

Long-Term Outcome of Patients With Biopsy-Proved Myocarditis: Comparison With Idiopathic Dilated Cardiomyopathy

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Objectives. The study objectives were 1) to assess the long-term outcome of patients with biopsy-proved lymphocytic myocarditis (Dallas criteria), and 2) to compare the outcome of these patients with that of patients with idiopathic dilated cardiomyopathy.

Background. Endomyocardial biopsy is frequently performed in patients presenting with dilated cardiomyopathy to identify lymphocytic myocarditis. Most previous studies of the natural history of myocarditis were performed before the establishment of the Dallas criteria. Thus, it is important to evaluate the prognostic value of positive endomyocardial biopsy findings in patients presenting with dilated cardiomyopathy, using standardized criteria for lymphocytic myocarditis.

Methods. All endomyocardial biopsy results from the Mayo Clinic (October 1979 to April 1988) with a diagnosis of myocarditis were reclassified according to the Dallas criteria. Patients whose biopsy specimens showed borderline or lymphocytic myocarditis were included in the study group; those with systemic inflammatory diseases known to be associated with myocardial involvement were excluded. Study group survival was compared with that for a cohort of patients with idiopathic dilated cardiomyopathy seen at the Mayo Clinic from 1976 to 1987 who had endomyocardial biopsy findings negative for myocarditis.

Results. Biopsy specimens from 41 patients met the Dallas criteria for a diagnosis of myocarditis ($n = 28$) or borderline myocarditis ($n = 13$). Of these 41 patients, 9 were excluded

because of the presence of systemic diseases known to be associated with myocarditis, and 5 patients were excluded because of lack of available follow-up data. The myocarditis study group therefore included 27 patients (10 with borderline myocarditis, 17 with myocarditis). Fifty-eight patients with a diagnosis of idiopathic dilated cardiomyopathy who underwent endomyocardial biopsy served as the comparison cohort. Ejection fraction was lower in patients with idiopathic dilated cardiomyopathy ([mean \pm SD] $25 \pm 11\%$) than in those with myocarditis ($38 \pm 19\%$, $p = 0.001$), even though a higher proportion of myocarditis group patients were in New York Heart Association functional class III or IV (63%) than patients in the dilated cardiomyopathy group (30%, $p = 0.005$). There was no difference in 5-year survival rate between the myocarditis and idiopathic dilated cardiomyopathy groups (56% vs. 54%, respectively).

Conclusions. This study demonstrates that the long-term outcome of patients with biopsy-proved myocarditis seen in a referral setting is poor, although no different from that of patients with idiopathic dilated cardiomyopathy. With the current lack of proved effective treatment for lymphocytic myocarditis and no demonstration of survival benefit for patients with myocarditis, these data suggest that endomyocardial biopsy performed to exclude myocarditis is of limited prognostic value in the routine evaluation of dilated cardiomyopathy.

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Despite three decades of study, lymphocytic myocarditis remains an elusive clinical entity. The diagnosis of myocarditis is challenging, and the reported prevalence has varied widely. The extent to which myocarditis is a precursor of idiopathic dilated cardiomyopathy is uncertain but continues to be a subject of intense investigation. Furthermore, controlled trials demonstrating effective therapy for lymphocytic myocarditis are currently lacking.

Most recent studies (1-4) suggest that biopsy-proved myo-

carditis diagnosed according to the Dallas criteria is relatively uncommon in the United States. Natural history studies of myocarditis performed before the establishment of the Dallas criteria probably included patients not fulfilling the current histologic criteria (5-10). However, endomyocardial biopsy continues to be performed frequently in patients presenting with dilated cardiomyopathy in the belief that identifying lymphocytic myocarditis will have prognostic value or therapeutic implications.

The purpose of the present study was 1) to assess the long-term outcome of patients with biopsy-proved lymphocytic myocarditis diagnosed according to the Dallas criteria, and 2) to compare the outcome of patients with myocarditis with that of patients with idiopathic dilated cardiomyopathy who had negative endomyocardial biopsy findings for lymphocytic myocarditis.

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Methods

Permission to conduct this study was granted by the Institutional Review Board of Mayo Foundation. All endomyocardial biopsies performed at the Mayo Clinic from October 1979 to April 1988 with a diagnosis of myocarditis were reviewed and classified according to the Dallas criteria.

