JACC Vol. 18, No. 7
December 1991:1617–26

CLINICAL STUDIES

Clinicopathologic Description of Myocarditis

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Histologic evidence of myocarditis was demonstrated in 35 of 348 patients submitted to endomyocardial biopsy over 5 years. Analysis of the histologic findings and clinical course of these patients resulted in a new clinicopathologic classification of myocarditis in which four distinct subgroups are identified. Patients with fulminant myocarditis become acutely ill after a distinct viral prodrome, have severe cardiovascular compromise, multiple foci of active myocarditis by histologic study and ventricular dysfunction that either resolves spontaneously or results in death. Patients with acute, chronic active and chronic persistent myocarditis have a less distinct onset of illness.

Patients with acute myocarditis present with established ventricular dysfunction and may respond to immunosuppressive therapy or their condition may progress to dilated cardiomyopathy. Those with chronic active myocarditis initially respond to immunosuppressive therapy, but they have clinical and histologic relapses and develop ventricular dysfunction associated with chronic inflammatory changes including giant cells on histologic study. Chronic persistent myocarditis is characterized by a persistent histologic infiltrate, often with foci of myocyte necrosis but without ventricular dysfunction despite other cardiovascular symptoms such as chest pain or palpitation.

(J Am Coll Cardiol 1991;18:1617–26)

Idiopathic myocarditis is an inflammatory disease of the myocardium of unknown etiology. Although the clinical (1–5) and histopathologic (4–10) features of the disease have been extensively studied, a unifying characterization of the disease has failed to emerge. Historically, cases of subclinical (11), lethal (4,5,11) and progressive (1,4–6) myocarditis have been observed and the disease has been variously described utilizing electrocardiography (2), echocardiography (2,12), serologic studies (13,14) or endomyocardial biopsy (4,8,13,15). In an effort to provide uniform criteria for the pathologic diagnosis of myocarditis, a panel of cardiac pathologists developed a classification of this disease based on histologic features of endomyocardial biopsy specimens. Known as the Dallas criteria (16), this system has been criticized for interobserver variability (17) and may be subject to sampling error (1,18). The failure to develop a clinical description of myocarditis to accompany the pathologic classification has impaired the development of therapeutic trials and fostered controversy as to the very existence of the disease (18).

The purpose of this study was to identify the clinical spectrum of myocarditis and to categorize this disease into four subgroups. This classification is supported by animal models and in humans by clinical and pathologic experience and, in addition, is analogous to the accepted classification of viral hepatitis (19,20). It is hoped that recognition of the clinical substrata of histologically documented myocarditis will allow a better understanding of the anticipated course of patients with this disease. Then, as in hepatitis (20), we may better define an individual patient's suitability for immunosuppressive therapy.

Methods

Study patients. Between December 1, 1983 and July 1, 1988, 348 patients underwent diagnostic endomyocardial biopsy to evaluate cardiac dysfunction. On histologic analysis, 60 patients (17.2%) exhibited active or borderline myocarditis as defined by the Dallas criteria (16):

Two separate classifications are used for the first and subsequent biopsies. On the first biopsy, *active myocarditis* is defined by myocyte necrosis or degeneration, or both, associated with an inflammatory infiltrate adjacent to the degenerating or necrotic myocytes. *Borderline myocarditis* is diagnosed when the inflammatory infiltrate is too sparse or when damage to myocytes is not demonstrable. *No myocarditis* implies that the myocardium is either entirely normal or shows nonspecific changes.

On subsequent biopsies, *ongoing myocarditis* means that myocyte damage or necrosis in association with inflammatory infiltrate persists. In *resolving myocarditis*, the inflammatory infiltrate is substantially reduced and is not inti-

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Manuscript received November 2, 1990; revised manuscript received June 20, 1991; accepted June 25, 1991.

