A Morphological Analysis of Chronic Myocarditis

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Eight patients with chronic myocarditis (CM), 2 showing postmyocarditis and 6 showing dilated heart with severe diffuse cell infiltration, were compared morphometrically with 27 patients with dilated cardiomyopathy (DCM, 8 with fibrosis type DCM and 19 with non-fibrosis type DCM) and 10 controls. Patients with CM had a mean age of 43.5 years (range, 17–75 years), a mean duration of clinical illness of 45.5 months, heart weight of 448 g, left ventricular wall thickness of 8 mm, number of myocyte layers of the stratum compactum layer of the left ventricle (Nf) of 125, myocyte size of 19.1 μm, and % area of fibrosis of 29.1%. The morphometric profile of patients with CM resembled that of patients with fibrosis type DCM; this appeared to be due primarily to a decrease in the number of myocardial cells and an increase in myocardial fibrosis.

In the past, most patients with myocarditis were believed to recover once they survived the acute phase. However, many studies disclosed that there were several complications and sequelae and recently, a co-operative study by the “Idiopathic Cardiomyopathy Research Committee of Japan” reported that 40% of the patients (87/218) suffered from sequelae and 8 patients showed dilated cardiomyopathy (DCM)-like features. Thus, myocarditis is generally regarded as a potential cause of DCM. But the exact relationship between myocarditis, especially the chronic form, and DCM is not yet clear. Therefore, a re-evaluation of chronic myocarditis is required.

In this study, 2 patients who contracted myocarditis and subsequently presented with a state resembling that of DCM and 4 patients with DCM showing severe and diffuse cell infiltration were examined and compared with other types of DCM.

Key words:
Postmyocarditic cardiomegaly
Myocardial fibrosis
Dilated cardiomyopathy

METHODS

For histological investigation, horizontal sections of both ventricles treated with hema-toxylin-eosin, azan, elastica-van Gieson’s, and pentachrome stains were observed under a light microscope. Fibrosis was evaluated in terms of the % area of fibrosis in the compact layer of the left ventricle, which was determined by the point-count method using an eye-piece as described previously. The number of myocardial fibers in the ventricular wall (Nf) and the diameter of myocytes also were determined by the procedures previously described.

SUBJECTS (Table I)

Two patients with a clinical diagnosis of post myocarditis and 4 with DCM ranging in age from 17 to 75 years (mean age, 43.5 years) were studied. Their mean cardiothoracic ratio was 65.8%. Patients 4 and 5 developed heart failure after showing symptoms resembling those of a common cold.

Patient 1: A 17-year-old female. She pre-
# TABLE 1 CLINICAL DATA

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical diagnosis</th>
<th>Materials CTR</th>
<th>ECG</th>
<th>Clinical course</th>
<th>History of myocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>F</td>
<td>post myocarditis</td>
<td>60% IVCD</td>
<td></td>
<td>11M</td>
<td>+ (Coxackie B2, B5)</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>M</td>
<td>DCM (post myocarditis)</td>
<td>75% abnorm. Q</td>
<td></td>
<td>9Y4M</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>F</td>
<td>DCM</td>
<td>70% RAD. LBBB</td>
<td></td>
<td>(10M)</td>
<td>-</td>
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<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>HCM → DCM</td>
<td>65% LBBB</td>
<td></td>
<td>(8Y)</td>
<td>- (common cold)</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>M</td>
<td>DCM</td>
<td>62% LBBB</td>
<td></td>
<td>(8M)</td>
<td>- (common cold)</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>M</td>
<td>DCM</td>
<td>63% Advanced block</td>
<td></td>
<td>(3Y4M)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: CTR = cardiothoracic ratio; ECG = electrocardiogram; IVCD = intraventricular conduction disturbance; RAD = right axis deviation; LBBB = left bundle block; HCM = hypertrophic cardiomyopathy

Fig.1. Histological findings of patient No.1.

- a: Panorama view of the both ventricle (azan stain). Left ventricle was dilated, and midcircular layer and outer layer were depleted. Mural thrombi were observed.
- b: Anterior wall of the left ventricle (H-E stain, ×20). Depletion of midcircular layer was marked and pathy and irregular fibrosis were seen.
- c: Lateral wall of the left ventricle (pentachrome stain, ×40). Elastic fibers increased at the depleted midcircular layer.
- d: Small round cell infiltration of left ventricle (H-E stain, ×200).

