ENDOMYOCARDIAL BIOPSY FINDINGS IN PEDIATRIC PATIENTS WITH POST MYOCARDITIC STATE

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Endomyocardial biopsy was performed on eight children 5 to 12 years old, who were in post myocarditic state. They were evaluated within 2 to 25 months (mean lyr and 1 m) after the onset of the symptoms. Two of the patients developed heart failure and six patients developed other cardiac manifestations such as syncope, palpitation or ECG abnormalities at onset. Definite elevation of viral antibody titer was observed in four patients. Radio-nuclide angiography was also performed in all eight patients. An abnormal perfusion area was observed in six patients as a focal hypoperfusion area by TI-201 myocardial imaging. Ejection fraction was examined by Tc-99m-HSA gated equilibrium ventriculography. LVEF was reduced in 3 patients and RVEF was reduced in 2 patients.

Judging from the histopathological findings, these patients were divided into three categories: chronic or smoldering myocarditis (3 patients); healing or healed myocarditis (4 patients); and post myocarditic hypertrophy (1 patient).

Measurement of left ventricular function was obtained by cardiac catheterization and left ventriculography (LVG), which revealed some abnormal findings such as increased left ventricular mass index, increased left ventricular end diastolic volume index (LVEDVI) and reduced left ventricular ejection fraction (LVEF).

Therefore, endomyocardial biopsy findings of pediatric patients in a post myocarditic state reveal certain histopathological abnormalities even in the long-term follow-up period in the absence of cardiac dysfunction.

MYOCARDITIS, especially in the acute stage, is sometimes followed by unexpected sudden cardiac death; sudden onset of severe congestive heart failure and life threatening arrhythmias. Although most patients with acute myocarditis seem to have a good prognosis after several months, a few deteriorate rapidly. Some patients exhibit reduced cardiac performance; recurrent inflammation and sustained arrhythmias.

Evaluation of the changes in myocardial

Key Words:
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Abbreviations: C.I = cardiac index; CoX = coxsackie; CTR = cardio-thoracic ratio; ECG = electrocardiogram; EDV = end diastolic volume; EF = ejection fraction; ESV = end systolic volume; LV = left ventricle; LVG = left ventriculography; PVC = paroxysmal ventricular contraction; RV = right ventricle

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structure and cardiac function in the post myocarditic state is very important, but most studies concern experimental animals\(^5\)–7 or human adults\(^8\) Such evaluation has not yet been made specifically for infants and children with myocarditis\(^{25}\).

Endomyocardial biopsy in children is not performed often because of the difficulty in obtaining tissue samples safely. With myocarditis in the acute stage, biopsy is potentially dangerous because of the proclivity for severe heart failure and the possibility of subsequent arrhythmia. In this report, we present our observations of endomyocardial biopsy findings in children in the post myocarditic state.

### PATIENTS AND METHODS

Eight pediatric patients with myocarditis were examined histopathologically using endomyocardial biopsies performed between July, 1979 and October, 1983. The patients were examined between 2 and 25 months (mean 13 months) after onset. Cardiac catheterization and endomyocardial biopsies were performed on all eight patients—5 males and 3 females—who were 5 years, 4 months to 12 years, 5 months of age (mean age: 8 years, 10 months). All were in a post myocarditic state. Their clinical features at onset are shown in Table I.