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0735-1097/91/$3.50

Table 1. Endomyocardial Biopsy Results in 348 Patients Evaluated for Cardiac Dysfunction at the Johns Hopkins Hospital

	Patients	
	No.	%
Active or borderline myocarditis associated with an underlying condition	25	7
Postpartum	15	
AIDS	3	
Systemic lupus erythematosus	3	
Sarcoidosis	3	
Hepatitis A	1	
Idiopathic active or borderline myocarditis	35	10
Fulminant	4	
Acute	26	
Chronic active	3	
Chronic persistent	2	
No myocarditis	288	83

mately associated with necrotic myocytes. An inflammatory infiltrate is absent in *resolved myocarditis* (16).

In 25 patients the myocarditis was attributed to an underlying condition (Table 1). The etiology of the myocarditis was unexplained in the remaining 35 patients and this latter group is the subject of this report. The myocarditis of these 35 patients is further categorized as fulminant, acute, chronic active or chronic persistent on the basis of clinical and histologic criteria (Table 2). One representative patient with fulminant, chronic active or chronic persistent myocarditis is presented. To illustrate the typical features of acute myocarditis, two patients from this large group are also discussed.

Endomyocardial biopsy. The patients underwent right ventricular endomyocardial biopsy percutaneously through the right internal jugular vein with use of a 50 cm modified Stanford Caves bioptome. At least five specimens were obtained and fixed by immediate immersion in 10% formalin. Each specimen was sectioned, stained with hematoxylin-eosin, and examined at a minimum of four levels by one investigator (G.M.H.) who did not know the clinical features of the subjects.

Several features of the endomyocardial biopsy were recorded in a standardized format: the number of foci of myocyte necrosis, the presence and type of myocyte changes other than necrosis; the amount, distribution and composition of any inflammatory infiltrates; and the extent and type (replacement or interstitial) of any fibrosis. The presence of active, borderline, ongoing, resolving or resolved myocarditis was then determined according to the Dallas criteria (16) (Table 3).

Therapy. Most of the patients who were treated for active or borderline myocarditis received a standard immunosuppressive regimen of prednisone, 1 mg/kg per day, and azathioprine, 1.5 mg/kg per day, for 6 to 8 weeks. Endomyocardial biopsy was then performed to assess the patient's response to therapy. The dosage of prednisone was then gradually tapered by 10 mg/day per week until the patient was receiving 20 mg/day and then the dose was decreased by 5 mg/day per week until administration of the drug was discontinued. Administration of azathioprine was stopped 2 weeks later. Individual exceptions to this protocol are noted in the text.

Clinical evaluation. Patients underwent right heart catheterization at the time of each endomyocardial biopsy and determination of cardiac output was performed in triplicate with <10% variability.

M-mode and two dimensional echocardiograms were obtained within 24 h of biopsy and were serially performed as clinically indicated. Standard dimensions were measured and formulas used to determine fractional shortening as a measure of left ventricular function (21). In some patients gated blood pool scans were obtained within 24 h of biopsy and then serially as clinically indicated.

All study patients had negative results of a full clinical evaluation to exclude secondary causes of myocardial dysfunction. This evaluation included measurements of serum thyroxide concentrations, 24-h urinary metanephrine excretion and reactive plasma reagin titer. Coronary angiography was performed when appropriate as determined by age or clinical history. Viral neutralization titers were not routinely measured.

Table 2. Clinicopathologic Classification of Myocarditis

	Fulminant	Acute	Chronic Active	Chronic Persistent
Onset of cardiac symptoms	Distinct	Indistinct	Indistinct	Indistinct
Initial presentation	Cardiogenic shock Severe LV dysfunction	CHF LV dysfunction	CHF LV dysfunction	Non-CHF symptoms Normal LV function
Initial endomyocardial biopsy	Multiple foci of active myocarditis	Active or borderline myocarditis	Active or borderline myocarditis	Active or borderline myocarditis
Clinical natural history	Complete recovery or death	Incomplete recovery or dilated CM	Dilated CM	Non-CHF symptoms; normal LV function
Histologic natural history	Complete resolution of active myocarditis	Complete resolution of active myocarditis	Ongoing or resolving myocarditis; fibrosis; giant cells	Ongoing or resolving myocarditis
Immunosuppressive therapy	No benefit	Sometimes beneficial	No benefit	No benefit

CHF = congestive heart failure; CM = cardiomyopathy; LV = left ventricular.

