Analysis of Histopathologic Findings in Cases with Dilated Cardiomyopathy with Special Reference to Formulating Diagnostic Criteria on the Possibility of Postmyocarditic Change

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From our study employing serial endomyocardial biopsy in patients with acute viral or idiopathic myocarditis, we were able to construct histopathologic criteria for acute, subacute and convalescent myocarditis. We realize that it is difficult for the inexperienced observer to make an appropriate diagnosis of myocarditis or postmyocarditic changes in patients with dilated cardiomyopathy (DCM). In order to overcome this problem, each finding was graded and the scores obtained were analyzed statistically and compared with those from hypertrophic cardiomyopathy (HCM) and chronic right ventricular overloading (CRVO). The scores were obtained by summing the gradings for each of the following findings: increase of fibrocytes, increase of fibroblasts in the interstitium, hypertrophy of myocytes, fragmentation of muscle bundles, interstitial fibrosis, disarrangement of muscle bundles, abnormal branching, variation in size, increased glycogen deposition in the sarcoplasm, scarcity of myofibrils, and nuclear degeneration of myocytes and endocardial thickening. Since the increase in number of fibrocytes was considered important, its value was doubled. Scores in each group were as follows: convalescent myocarditis: 17.1 ± 4.7 ($n = 10$), DCM: 13.2 ± 3.3 ($n = 47$), HCM: 9.7 ± 2.4 ($n = 20$), CRVO: 7.0 ± 3.6 ($n = 21$). It was found that the scores for cases with myocarditis in the convalescent stage and in DCM were higher than those found for cases with either HCM and CRVO ($p < 0.05$). In summary, the high score for postmyocarditis in DCM could suggest that prior myocarditis is an important causative factor of this disease.

VIRAL myocarditis is considered to be the most likely etiological agent of dilated cardiomyopathy (DCM).¹⁻⁴ The incidence of endomyocardial biopsy-defined myocarditis varies extensively, from 6% to 25%, according to the investigator.⁵ As we have long-term experience in interpreting endomyocardial biopsy findings in

patients with myocarditis and other myocardial diseases,⁶⁻¹⁷ we analyzed the biopsy findings in DCM cases and noted findings similar to those seen in viral or idiopathic myocarditis.¹⁴ This report describes the semi-quantitative assessment of the postmyocarditic change.

Key Words:

Endomyocardial biopsy
Myocarditis
Dilated Cardiomyopathy
Diagnostic Criteria

MATERIALS AND METHODS

Forty-seven patients with DCM, who were admitted to the Heart Institute of Japan, Tokyo Women's Medical College, during 1977-1982,

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TABLE I ESSENTIAL HISTOPATHOLOGIC FINDINGS IN THE THREE STAGES OF MYOCARDITIS OBTAINED BY RIGHT VENTRICULAR ENDOMYOCARDIAL BIOPSY¹⁰