...sent with congestive heart failure after a common cold in December, 1979, and showed elevated antibody titers to Coxsackie B2 and B5 in March, 1980. Cardiac catheterization on April 30 showed a LVEF of 29%, a LVEDP of 38 mmHg, and grade II mitral regurgitation. Endomyocardial biopsy revealed lymphocyte infiltration. Biopsy 3 months later showed fibrosis and...

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CASE 2

Fig. 2. Chest X-ray films of patient No.2.

Fig. 3. Histopathological findings.

a: Anterior view of the heart (Patients No.2). Ventricular aneurysms was observed in the conus.

b: Small round cell infiltration of the left ventricular interstitium (Patients No.2, H-E stain, ×200).

c: Diffuse interstitial fibrosis and cell infiltration in patient No.3 (H-E stain ×40).

d: Medium power view of the ventricle (patient No.3, H-E stain, ×200). Small round cells and fibroblasts were observed.

less prominent lymphocyte infiltration. The patient died after 10 months due to progression of heart failure. At autopsy, the heart weighed 370 g. Slight dilation of the left ventricle, thinning of the ventricular wall, and mural thrombi were noted. (Fig. 1a) The trabecular layer remained nearly intact despite depletion of the midcircular layer in the anterior wall of the left ventricle and ventricular septum and partial loss of the outer layer of the posterolateral wall of the left ventricle. (Fig. 1b) Elastic fibers increased slightly at the depleted midcircular layer. (Fig. 1c) Residual small round cell infiltration was noted in part of the myocardial interstitium. (Fig. 1d)

Patient 2: A 20-year-old male. He was treated on March 20, 1974 for symptoms resembling a common cold. On the 25th of the same month, he experienced anterior chest pain and vomiting. Q waves were observed in leads II, III, aVF, V3 and V4, and serum GOT, GPT, LDH and CPK levels were elevated. A diagnosis of myocarditis was made. After discharge on April 13, the patient was followed up with only exercise restriction, but the cardiothoracic ratio (CTR) increased. (Fig. 2) Dyspnea on effort was noted when he entered a university in 1982, cerebral infarction developed, and the patient died of heart failure. At autopsy, the heart weighed 420 g, and a ventricular aneurysm (5 x 5 cm) was noted in the right ventricular conus. (Fig. 3a) Both ventricles were dilated, and the posterior wall of the left ventricle showed scarring. Histologically, the compact layer of the right ventricular free wall was completely lost, the myocardium was extensively depleted in fascicular units and local accumulation of small round cells was observed. (Fig. 3b)

Patient 3: A 36-year-old housewife. She had been healthy but noted general malaise in April, dyspnea on effort in August, and edema of the legs in October, 1982, and was hospitalized in March, 1983. Her blood pressure was 100/84

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mmHg, and the pulse was regular at 84/min. High-pitched systolic murmur was heard in the apical region. Hepatomegaly and pretibial edema were noted. The leukocyte count was 13,500/ mm³, erythrocyte sedimentation rate was 3 mm/hr, and CRP was 7(+). Electrocardiograms indicated sinus rhythm, bialtrial overload, right axis deviation, and left bundle branch block. She died of heart failure. Autopsy showed a heart weight of 360 g, moderate dilation of both ventricles, diffuse interstitial fibrosis, and severe infiltration, primarily of fibroblasts and small round cells. (Fig. 3cd)

Patient 4: A 44-year-old male. His older brother was diagnosed as HCM with congestive heart failure and received a heart transplant in the USA, and his younger brother suffered from HCM with obstruction. He was diagnosed at age 18 to have heart disease but was capable of exercises, including long distance running and baseball. In his 20's, he had syncopal attacks about twice a year, and at 36, his application for life insurance was rejected on the basis of electrocardiographic findings. He contracted a common cold the same year, and thereafter noted dyspnea on effort, but there were no further syncopal attacks. In 1980, echocardiographic measurement showed a thickness of the interventricular septum of 18 mm and that of the posterior septum of 16 mm. Left ventriculography indicated thickening of the left ventricular wall and dilatation of the left ventricle. Subsequently, the wall thickness decreased (6 mm in the septum and 9 mm in the posterior wall), CTR increased,
and death occurred due to heart failure. These findings suggested transition from HCM to DCM. Autopsy revealed a heart weight of 490 g, dilatation of the left ventricle and atrium, and discrete subaortic stenosis with a fibroelastotic band running transverse immediately below the aortic valve. (Fig. 4a) Horizontal sections of the ventricle showed severe fibrosis in the posterior wall and diffuse fibrotic foci accompanied by small round cell infiltration in the interstitium. (Fig. 4b) No myocardial disarray was noted.