Table 3. Histologic Characteristics of 11 Patients With Myocarditis on Endomyocardial Biopsy

Case No.	Time After Presentation	No. of Foci of Myocyte Necrosis	Other Myocyte Changes	Inflammatory Infiltrate			Fibrosis		Dallas Criteria Diagnosis
				Amount*	Distribution	Composition	Extent*	Type	
Fulminant Myocarditis									
1	Day 7	>5		2	Diffuse, focal	L,P,M	1	I	Active myocarditis
	Day 58	0		1	Diffuse, focal	L	0		Resolving myocarditis
	Day 120	0		0			1	I	Resolved myocarditis
2	Day 4	>5		3	Diffuse, focal	L	1	I	Active myocarditis
3	Day 28	>5		3	Diffuse, focal	L	0		Active myocarditis
4	Day 3	>5		2	Diffuse, focal	L	~2	R	Active myocarditis
Acute Myocarditis									
5	Month 1	<5		2	Diffuse, focal	L,N	0		Active myocarditis
	Month 3	0	MR	1	Focal	L	1	I	Resolving myocarditis
6	Month 1	<5		1	Focal	L	0		Active myocarditis
	Month 3	0		0			1	I	Resolved myocarditis
Chronic Active Myocarditis									
7	Month 0	0		1	Diffuse, focal	L	1	R	Borderline myocarditis
	Month 2	0		1	Diffuse, focal	L	0		Resolving myocarditis
	Month 7	0		2	Diffuse, focal	L	0		Resolving myocarditis
	Month 13	0	H	1	Diffuse, focal		1	I,R	Resolving myocarditis
	Month 37	0	H	1	Diffuse, focal	L	2	I,R	Ongoing myocarditis
	Month 25	0	H	1	Diffuse, focal	L,G	2	I,R	Resolving myocarditis
8	Month 37	0	H	3	Diffuse, focal	L,P	1	R	Borderline myocarditis
	Month 54*	>5	H	3	Diffuse, focal	L,G	3	R	Ongoing myocarditis
9	Month 14	>5		3	Diffuse, focal	L,P,M,G	1	R	Active myocarditis
	Month 16	0	H	1	Diffuse, focal	L	1	R	Resolving myocarditis
	Month 17	0	H	1	Diffuse, focal	L	1	R	Resolving myocarditis
	Month 29	1		1	Focal	L	0		Ongoing myocarditis
	Month 44	0	H	1	Diffuse, focal	L	2	I,R	Resolving myocarditis
Chronic Persistent Myocarditis									
10	Month 0	1		1	Focal	L	0		Active myocarditis
	Month 3	0		1	Diffuse, focal	L	0		Resolving myocarditis
	Month 9	0		0			0		Resolved myocarditis
	Month 16	2		1	Diffuse, focal	L	0		Ongoing myocarditis
11	Month 1	<5		1	Diffuse, focal	L,M		R	Active myocarditis
	Month 3	0		1	Focal	L	1	R	Resolving myocarditis
	Month 7	0		1	Diffuse, focal	L	2	I,R	Resolving myocarditis
	Month 28	0		1	Diffuse, focal	L	3	I,R	Resolving myocarditis

*Autopsy or cardiectomy specimen. †0 = none; 1 = mild; 2 = moderate; 3 = severe. ‡0 = disruption of myocyte architecture; G = giant cells; H = hypertrophy; I = interstitial; L = lymphocytes; M = macrophages; MR = macrophagic removal of necrotic myocyte; N = neutrophils; P = plasma cells; R = replacement. The following histologic findings are demonstrated: 1) fulminant myocarditis is histologically unique for the multiple foci of necrosis (>5) and extent (2–3) of lymphocytic infiltrate on presentation, with complete resolution over time; 2) acute myocarditis displays less intense lymphocytic infiltrate with histologic resolution over 3 months and little fibrosis; 3) chronic active myocarditis demonstrates a variable and less intense inflammatory infiltrate initially. However, over time the infiltrate persists and in each case is associated with giant cells, myocyte hypertrophy and progressive replacement fibrosis; 4) chronic persistent myocarditis demonstrates a mild inflammatory infiltrate that persists without significant fibrosis or myocyte disruption.