Patients. Patients whose biopsy findings met the criteria for borderline or definite lymphocytic myocarditis were included in the study. Patients with systemic inflammatory diseases known to be associated with myocardial involvement and patients without available follow-up were excluded.

Patients with lymphocytic myocarditis were compared with a cohort of patients with idiopathic dilated cardiomyopathy seen at the Mayo Clinic from 1976 to 1987 who had negative endomyocardial findings for myocarditis according to the Dallas criteria. Idiopathic dilated cardiomyopathy was defined as global left ventricular dilatation with impaired systolic function, with or without overt heart failure, occurring in the absence of a known cardiac or systemic cause. Patients were excluded from the idiopathic dilated cardiomyopathy group if they demonstrated evidence of uncontrolled hypertension, history of myocardial infarction or coronary artery disease with $\geq 40\%$ stenosis of one or more epicardial coronary arteries by coronary angiography.

In both groups of patients, the medical record was reviewed for clinical details at the time of diagnosis. Data recorded included age, gender, duration of heart failure symptoms, New York Heart Association functional class, history of viral illness within the 3 months preceding diagnosis, pregnancy within 12 months of diagnosis, family history of cardiomyopathy and excessive alcohol consumption (>4 fl oz [120 ml] of alcohol/day or frequent binge drinking). For patients in the myocarditis group the use of immunosuppressive therapy was also recorded.

Left ventricular function. Evaluation of left ventricular function was determined by radionuclide angiography, two-dimensional and M-mode echocardiography or contrast left ventriculography. When more than one modality was utilized in a single patient, the rank order of preference for assessment of ejection fraction was 1) radionuclide angiography; 2) echocardiography; 3) contrast left ventriculography. Left ventricular systolic dysfunction was defined as an ejection fraction $<50\%$.

Endomyocardial biopsy. Endomyocardial biopsy specimens were obtained from the right ventricular septum using standard techniques, and all were reviewed by a single examiner (W.D.E.) and classified according to the Dallas criteria as positive for lymphocytic myocarditis, positive for borderline lymphocytic myocarditis or negative for myocarditis (10).

Follow-up. Follow-up information was obtained from the Mayo Clinic medical record, by mailed questionnaire and by telephone follow-up, if necessary. Questionnaires were mailed to all patients not already known to have died on the basis of the Mayo Clinic medical record. For deceased patients, the date of death or cardiac transplantation (considered as death)

was recorded; no effort was made to determine the cause of death. Current medications at the time of follow-up were recorded.

Statistical analysis. Group comparisons of the baseline characteristics of the myocarditis and idiopathic dilated cardiomyopathy groups were based on the chi-square test of proportions for dichotomous variables and the two-sample *t* test for continuous variables. Cumulative survival was estimated by the method of Kaplan-Meier, and the myocarditis and idiopathic dilated cardiomyopathy curves, overall and within subgroups, were compared by the log rank test. Statistical significance was judged at the $p < 0.05$ level.

Results

Myocarditis. From October 1979 to April 1988 a total of 850 endomyocardial biopsies were performed at the Mayo Clinic (excluding biopsies of cardiac allografts). The specified clinical indications for biopsy consisted of unexplained heart failure or dilated cardiomyopathy (53%), possible myocarditis (16%), possible amyloidosis (7%), restrictive cardiomyopathy (4%), ventricular dysrhythmia (6%), sarcoidosis (2%), eosinophilic syndrome (2%), ischemic heart disease (2%), possible constrictive pericarditis (2%) and miscellaneous (6%). Among 56 patients originally diagnosed as having myocarditis, 41 met the Dallas criteria for a diagnosis of myocarditis ($n = 28$) or borderline myocarditis ($n = 13$), and 15 did not. From these 41 patients, 9 (7 with myocarditis, 2 with borderline myocarditis) were excluded because of the presence of systemic inflammatory diseases known to be associated with myocarditis (3 with sarcoidosis; 2 with undifferentiated connective tissue disease; and 1 each with scleroderma, polymyositis, systemic lupus erythematosus and systemic streptococcal infection). Five patients were excluded because of lack of follow-up. After exclusions, the study group included 27 patients with myocarditis ($n = 17$) or borderline myocarditis ($n = 10$).