**Patient 5:** A 69-year-old male. Complete left bundle branch block was noted in 1959. In December, 1983, he developed orthopnea after symptoms of a common cold, and was admitted. Despite treatment for congestive heart failure, he died on October 1, 1983. At autopsy, the heart weighed 600 g; both ventricles were moderately dilated, but the wall thickness (5-12 mm) was nearly normal. Histologically, scattered focal fibrosis and diffuse infiltration of inflammatory cells were noted. (Fig. 5a)

**Patient 6:** A 75-year-old male showed exertional dyspnea, and CTR was 59% in February, 1977. In June the same year, the QS pattern was noted in leads V₁-V₃, but findings in September were I, AV block, left axis deviation, and complete right bundle branch block. He presented with orthopnea and anorexia in March, 1978, and III, AV block in November, and died of heart failure in June, 1980. Autopsy showed a heart weight of 450 g and marked thinning of the lateral wall of the right ventricle. Myocardial fibrosis was macular or fascicular, and tended to be severe in the middle and inner layers. Moderate inflammatory cell infiltration was noted in tissues histologically suggested to be fibrotic. (Fig. 5b)

Table II shows morphometric data for each patient. The mean heart weight increased to 448 ± 89 g. Myocardial fibrosis was evaluated as (++), and more than 20% quantitatively. The left ventricular wall thickness was small (5-9 mm), and the mean Nf was 125, suggesting not only structural dilatation but also myocyte depletion. The size of myocytes ranged from 23.9 to 13.9 μm, indicating hypertrophy of residual myocytes.

Table III compares morphological data between the patients with DCM and those with chronic myocarditis. DCM was classified into fibrosis and non-fibrosis types on the basis of a 25% area of fibrosis. Ten hearts without significant coronary stenosis of non-diabetic individuals free of heart disorders were studied as the controls.

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The total clinical course of non-fibrosis type DCM was shorter than that of the fibrosis type DCM, but the difference was not statistically significant. The wall thickness of the left ventricle was reduced in patients with chronic myocarditis and non-fibrosis type DCM. NF was significantly smaller, and the myocyte size was significantly greater in patients with chronic myocarditis than in those with non-fibrosis type DCM or the controls.

DISCUSSION

Historically, a diagnosis of chronic myocarditis was made in patients with non-valvular disease showing congestive heart failure without morphological considerations. Since criticism against this diagnosis by Dr. P.D. White, the diagnosis of chronic myocarditis was nearly replaced with that of primary myocardial disease or idiopathic cardiomyopathy. Okada stated in his study in 1961 that postinflammatory cases accounted for about 30% of the cardiomyopathy cases, but little attention was paid to this finding in those days because DCM had been regarded as a homogeneous disease. Recently, DCM is increasingly understood as a heterogeneous disease which exhibits multiple pathological conditions.

The frequency of occurrence of interstitial cell infiltration in patients with DCM has been varyingly reported at 6% to 63%. A diagnosis of myocarditis has usually been made on the presence of cell infiltration in biopsy specimens. However, the inflammation is often focal when the condition is mild to moderate, so the wide range of frequency in biopsy specimens may reflect sampling errors. This problem can be avoided in autopsy cases because of the large volume of the sample. In this study, the subjects were limited to patients with definite diagnoses showing postmyocarditic cardiomegaly (PMC) or marked diffuse cell infiltration. Our 6 patients exhibited marked interstitial fibrosis. Chronic myocarditis and fibrosis type DCM both showed a large % area fibrosis.

The increase in the myocyte size may be regarded as a compensatory change for the decrease in NF. With respect to the changes in NF and myocyte size, chronic myocarditis appears to resemble fibrosis type DCM rather than non-fibrosis type DCM. If the lack of capacity for compensatory hypertrophy is assumed to be a sign of impairment of the myocardium itself, the reduced cardiac function in patients with chronic myocarditis and fibrosis-type DCM, in whom the compensatory hypertrophy ability appears to be retained, is considered to be due to a decrease in contraction elements (myocytes) and an increase in stiffness (fibrosis) rather than to a disease of the myocardium per se.

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REFERENCE