Case Reports

Fulminant Myocarditis

Case 1. A 21-year old white man was admitted to his local hospital after describing the acute onset of abdominal pain and fever. He underwent exploratory laparotomy and appendectomy; the appendix was histopathologically normal. The fever persisted, and myalgias, arthralgias and hypotension developed postoperatively. No intraabdominal process was found on a repeat exploratory laparotomy 2 days later, and broad spectrum antibiotic therapy was begun empirically. An acutely increased cardiothoracic ratio was noted on chest radiography and a right heart catheterization revealed elevated pulmonary artery pressure (64/40 mm Hg) and pulmonary capillary wedge pressure (40 mm Hg) with a low cardiac index (1.56 liters/min per m^2). The following day clinically evident pulmonary edema developed and the patient was intubated for ventilation. He was transferred to The Johns Hopkins Hospital on his 6th hospital day.

JACC Vol. 18, No. 7
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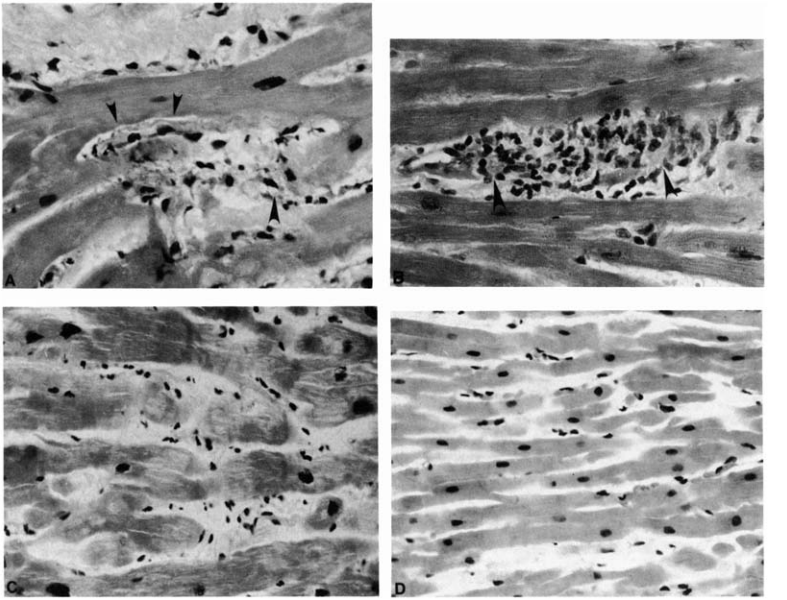

Figure 1. *Case 1.* **A and B,** High power photomicrographs highlighting two foci of active myocarditis taken from the same endomyocardial biopsy sample. Note the mixed inflammatory infiltrate engulfing small clusters of adjacent myocytes (**arrows**). **C,** Follow-up endomyocardial biopsy 6 weeks after discharge showing resolving myocarditis; note the scattered increase in interstitial mononuclear cells. No myocyte necrosis is present. **D,** Six months after discharge, the endomyocardial biopsy is normal, consistent with resolved myocarditis. Hematoxylin-eosin ×625 reduced by 29% (**A** and **D**), 23% (**B**) and 28% (**C**).