<table>
<thead>
<tr>
<th>Case Age No.</th>
<th>Clinical features</th>
<th>Etiologic agent</th>
<th>ECG</th>
<th>CTR</th>
<th>TI-201</th>
<th>99m-Tc-HSA LVEF</th>
<th>RVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 11y10m</td>
<td>Heart failure</td>
<td>Cox B5</td>
<td>LPHB, Q, ST-T, LB PVC</td>
<td>62%</td>
<td></td>
<td></td>
<td>Hypo</td>
</tr>
<tr>
<td>2 10y 2m</td>
<td>Heart failure</td>
<td>LAHB, LB PCV</td>
<td></td>
<td>60%</td>
<td></td>
<td></td>
<td>Nor</td>
</tr>
<tr>
<td>3 12y 5m</td>
<td>Syncope</td>
<td>PVC, ST-T</td>
<td></td>
<td>44%</td>
<td></td>
<td></td>
<td>Hypo</td>
</tr>
<tr>
<td>4 5y 4m</td>
<td>fever, Palpitation</td>
<td>PVC</td>
<td></td>
<td>50%</td>
<td></td>
<td></td>
<td>Nor</td>
</tr>
<tr>
<td>5 7y 2m</td>
<td>fever abdominal pain</td>
<td></td>
<td>PVC ST-T</td>
<td>59%</td>
<td></td>
<td></td>
<td>Hypo</td>
</tr>
<tr>
<td>6 5y 7m</td>
<td>fever</td>
<td>PAC</td>
<td></td>
<td>48%</td>
<td></td>
<td></td>
<td>Hypo</td>
</tr>
<tr>
<td>7 9y 3m</td>
<td>fever, leg pain</td>
<td>Rubella ST-T</td>
<td></td>
<td>45%</td>
<td></td>
<td></td>
<td>Hypo</td>
</tr>
<tr>
<td>8 9y 7m</td>
<td>fever, rash, joint pain</td>
<td></td>
<td>Cox B1, B3 ST-T, LB</td>
<td>60%</td>
<td></td>
<td></td>
<td>Hypo</td>
</tr>
</tbody>
</table>

*Abbreviations used are: Cox = Coxsackie virus; LPHB = left posterior hemic block; Q = abnormal Q wave; ST-T = ST-T wave change; PVC = paroxysmal ventricular contraction; LAHB = left anterior hemic block; PAC = paroxysmal atrial contraction; LB = low voltage; Hypo = hypoperfusion area; Nor = normal; Red = reduced; TI-201 = Thallium-201 image scan; 99m-Tc-HSA = 99m Technetium-HSA equilibrium ventriculography; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction.*
(Cook, CYCFW-YABE-111883) from the RV septum in 5 patients and from the LV free wall in 3 patients. LVEDV, LVESV and LVEF were calculated from LVVG (Table II). One or two biopsy specimens were obtained from each patient: the samples were 2 to 3 mm in greatest diameter.

Specimens were processed routinely for light microscopy, initially by fixation in 2.5% glutaraldehyde at room temperature and subsequently by embedding in paraffin. Sections were cut and mounted and three slices from each block were stained with hematoxylin-eosine, PTAH, and the elastica-Masson trichrome method. Each slide was examined by two observers.

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Fig.1. Biopsy findings of Case 2
Disarrangement, variation in size of myocyte and degeneration, edema and fibrosis were observed.

Hypertrophy was graded according to myocyte diameter as (+) over mean ± 2SD, (+++) over mean ± 4SD and (++++) over mean ± 7SD. Arrangement, degeneration, change of nucleus, edema, endothelial hyperplasia, fibrosis and afteriolar thickening were graded as: (+) mild, (+++) moderate and (++++) marked. Capillary proliferation was graded as: (−) under 10, (+) 10–15, (+++) 16–20, (++++) over 21 capillaries in one visual field of x 400 magnification (1F/x 400). Cellular infiltration was graded as (−) under 10, (+) 11–20, (+++) over 21 mononuclear cells 1F/x 400.

Healed or healing myocarditis was defined as follows: mild cellular infiltration (–) (+), proliferation of capillaries (–) (+) and myocardial degeneration (–) (+); mild-to-moderate disarrangement of myofibrils (–) (++), fibrosis (–) (+++) and edema (–) (+++).

Chronic or smoldering myocarditis was

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defined as follows: mild-to-moderate cellular infiltration, moderate edema and proliferation of capillaries, but with mild fibrosis and degeneration. The degree of post myocarditic hypertrophy was recorded as moderate-to-severe hypertrophy, disarrangement, degeneration, change of nucleus and fibrosis, although proliferation of capillaries and edema were mild and cellular infiltration was almost absent.