Dilated cardiomyopathy. From 1976 to 1987, 222 patients seen at the Mayo Clinic met the criteria for a diagnosis of idiopathic dilated cardiomyopathy (11). Of these, 58 patients underwent endomyocardial biopsy performed at this institution and served as the idiopathic dilated cardiomyopathy cohort for comparison with the myocarditis group. The endomyocardial biopsy specimens of these 58 patients were all reviewed by a single examiner (W.D.E.) and were considered to be negative for myocarditis according to the Dallas criteria.

Age, gender, family history of cardiomyopathy and pregnancy history were not significantly different between the myocarditis and idiopathic dilated cardiomyopathy groups (Table 1). The myocarditis group had a higher prevalence of viral illness within the 3 months before biopsy (40% vs. 19%, $p = 0.03$), a higher proportion of patients with excessive alcohol intake (22% vs. 7%, $p = 0.04$) and a higher proportion of patients in functional class III or IV (63% vs. 30%, $p = 0.005$). Ejection fraction, however, was significantly lower in the idiopathic dilated cardiomyopathy group ($25 \pm 11\%$) than in the myocarditis group ($38 \pm 19\%$, $p = 0.001$). Therefore,

Table 1. Comparison of Clinical Features of Patients With Myocarditis and Idiopathic Dilated Cardiomyopathy

	MC (n = 27)	IDCM (n = 58)	p Value
Age (yr)	47 ± 17	48 ± 12	0.67
Male gender (%)	16 (59%)	42 (72%)	0.23
NYHA functional class III or IV	17 (63%)	16 (30%)	0.005
Viral syndrome history	11 (40%)	11 (19%)	0.03
History of excessive alcohol consumption	6 (22%)	4 (7%)	0.04
Recent pregnancy	1 (4%)	2 (3%)	0.95
Family history of cardiomyopathy	2 (7%)	5 (9%)	0.85
Baseline ejection fraction (%)	38 ± 19	25 ± 11	0.001

Data presented are mean value ± SD or number (%) of patients. IDCM = idiopathic dilated cardiomyopathy; MC = myocarditis; NYHA = New York Heart Association.

there appeared to be a group of patients with myocarditis with a preserved ejection fraction but (by definition) no such group in those with idiopathic dilated cardiomyopathy. Despite this difference in ejection fraction, symptoms were worse in the myocarditis group.

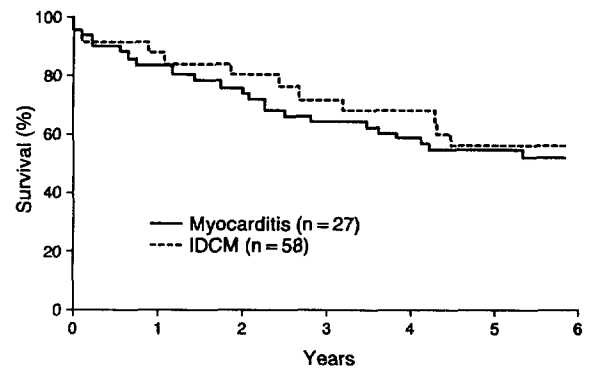
The median interval from onset of symptoms to diagnosis was 3.5 months in the myocarditis group and 7.4 months in the idiopathic dilated cardiomyopathy group ($p = 0.12$). Mean follow-up in years was similar for both groups (4.7 ± 2.7 for the myocarditis group vs. 4.4 ± 3 for the idiopathic dilated cardiomyopathy group). Medications at the time of follow-up (Table 2) were similar with the exception of digoxin (more common in idiopathic dilated cardiomyopathy) and antiarrhythmic therapy (more common in myocarditis).