<i>Stage, days after the onset of the disease, and case number</i>	<i>Findings for scoring</i>
<i>Acute (0–10 days)</i>	<i>Infiltration of lymphocytes</i> <i>Infiltration of plasma cells</i> <i>Infiltration of macrophages</i> <i>Myocytolysis</i> <i>Swelling of nuclei of myocyte</i> <i>Swelling of myocytes</i> <i>Interstitial edema</i> <i>Increase of fibroblasts</i>
<i>6 biopsy & 3 autopsy cases</i>	<i>Fragmentation of muscle bundles</i> <i>Interstitial fibrosis</i> <i>Disarrangement of muscle bundles</i> <i>Abnormal branching of myocytes</i> <i>Variation in size of myocytes</i> <i>Deposition of glycogen in myocytes</i> <i>Scarcity of myofibrils</i> <i>Endocardial thickening</i>
<i>Subacute (11–21 days)</i>	<i>Infiltration of lymphocytes</i> <i>Infiltration of plasma cells</i> <i>Infiltration of macrophages</i> <i>Myocytolysis</i> <i>Swelling of nuclei of myocytes</i> <i>Interstitial edema</i> <i>Increase of fibroblasts</i> <i>Increase of fibrocytes</i>
<i>6 biopsy & 3 autopsy cases</i>	<i>Fragmentation of muscle bundles</i> <i>Interstitial fibrosis</i> <i>Disarrangement of muscle bundles</i> <i>Abnormal branching of myocytes</i> <i>Variation in size of myocytes</i> <i>Deposition of glycogen in the myocytes</i> <i>Scarcity of myofibrils</i> <i>Endocardial thickening</i> <i>Swelling of myocytes</i>
<i>Convalescent (more than 22 days, postmyocarditis)</i>	<i>Increase of fibrocytes</i> <i>Increase of fibroblasts</i> <i>Hypertrophy of myocytes</i> <i>Fragmentation of muscle bundles</i> <i>Interstitial fibrosis</i> <i>Disarrangement of muscle bundles</i> <i>Abnormal branching of myocytes</i> <i>Variation in size of myocytes</i> <i>Deposition of glycogen in the myocytes</i> <i>Scarcity of myofibrils</i> <i>Endocardial thickening</i> <i>Degeneration of nuclei of myocytes</i> <i>(deformities, pyknosis, double nuclei, enlargement)</i>
<i>13 biopsy cases</i>	

TABLE II

PMC classification		acute	subacute	convalescent —healed	
PM n = 10	definitely			3	30%
	highly	not	not	5	50%
	slightly	applicable	applicable	2	20%
	not			0	0%
DCM n = 47	definitely	0	0	0	0%
	highly	0	0	8	17%
	slightly	0	1	22	47%
	not	0	0	17	36%
HCM n = 20	definitely	0	0	0	0%
	highly	0	0	0	0%
	slightly	0	0	4	20%
	not	0	0	16	80%
CRVO n = 21	definitely	0	0	0	0%
	highly	0	0	0	0%
	slightly	0	0	4	19%
	not	0	0	17	81%

Number of cases and percentages classified according to the postmyocarditic scores and also into the three stages of myocarditis. The results of the postmyocarditic (PMC) scores are categorized into 4 groups regarding the myocarditis, i.e. definitely (more than 22 points), highly (17–21 points), slightly (12–16 points), and not (less than 11 points) suggestive.

were studied. Diagnosis was made by means of a conventional cardiologic survey which included cardiac catheterization, and endomyocardial biopsy from the right ventricle^{6,7}. In all cases, coronary arteriographic findings revealed no significant stenosis of the coronary arteries. Also, 20 cases (14 biopsy and 6 autopsy) with acute viral or idiopathic myocarditis were analyzed.⁹ Biopsied cases consisted of 9 patients with subacute and 13 patients with convalescent myocarditis (Table I). Right ventricular endomyocardial biopsy findings in 20 patients with hypertrophic cardiomyopathy (HCM) and 21 patients with chronic right ventricular overloading (CRVO) were analysed for the control study. Clinical and histopathologic profiles of the myocarditis and of the CRVO cases were reported previously.^{6–12} A semi-quantitative histopathologic assessment of the biopsied samples was done using our own method of interpretation.^{10,13,16} The histopathologic findings of myocarditis were classified into acute, subacute and convalescent stages (Table I)^{10–12}. And, at each stage, the interpreted findings were classified into four categories as follows: 1) Definitely, 2) Highly, 3)