RESULTS

The histopathological findings of the eight patients are presented in Table III. Diagnosis in cases 1, 2 and 5 was chronic myocarditis with cellular infiltration. Cases 4, 6, 7 and 8 had healed or healing myocarditis with scanty or mild cellular infiltration, mild fibrosis and mild myocardial disarrangement. Case 3 was classified as postmyocarditic hypertrophy with marked fibrosis, disarrangement or disarray and scanty cellular infiltration. Case 2 was a girl, aged 10 years, 2 months, who had severe heart failure and syncope at onset. A left anterior hemiblock and short run.of.-PVCs were observed on ECG. Cardiac catheterization and endomyocardial biopsies were done at 5 months after the onset. CTR on chest X-ray was reduced from 60% at admission to 42%, 2 months after the onset. Data from cardiac catheterization showed LVEDVI 55 ml/M2, LVEF 0.59 and C.I. 4.7 L/min/M2. Disarrangement, variation in size of myocyte and degeneration were mild, but moderate cellular infiltration, edema and fibrosis were observed. This case was determined to be smoldering or chronic myocarditis (Fig. 1). Case 8 was a girl aged 9 years, 7 months, who had fever, erythema multiform, joint pain and palpitation at onset. Pericardial effusion was observed on echocardiography. Elevation of Coxsackie B1 and B3 virus antibody titer was from x 1024 to x 4096. CTR on chest X-ray was 60%. The patient had reactivated ESR, CPR, CPK and edema and was treated with 40 mg
prednisolone for two years with tapering. Data from cardiac catheterization were LVEDVI 75 ml/M2, LVEF 0.79, and C.I. 6.8 L/min/M2. Degeneration, fibrosis and cellular infiltration were mild; edema, capillary proliferation and disarrangement were moderate. This case was confirmed as healing myocarditis. (Fig. 2)

Case 3 was a boy aged 12 years, 5 months, who developed syncope five days after a febrile illness. ECG findings at admission revealed PVC and ST-T changes and CTR on chest X-P was 52%, which reduced to 44% at two months after the onset. TI-201 myocardial imaging revealed an RV image; RVEF was 0.18 and LVEF was 0.53 on Tc-99m-HSA GEV. LV mass I had increased to 146 gm. Endomyocardial biopsy from the septum of the RV revealed marked hypertrophy, variation in size of myocytes, and disarrangement. Fragmentation, degeneration of nucleus and fibrosis were also observed, but capillary proliferation was mild. The case was considered to be post myocarditic hypertrophy. (Fig. 3)

Selective coronary angiography done for these eight patients revealed no stenotic or occlusive lesions. A hypoperfusion area was observed on TI-201 myocardial imaging at the time of catheterization in six patients cases 1, 3, 5, 6, 7 and 8.

Reduced LVEF and reduced RVEF was observed in Tc-99m-HSA GEV in cases 2, 5 and 8 and case 3 and 5, respectively (Table I). Table III shows the data of cardiac parameters. Reduced LVEF was observed in case 1 and increased LV mass index was observed in cases 3 and 5.

**DISCUSSION**

The prognosis for patients with previous viral myocarditis is variable. Acute myocarditis may be followed by residual damage. The viral-induced myocardial injury may lead to later cardiomyopathy. Complications and sequelae of myocarditis include chronic myocarditis, continuing inflammation, ventricular aneurysm, impaired myocardial function, arrhythmia and rapid deterioration.

