 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 LNs, 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 the complaint of dyspnea on exertion since October 2005 was admitted to hospital. He had previously been implanted with a permanent cardiac pacemaker for complete atrioventricular block in 1993. A chest radiograph revealed cardiomegaly (cardiothoracic ratio = 54%), but BHL was not definite (Fig 1A). Echocardiography showed dilatation of the left ventricle with diffusely reduced wall motion (LVDd/LVDs=81 mm/71 mm, LVEF=11%). Severe mitral regurgitation was noted. 67Ga scintigraphy did not demonstrate abnormal uptake in either the hilar or mediastinal LNs nor in the heart. The plasma concentration of ACE was not elevated (15.8 IU/L). Coronary angiography 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 under the diagnosis of refractory congestive heart failure. Histological examination of the intraoperative biopsy specimens revealed non-caseating epithelioid granulomas with Langhans giant cells, so definite diagnosis of cardiac sarcoidosis was obtained. The preoperative thoracic CT of this patient revealed marked mediastinal lymphadenopathy (Figs 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 the 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 with severe myocardial involvement.11 Therefore, 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 ante mortem.12 Donsky et al reported a patient who underwent heart transplantation for presumed idiopathic DCM, but 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 a histological diagnosis are treated as idiopathic DCM.

Electrocardiography and echocardiography are commonly used to detect cardiac involvement in sarcoidosis patients.6,17 In the present study there were statistical differences in gender, existence of complete atrioventricular block, LV diameters, and LV aneurysm between the DCM and cardiac sarcoidosis groups (Table 1). These factors may be useful markers for differentiating cardiac sarcoidosis from idiopathic DCM, as reported previously.18 Although it was not obvious in this study, a higher incidence of thinning of the basal portion of the interventricular septum has been suggested by some investigators as specific for the diagnosis of sarcoidosis.13 However, both the diagnosis of cardiac involvement and the differentiation between cardiac sarcoidosis and idiopathic DCM is still difficult.20 201Tl scintigraphy is also used to detect cardiac involvement in patients with sarcoidosis, but although it is a sensitive method, 201Tl scintigraphy is nonspecific for the detection of active cardiac sarcoidosis because it detects myocardial injury with or without active inflammation.20 67Ga scintigraphy is a well-known imaging method for diagnosing and assessing the disease activity of sarcoidosis. Abnormal 67Ga accumulation in the skin, LNs or skeletal muscles may lead to histological confirmation of sarcoidosis; however, it has lower sensitivity for the detection of cardiac inflammation.20

In the present study, none of the cardiac sarcoidosis patients exhibited LN involvement, including BHL, on conventional chest radiographs. However, thoracic CT demonstrated significant mediastinal LNS in 7 of 8 cardiac sarcoidosis patients, compared with only 1 of 20 idiopathic DCM patients. As shown in this study, when limited to end-stage DCM or DCM-like patients, the sensitivity of examination for mediastinal lymphadenopathy on thoracic 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. Thus, it may be worthwhile conducting CT on every DCM patient, particularly if they are female and have the clinical features of complete atrioventricular block, LV aneurysm, interventricular septal thinning, and/or other reported factors suspicious for cardiac sarcoidosis.18,19

Although cardiac lymphatic drainage in humans is not completely understood, the principal lymphatics may drain from the ventricular muscle and pass to the upper mediastinum via the cardiac LNS.21 BHL on the chest radiographs mainly involves the hilar, interlobar and lobar LNs (#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 present patients with cardiac sarcoidosis (Table 3).

One patient with cardiac sarcoidosis did not show definite...
mediastinal lymphadenopathy, which may be related to the fact that the degree of inflammation found on histological examination was mild. One idiopathic DCM patient had swelling of the lower paratracheal LNs (#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 is the first report describing the details of mediastinal lymphadenopathy observed on thoracic CT of DCM-like patients with histologically proven cardiac sarcoidosis. Non-invasive techniques such as 201Tl, 67Ga or 123I-metaiodobenzyl-guanidine scintigraphy and positron emission tomography have been recently revealed as useful for the identification and assessment of disease activity in cardiac sarcoidosis. In addition to these modalities, evaluation of mediastinal lymphadenopathy on thoracic CT is 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). An assessment of the superiority of either thoracic CT or the other modalities, and probably the increased value of a combination, as a diagnostic tool for cardiac sarcoidosis will be an interesting study in the future.

Acknowledgments

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