On transfer, the pulmonary capillary wedge pressure was 29 mm Hg and the patient was receiving intravenous dopamine, dobutamine and nitroglycerin. An electrocardiogram (ECG) revealed sinus tachycardia but no other abnormal findings. An endomyocardial biopsy performed the following day revealed severe active myocarditis (Fig. 1, A and B). An echocardiogram revealed minimal left ventricular dilation with global hypokinesia and fractional shortening of only 15% (normal 28% to 41% [22]). Over the next 4 days the patient's hemodynamic status improved (pulmonary artery pressure 30/18 mm Hg, pulmonary capillary wedge pressure 18 mm Hg) and inotropic medications were discontinued on the 8th hospital day. By day 12, fractional shortening had increased to 47% and the patient was discharged in his baseline state of good health.

The patient returned to full-time employment. Follow-up endomyocardial biopsies performed 6 weeks and 3 months after hospital discharge were consistent with resolving and resolved myocarditis, respectively (Fig. 1, C and D). Hemodynamic status continued to improve (pulmonary artery pressure 25/12 mm Hg, pulmonary capillary wedge pressure 11 mm Hg, cardiac index 2.7 liters/min per m^2).

Three years after his initial presentation, the patient remains fully employed without signs or symptoms of cardiac disease. He is taking no medications and there are no limitations on his activity. He received no immunosuppressive therapy with the exception of 2 days of empiric intravenous corticosteroids before his transfer to The Johns Hopkins Hospital.

Summary of four cases. The four cases of fulminant myocarditis are distinguished by five characteristics. The development of myocarditis is heralded by a nonspecific flu-like illness and the onset of cardiac involvement is distinct. These patients' condition rapidly deteriorates and

they develop profound hemodynamic compromise. Their endomyocardial biopsy reveals unequivocal active myocarditis by the Dallas criteria and is particularly notable for very extensive inflammatory infiltrates and numerous foci of myocyte necrosis. Finally, within 1 month the patients either completely recover left ventricular function (three of four) or they die (one of four) of their disease. The natural history of this type of myocarditis appears uninfluenced by immunosuppressive therapy. The only patient who received immunosuppressive therapy died. Because of this early experience, the concern that the persistent virus may be present and the rapid spontaneous improvement, no immunosuppressive treatment was given to the remaining three patients; the illness in all three patients resolved.

Acute Myocarditis

Case 5. A 71-year old woman presented to her local hospital with progressively worsening dyspnea and fatigue of at least 1 month's duration. Severe congestive heart failure was evident on examination and the ECG revealed new onset atrial fibrillation, left axis deviation and nonspecific ST segment changes. The cardiothoracic ratio on chest roentgenogram was 11.5/23.5. She was treated with diuretic drugs and transferred to The Johns Hopkins Hospital for evaluation.

On transfer, hemodynamic study revealed depression of left ventricular contractility with mild elevation of pulmonary vascular pressures (pulmonary artery pressure 38/12 mm Hg, pulmonary capillary wedge pressure 16 mm Hg, cardiac index 1.4 liters/min per m^2, stroke index 11.7 [normal 38 to 54]). The initial endomyocardial biopsy was consistent with active myocarditis and immunosuppressive therapy was initiated (prednisone, 60 mg/day, azathioprine, 100 mg/day). Electrical cardioversion successfully converted the patient's rhythm to normal sinus rhythm and she was discharged.

The patient returned for a second endomyocardial biopsy after 6 weeks of immunosuppressive therapy. During this time her normal functional state had returned. Her hemodynamic status had improved (pulmonary artery pressure 27/6 mm Hg, pulmonary capillary wedge pressure 1 mm Hg, cardiac index 2.8 liters/min per m^2, stroke work index 28.9) and the endomyocardial biopsy revealed resolving myocarditis. A slow tapering of the prednisone dose was planned but all immunosuppressive therapy was discontinued only 1 month later (a total 10 week course) because of adverse neuropsychiatric effects.

After 12 months of follow-up the patient remains in normal sinus rhythm and is without further symptoms of heart failure.