Histopathological findings of Coxsackie virus myocarditis in experimental animals have been previously reported. These reports suggest that fibrosis, myocardial hypertrophy, and disarrangement were present even during the long-term follow-up period. In the acute phase, light-microscopic examination revealed massive cellular infiltration and myocytolysis within the first few weeks. Myocardial swelling fragmentation, interstitial edema, degeneration and mineralization was present in some cases. After the acute phase, perimyocardial fibrosis increases but cellular infiltration gradually decreases at about one month after the onset. In the chronic phase, most animals developed no cardiomegaly, but minimal interstitial fibrosis and various degenerative conditions were found in some cases. In addition, myocardial cellular hypertrophy or atrophy or residual inflammatory foci were also present. A few animals revealed significant cardiomegaly with moderate-to-severe interstitial fibrosis. In humans, Burch observed that the inner one-third of myocardium was involved more often than the outer two-thirds but pathological findings may vary with the animal species, age and strain of virus. Myocarditis has been reported to develop more easily in human infants and in younger animals. Repeated endomyocardial biopsy findings in the course of human myocarditis are similar to those of experimental animal models. In its acute phase, there is interstitial infiltration of lymphocytes, plasma cells and mononuclear cells at the perivascular area, interstitial edema, myocytolysis or necrosis, dilatation of capillaries and various grades of degeneration. In the subacute phase, interstitial fibrosis develops as interfiber, perivascular and/or subendocardial fibrosis. Endothelial swelling of capillaries is usually present. When infiltration of inflammatory cells decreases, fibroblast may increase. Fragmentation of myocardium, interstitial fibrosis, myocardial disarrangement or disarray or myocardial hypertrophy are sometimes present. Kitaura suggested that subclinical myocarditis could result in dilated cardiomyopathy in some cases. He also reported that characteristic findings of post myocarditic cardiomegaly include scattered and perivascular fibrosis, proliferation of capillaries and remaining small inflammatory foci with infiltration into inflammatory cells, in addition, he stated that this condition is sometimes associated with pericarditis. In his study, proliferation of capillaries was present one month after the onset and proliferation increased as the inflammation healed. Endothelial swelling and narrowing of the lumen usually occurred, but capillary thrombosis was rarely detected.

Fenglio et al. proposed the pathological classification of myocarditis by endomyocardial biopsy and divided the patients into three

groups: acute myocarditis, rapidly progressive myocarditis, and chronic myocarditis. According to their classification, the diagnosis of acute myocarditis is based on the finding of acute cell damage. In contrast to acute myocarditis, rapidly progressive or chronic myocarditis is diagnosed when acute healing and healed cell damage are present in the same biopsy specimen. Healing cell damage is defined as myocyte-loss and replacement by granulation tissue associated with mononuclear cell infiltration. Healed cell damage is defined as focal fibrosis with the absence of inflammatory cell infiltrate and is graded as the degree of fibrosis. In chronic myocarditis, scattered foci of acute and healing cell damage were found throughout the samples.

Mechanisms of myocardial damage and the continuing inflammatory process have not been fully discussed in the literature to date. Abnormal immune reactions such as delayed hypersensitivity, cytotoxic T lymphocyte, immuno-globulin, cell-mediated immunity, and anti-hepat antibody have been reported to play an important role in myocarditis.

In this study, we did not detect any signs of dilated cardiomyopathy in the post myocarditic state, as has been reported in some of the previous literature on acute myocarditis. In our series, heart failure developed in cases 1 and 2 and other cardiovascular symptoms, including palpitation, syncope, arrhythmia, mild ST-T change on ECG and transient increase in CTR on chest X-ray, were observed in mild cases. The terms as mild acute myocarditis or subclinical myocarditis may be used for these mild cases. Cases 2 and 5 were considered to be chronic myocarditis or continuing inflammatory process based on pathological findings, but cardiac function was not impaired at the time of catheterization. Case 8 represented repeated deterioration and, in this case, corticosteroid was effective. Although the clinical course revealed chronic myocarditis, pathological findings after using corticosteroid appeared to be that of healing or healed myocarditis.

The natural history of myocarditis should be discussed more exactly. Myocardial dysfunction resulting from previous myocarditis was examined in our series by Tc-99m-HSA ECG-gated equilibrium angiography and left ventriculography, and verified by endomyocardial biopsy. But no significant correlation between severity of clinical manifestations at onset and endomyocardial biopsy findings was found.

We conclude that, if possible, endomyocardial biopsy may be attempted during the long-term follow-up period of pediatric patients in a post myocarditic state in order to evaluate residual pathological changes. Abnormal histopathological findings may be present in acute myocarditis and also in subclinical or mild acute myocarditis during the patient’s convalescent stage.

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