Survival. There was no significant difference between the two groups in overall survival: The 5-year survival rate was 56% in the myocarditis group and 54% in the dilated cardiomyopathy group (Fig. 1). When analyzed separately according to the diagnosis of myocarditis, borderline myocarditis and idiopathic dilated cardiomyopathy, there were also no significant differences in overall survival (Fig. 2). Although the borderline myocarditis group demonstrated a trend toward

Table 2. Comparison of Medication at Follow-Up for Patients With Myocarditis and Idiopathic Dilated Cardiomyopathy

	MC	IDCM	p Value
Follow-up (yr)	4.7 ± 2.7	4.4 ± 3.0	0.66
Medications			
Digoxin	1 (8%)	20 (74%)	0.001
Diuretic drugs	4 (31%)	16 (59%)	0.09
Vasodilators	5 (39%)	18 (67%)	0.09
Coumadin	3 (23%)	12 (44%)	0.19
Aspirin	0 (0%)	3 (11%)	0.21
Antiarrhythmic agents	6 (46%)	4 (15%)	0.03

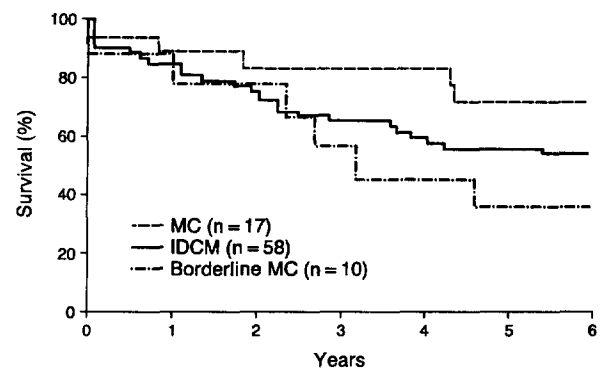
Data presented are mean value ± SD or number (%) of patients. Abbreviations as in Table 1.

**Figure 1.** Survival of patients with biopsy-proved myocarditis (definite or borderline) compared with that for patients with idiopathic dilated cardiomyopathy (IDCM) and negative endomyocardial biopsy findings.

decreased survival compared with the other two groups, the number of patients is small, and firm conclusions cannot be drawn. Seven patients in the myocarditis group were treated with immunosuppressive therapy at the discretion of their physician; three of these seven patients (43%) were alive at follow-up, a proportion similar to patients treated without immunosuppressive therapy.

Discussion

The reported prevalence of lymphocytic myocarditis in biopsy series has varied widely. The frequency of myocarditis in patients presenting with dilated cardiomyopathy has ranged from as low as 0% to as high as 89% (5,12-19). The wide range of estimates most likely has several causes. In addition to changing histologic criteria, the frequency of lymphocytic myocarditis may be related to the acuity of heart failure in the population under study, to institutional referral patterns, to sporadic viral epidemics and to the clinical threshold for performing endocardial biopsy in patients presenting with congestive heart failure, systolic dysfunction and normal coronary arteries (3). Recent reports (1-4) since the establishment of the Dallas criteria, however, have demonstrated a

Figure 2. Survival of patients with biopsy-proved myocarditis (MC) compared with that for patients with borderline myocarditis and idiopathic dilated cardiomyopathy (IDCM).

more consistent frequency of myocarditis, ranging from 4% to 10% in referral series. The potential prognostic or therapeutic value of establishing the diagnosis of myocarditis may account for the continued use of endomyocardial biopsy in patients presenting with acute congestive heart failure despite recent reports questioning the clinical utility of the procedure (20-23).

The results of the present study confirm that biopsy-proved lymphocytic myocarditis diagnosed according to the Dallas criteria is indeed uncommon. Specifically, during an 8-year time period, only 28 biopsy findings in our institution met the Dallas criteria for definite and 13 for borderline myocarditis. These represented 3.2% and 1.5%, respectively, of the total of 850 endomyocardial biopsies (excluding biopsies from allografts) performed at this institution during that time period; they were 4.8% and 2.2%, respectively, of the 587 biopsies performed to evaluate idiopathic heart failure. Of the 41 patients, 9 were found to have systemic diseases known to be associated with myocarditis, thus further reducing the biopsy frequency of idiopathic lymphocytic myocarditis.

Some have suggested that previous myocarditis is a common cause of dilated cardiomyopathy (9) and that spontaneous recovery from unexplained heart failure indicates myocarditis rather than cardiomyopathy as the underlying disease process (8). However, spontaneous improvement in ventricular function has also been observed in patients without biopsy evidence of myocarditis (1,13). The long-term prognosis of small groups of patients presenting with clinical features suggesting viral myocarditis (but without biopsy confirmation) has been reported to be good (6,7,20). In a series of patients with biopsy-proved lymphocytic myocarditis by the Dallas Criteria, the 3-year survival rate has been reported to be 83% (21). Our data confirm and extend this observation to a larger group with a longer follow-up.