Case 6. A 53-year old man was admitted to his local hospital after progressively developing congestive heart failure over the preceding 6 weeks. He was found to have a left ventricular ejection fraction of 19% by gated blood pool scan and an echocardiogram revealed left ventricular dilation (internal diastolic diameter 5.7 cm, systolic diameter 4.9 cm). A gallium-67 scan (23) demonstrated increased myocardial uptake and the patient was transferred to The Johns Hopkins Hospital for evaluation.

An endomyocardial biopsy and right heart catheterization were performed. Hemodynamic studies revealed depressed left ventricular contractility with elevation of filling pressures (pulmonary artery pressure 45/18 mm Hg, pulmonary capillary wedge pressure 26 mmHg, cardiac index 2 liters/min per m^2, stroke index 17.1) and the biopsy demonstrated active myocarditis. Administration of immunosuppressive medications (prednisone, 60 mg, and azathioprine, 100 mg, both four times daily) was begun and the patient was discharged.

A repeat endomyocardial biopsy was performed after 6 weeks of immunosuppressive and diuretic therapy. Hemodynamic status was improved (pulmonary artery pressure 20/6 mm Hg, pulmonary capillary wedge pressure 6 mm Hg, cardiac index 2.9 liters/min per m^2, stroke index 34.6). Results of the biopsy were normal and consistent with resolved myocarditis, and the patient reported an improved but limited exercise tolerance. An echocardiogram demonstrated persistent left ventricular dilation and the left ventricular ejection fraction, determined by gated blood pool scan, remained at 19%. Nonsustained ventricular tachycardia was discovered on several Holter monitor ECG tracings and antiarrhythmic therapy was begun. The prednisone and azathioprine were discontinued after 3 months of therapy because of a lack of demonstrable efficacy in this patient.

Five months after his initial presentation the patient developed worsening of his congestive failure characterized by nocturnal cough, cardiomegaly and perihilar pulmonary infiltrates. He was enrolled in an experimental inotropic drug trial.

Summary of 26 cases. These illustrative cases of acute myocarditis represent the clinical spectrum of the largest group of patients (n = 26) with myocarditis or borderline myocarditis. These patients have a minimally dilated, hypokinetic left ventricle on presentation. The onset of their cardiac symptoms is indistinct and they experience a gradual deterioration of cardiac function before their presentation for medical care. Active or borderline myocarditis is present on initial but not subsequent endomyocardial biopsies. It has been our experience that immunosuppressive therapy may alter the course of this disease (24); patients may respond and experience a partial recovery in ventricular contractility. Those who do not respond to immunosuppressive therapy continue to show deterioration to end-stage dilated cardiomyopathy.

Chronic Active Myocarditis

Case 7. A 25-year old male roofer presented to his local hospital describing the insidious onset of dyspnea on exertion, palpitation and stabbing chest pains. He denied having any recent viral illnesses. Although results of a physical examination were normal, an ECG demonstrated sinus