Slightly and 4) Not suggestive, of myocarditis. Table I shows the histopathologic criteria for diagnosing the three stages of myocarditis. The table was constructed from our data analysis of biopsied cases with acute myocarditis that underwent serial endomyocardial biopsy and from the autopsied cases.¹⁰ Table I includes our biopsy experience in 10 cases, in 9 of which the biopsies were performed at the acute or subacute stage of myocarditis.¹⁰ As can be seen in the table, the small round cell infiltrations disappeared and instead, an increase in fibrocytes occurred. Also, the degree of pathology observed at the subacute stage became less severe. At the convalescent stage, the myocarditic changes were less prominent and many non-specific changes were observable. Therefore, it was difficult to make a definite histopathologic diagnosis of preceding myocarditis.^{14,15} In order to overcome this problem, we have made a scoring system to assess convalescent myocarditis, which is now defined as postmyocarditic change (PMC), by summing the scores of each finding. The scores were obtained by grading the histopathologic findings according to the severity into 0, 1+, 2+ and 3+.¹⁰

Fig.1. Right ventricular endomyocardial biopsy finding in a case with dilated cardiomyopathy. Post myocarditic score as indicated in Table I amounted to 18 in this case.

Fig.2. Right ventricular endomyocardial biopsy finding in a case with dilated cardiomyopathy. The changes are not so striking and the postmyocarditic score was 6.

In the assessment of convalescent myocarditis, the severity of the degree of fibrocytic infiltration is doubled as this is regarded as the most important finding that characterizes PMC. The scores thus calculated revealed that the mean $\pm$ standard deviation was 17.1 ± 4.7 . The criteria for assessing the degree of suggestiveness of postmyocarditic change are as follows: when the mean value is over 22 points, it is classified as definitive PMC. When the value is between 17 to 22, it is assessed as highly suggestive, when the

value is between 12 and 16, (mean - 1SD), it is classified as slightly suggestive, and when the change is less than 11, as not suggestive of PMC. By employing this method, biopsy-obtained histopathologic findings in the DCM, HCM, and CRVO groups were scored and compared. Furthermore, in cases with DCM, the case histories of the patients were examined and when influenza-like symptoms (flu-syndrome) had preceded the onset of severe heart disease within 10 days the patients were classified into a positive

Fig. 3. Incidence of suggestiveness of postmyocarditic change in various diseases. Bars indicate the percentages of the suggestiveness of the postmyocarditic changes in four categories (definitely, highly, slightly and not suggestive). (See text for explanations).

flu-syndrome group, and, if these symptoms were absent, as a negative flu-syndrome group. Statistical analysis was made using one-way analysis of variance, and the multi comparison method by Scheffe's test.

RESULTS

Results of the histopathologic analysis of myocarditic change in 47 cases with DCM are shown in Table II. Subacute myocarditic change was seen in only one case, in which there was a slight amount of lymphocytic infiltration. However, the other myocardial changes were not so prominent and the biopsied finding was classified as slightly suggestive of subacute myocarditis. The other 47 cases revealed notable findings of PMC (postmyocarditic change) and when the suggestiveness of PMC was classified, no cases were definitely suggestive, 8 cases (17%) were highly, and 22 cases (47%) were slightly suggestive and 17 cases (36%) were not suggestive (Table II).

In Fig. 1, a histopathologic picture with a PMC score of more than 18, i.e., highly suggestive, is shown. This patient had a cardiothoratic ratio of 71% and cardiac catheterization showed a left ventricular enddiastolic volume of 180 ml/m², and a left ventricular ejection fraction of 10%. A biopsy revealed prominent fibrocyte

infiltration in the interstitium as well as hypertrophy of myocytes, disarrangement of the muscle bundles, increase in abnormal branching, scarcity of myofibrils and interstitial fibrosis. This patient had had a fever of 38°C three weeks prior to the onset of congestive heart failure. The biopsy was performed 6 months after the onset of congestive heart failure.

In Fig. 2, an example of the not suggestive category with a PMC score of point 6 from a case with DCM is shown. This patient had a cardiothoratic ratio of 58%, left ventricular end-distolic volume of 108 ml/m², and a left ventricular ejection fraction of 35% when the symptoms had stabilized, and the biopsy revealed a slight amount of hypertrophy of myocytes, disarrangement of muscle bundles and interstitial fibrosis.