Findings in the current study suggest that patients with biopsy-proved myocarditis diagnosed according to the Dallas criteria do not demonstrate a different survival compared with those with idiopathic dilated cardiomyopathy and negative endomyocardial biopsy findings. Patients with borderline myocarditis showed a trend toward decreased survival compared with those with definite myocarditis. However, the small number of patients with borderline myocarditis makes it difficult to draw meaningful conclusions about survival in this group. Some investigators (2) have suggested that patients with borderline myocarditis may respond more favorably to immunosuppressive treatment and may perhaps represent a separate pathologic entity. Others, however, have reported (24) a high percent of positivity for myocarditis on repeat biopsy in patients whose first biopsy demonstrated only borderline myocarditis. The distinction between definite and borderline myocarditis may be further confounded by the sampling error known to be associated with the endomyocardial biopsy technique (25).

The current study showed no survival difference between patients with biopsy-proved myocarditis and dilated cardiomyopathy with negative biopsy findings and may also be viewed within the context of previous studies of the clinical course of

dilated cardiomyopathy from this institution. Although there was referral bias inherent in both the myocarditis and idiopathic dilated cardiomyopathy populations (26), there was also no difference in survival of patients with idiopathic dilated cardiomyopathy who had, or did not have, an endomyocardial biopsy (11).

Diagnostic criteria. The diagnosis of myocarditis remains challenging. The Dallas criteria were established for the purpose of defining a working classification of myocarditis primarily for consistency in the National Heart, Lung, and Blood Institute-funded Multi-Center Myocarditis Trial (4). The Dallas criteria were not intended to be used as a sine qua non for the histologic diagnosis of myocarditis, and the investigators specifically stated that "histology itself may prove not to be the gold standard" for the diagnosis of myocarditis (10,27). The problems of sampling error as well as timing of biopsy in relation to onset of symptoms continues to make the role of myocarditis in the etiology of idiopathic dilated cardiomyopathy difficult to determine (15). Furthermore, even among the investigators who developed the Dallas classification, some discordance in biopsy interpretation may occur (28). One-third of the patients entered in the Multi-Center Myocarditis Trial on the basis of interpretation of the biopsy tissues by the local pathologist were considered by the study panel of cardiac pathologists to have negative findings for myocarditis (28).

Nevertheless, other more sensitive and specific analytic techniques are not widely available at this time for the diagnosis of lymphocytic myocarditis by endomyocardial biopsy. It may be that the evolution of more effective diagnostic methodology will permit more accurate identification of lymphocytic myocarditis in the future. Similarly, more specific therapy, coupled with more accurate diagnosis, may result in improved survival for patients with lymphocytic myocarditis.

Limitations of the study. It should be noted that the present study was limited to idiopathic lymphocytic endocarditis. Patients with giant-cell myocarditis, eosinophilic myocarditis, sarcoidosis or secondary forms of lymphocytic myocarditis (e.g., those associated with multisystem inflammatory disorders) may represent a different pathophysiology and have different long-term outcomes. Insofar as some of these other forms of myocarditis are treatable or have a different prognosis, the endomyocardial biopsy may be of clinical utility.

Summary and future directions. To our knowledge, the present study represents the longest follow-up period of patients with lymphocytic myocarditis diagnosed in biopsy tissues according to the Dallas criteria. It demonstrates that the 6-year survival of patients with biopsy-proved lymphocytic myocarditis seen in a referral setting is seriously compromised, although no different from that of patients with idiopathic dilated cardiomyopathy. Our study highlights the limitations of the conventionally analyzed endomyocardial biopsy in the evaluation of patients presenting with dilated cardiomyopathy. Further studies will need to be directed toward developing analytic techniques that enhance the prognostic and diagnostic utility of the endomyocardial biopsy. Furthermore, until effective therapy for lymphocytic myocarditis is clearly established, the

value of establishing this diagnosis by endomyocardial biopsy will remain low.

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