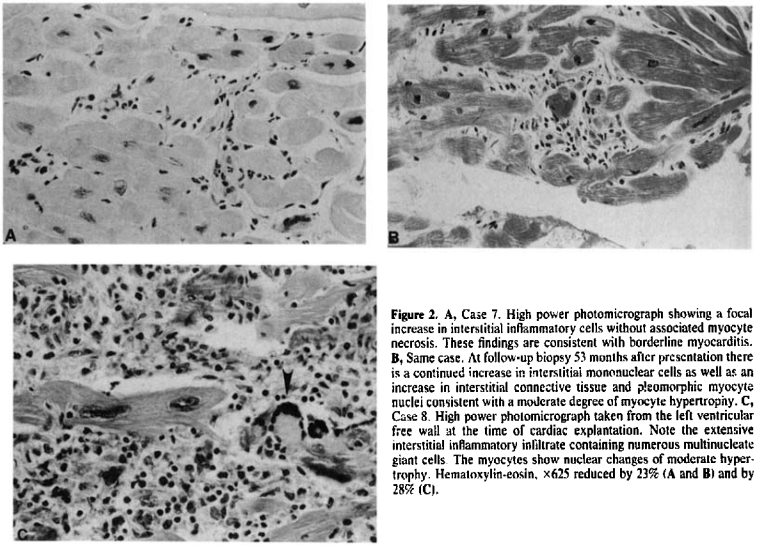

Figure 2. **A,** Case 7. High power photomicrograph showing a focal increase in interstitial inflammatory cells without associated myocyte necrosis. These findings are consistent with borderline myocarditis. **B,** Same case. At follow-up biopsy 53 months after presentation there is a continued increase in interstitial mononuclear cells as well as an increase in interstitial connective tissue and pleomorphic myocyte nuclei consistent with a moderate degree of myocyte hypertrophy. **C,** Case 8. High power photomicrograph taken from the left ventricular free wall at the time of cardiac explantation. Note the extensive interstitial inflammatory infiltrate containing numerous multinucleate giant cells. The myocytes show nuclear changes of moderate hypertrophy. Hematoxylin-eosin, ×625 reduced by 23% (**A** and **B**) and by 28% (**C**).

tachycardia with inferolateral T wave inversions. These changes did not evolve, cardiac enzyme levels remained within the normal range and the patient was transferred to The Johns Hopkins Hospital for evaluation.

Echocardiography demonstrated moderate global left ventricular hypokinesia, moderate left ventricular hypertrophy and a dilated left atrium. The left ventricular ejection fraction, measured by gated blood pool scan, was 36% and hemodynamic studies at the time of endomyocardial biopsy revealed elevated pulmonary vascular pressures (pulmonary artery pressure 48/22 mm Hg, pulmonary capillary wedge pressure 22 mm Hg) and a depressed cardiac index (1.8 liters/min per m^2). The biopsy revealed borderline myocarditis (Fig. 2A) and immunosuppressive therapy (prednisone, 50 mg/day and azathioprine, 75 mg/day) was begun. The patient was discharged and returned to full-time employment.

After 6 weeks of therapy, the patient's echocardiogram showed complete resolution of the left ventricular hypokinesia; the gated left ventricular ejection fraction was now 65%. Hemodynamic variables had normalized (pulmonary artery pressure 21/10 mm Hg, pulmonary capillary wedge pressure 7 mm Hg, cardiac index 2.6 liters/min per m^2) and endomyocardial biopsy was consistent with resolving myocarditis. Administration of prednisone was slowly tapered while treatment with azathioprine continued.

Seven months after his initial presentation, the patient returned with severe congestive heart failure. Severe global left ventricular hypokinesia, four-chamber dilation and a moderately large pericardial effusion were seen on echocardiography while hemodynamic studies mirrored the decline in the patient's condition (pulmonary artery pressure 50/22 mm Hg, pulmonary capillary wedge pressure 28 mm Hg, cardiac index (1.62 liters/min per m^2). Yet, the endomyocardial biopsy demonstrated only resolving myocarditis. Initially, the patient was treated with corticosteroids (prednisone, 60 mg/day) and azathioprine 75 mg/day, but administration of cyclosporine A, 4 mg/kg per day, was started after 1 month when standard immunosuppressive therapy failed to normalize echocardiographically determined ventricular dysfunction. The addition of cyclosporine resulted in symptomatic improvement; however, right and left ventricular filling pressures remained elevated. Echocardiography demonstrated only partial recovery of left ventricular contractility, and the rest radionucleotide angiographic ejection fraction improved to only 45%.

The patient has subsequently experienced several relapses of congestive heart failure despite immunosuppres-

sive regimens. Posttreatment radionucleotide ejection fraction has progressively deteriorated from 65% to 45% to 24% and now 8% over a 29-month follow-up period. Echocardiograms have shown progressively severe biventricular dysfunction accompanied by only minimal chamber dilation. Three subsequent endomyocardial biopsies (Fig. 2B), while consistent with resolving myocarditis, have shown the progressive development of replacement fibrosis, myocardial cell hypertrophy and giant cells.