Table II also shows the results of the classification thus obtained in HCM, and CRVO groups. No case in either group showed histopathologic changes compatible with the acute and subacute stages of myocarditis; also, no case showed a PMC score of more than 17.

Figure 3 shows the results of the classification of suggestiveness where a biopsy diagnosis of convalescent myocarditis was made. It was also noted that even those cases with biopsy-proven myocarditis could be placed in the slightly suggestive category at the convalescent stage. In

Fig.4. Postmyocarditic scores determined by the authors in various diseases. Each score is statistically analyzed for difference. PM: Postmyocarditis (Biopsy proven cases with myocarditis in convalescence). Flu ⊕ or ⊖ indicate positive or negative influenza-like illness (see text).

DCM, 17% of the cases showed highly suggestive, which was in contrast to the HCM or CRVO groups in which all cases showed only slightly suggestive or not suggestive. Also, slightly suggestive PMC was recognized in 47% of the cases.

When the PMC scores from each group were compared, as shown in Fig. 4, the highest score was found in postmyocarditis (PM) group, i.e., 17.1 ± 4.7 . On the other hand, the DCM group showed the next highest score, 13.2 ± 3.3 . When the DCM was divided into positive flu-syndrome and negative flu-syndrome (prior to the onset of heart disease), the individual scores were 14.1 ± 3.6 and 12.8 ± 3.2 , respectively. When the scores were analyzed statistically, the scores in DCM with negative flu-syndrome were found to be significantly lower than those of the postmyocarditis group. The scores in HCM and CRVO were 9.7 ± 2.4 and 7.0 ± 3.6 respectively, and were significantly lower than those of the other 3 groups.

DISCUSSION

We have been studying endomyocardial biopsy findings in cases with acute viral or idiopathic myocarditis and from our experience of serial biopsy, we reported that some cases show clinical symptoms and signs of dilated cardiomyopathy (DCM) at the convalescent stage of the disease^{2,9,17}. Also, through our observation by means of serial biopsy, a list of the histopathologic findings has been made.⁹ We were able to quantify essential histopathologic features of each stage of the disease (Table I). Take et al.¹⁴ reported that postmyocarditic change was observed in 15% of 148 patients with DCM that they examined. We further classified histopathologic changes according to the stage of the disease, and found four categories of suggestiveness of myocarditis in the histopathologic findings in cases with DCM. As stated in the method section, the postmyocarditic score was designed

and calculated semiquantitatively. This type of scoring system was devised because conventional histopathologic assessment^{12,15} is very difficult for beginners in this field. The diagnoses of one of the authors, who has had 20 years of biopsy interpretation experience, showed similar results to those obtained by using the scoring system in 78% of the cases. Therefore, this system appears to be a reliable method for detecting postmyocarditic change (PMC).

In a histopathologic analysis of 47 patients with DCM, 64(17 + 47)% were classified into the PMC group. A more detailed analysis of the histopathologic findings showed that the PMC was highly suggestive in 17% of the 47 cases (Table II, Fig. 3).

In cases with either HCM or CRVO, highly suggestive findings were never seen. Furthermore, it was noticed that the postmyocarditic score in DCM cases with negative flu-syndrome was the same as that of convalescent myocarditis.

It was further noted that the incidence of myocarditic change in both HCM and CRVO was infrequent. It can be said that in some cases, DCM is derived from the end result of preceding myocarditis. It was noted that there were no cases of DCM which showed definitive myocarditic change because those with preceding myocarditis usually show non-specific myocardial changes only. Therefore, it seems impossible to diagnose definitive myocarditis at the histopathologic level. This type of histopathologic diagnosis has limitations in that the preceding myocarditis cannot be ascertained. It should also be stated here that when the "slightly suggestive" category of PMC is obtained by the biopsy, it may have a risk of about 20% false-positive interpretation of the biopsy findings, as was seen in 20% and 19% of the cases with HCM and CRVO, respectively. A more refined technique using monoclonal antibodies to lymphocyte subsets¹⁸ should be incorporated.

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