Thirty months after initial presentation, the patient has become incapacitated by refractory congestive heart failure. All immunosuppressive medications have been stopped because of lack of efficacy: the patient is currently enrolled in an experimental inotropic drug trial.

Summary of three cases. The three patients with chronic active myocarditis have a disease that is characterized by progressive clinical deterioration and the development of cardiomyopathic changes on serial biopsies. The onset of their disease is indistinct. After presentation with heart failure, these patients have a slowly progressive but inevitably deteriorating course that may be punctuated by brief, often dramatic but unsustained responses to immunosuppressive therapy. The initial endomyocardial biopsy reveals active or borderline myocarditis; subsequent biopsies demonstrate persistence of an inflammatory infiltrate, the development of giant cells and extensive fibrosis. Ultimately, these patients develop an end-stage dilated cardiomyopathy.

Chronic Persistent Myocarditis

Case 10. A 39-year old black woman was admitted to her local hospital describing palpitation and chest tightness. An ECG obtained during a symptomatic episode revealed runs of ventricular bigeminy and frequent premature ventricular beats. There was no elevation in serum creatine kinase. The patient described recurrent episodes of substernal chest discomfort that were relieved by sublingual nitroglycerin and she was transferred to The Johns Hopkins Hospital for evaluation.

On admission the patient was tachycardic but had an otherwise normal physical examination and ECG. Coronary cineangiography revealed normal coronary arteries and a left ventricular ejection fraction of 70%. Right heart catheterization and endomyocardial biopsy were performed to evaluate the patient's symptoms and sinus tachycardia. Hemodynamic variables were normal (pulmonary artery pressure 28/6 mm Hg, pulmonary capillary wedge pressure 5 mm Hg, cardiac index 2.4 liters/min per m^2) but the endomyocardial biopsy demonstrated active myocarditis (Fig. 3). The myocarditis was treated with prednisone (40 mg/day) for 1 month, but it was discontinued after the patient developed adverse neuropsychiatric side effects.

The patient's palpitation and associated ventricular ectopic rhythm were treated with flecainide. A repeat endomyocardial biopsy was performed 3 months after initial presentation and it demonstrated resolving myocarditis. The

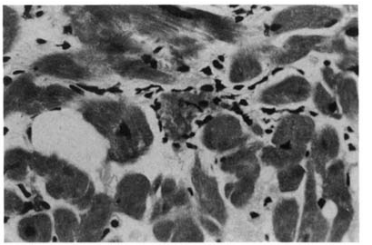

Figure 3. Case 10. High power photomicrograph highlighting a single focus of myocyte necrosis. Note the predominantly mononuclear infiltrate engulfing what appears to be a single necrotic myocyte.

echocardiogram remained normal. She remained free of congestive heart failure symptoms and returned 9 months after initial presentation for an endomyocardial biopsy to assess the progression of her untreated myocarditis. Her hemodynamic variables remained normal (pulmonary artery pressure 20/6 mm Hg, pulmonary capillary wedge pressure 3 mm Hg, cardiac index 3.2 liters/min per m^2); the endomyocardial biopsy revealed the persistence of mild diffuse interstitial mononuclear cell infiltrates. No foci of myocyte necrosis were seen and the patient was discharged without immunosuppressive therapy.

Thirteen months after initial presentation the patient was admitted for evaluation of multiple nonspecific, multisystem complaints including substernal chest discomfort. Coronary cineangiography again demonstrated disease-free coronary arteries and a left ventricular ejection fraction of 70%. An echocardiogram was entirely normal. Despite normal ventricular function, an endomyocardial biopsy demonstrated ongoing myocarditis. It was decided to further withhold immunosuppressive therapy and to continue close observation of this patient. She remains without cardiovascular limitations 36 months after initial presentation.

Summary of two cases. Two patients with chronic persistent myocarditis came to medical attention with atypical chest pain or palpitations. They display no signs or symptoms of left ventricular dysfunction and results of all noninvasive and invasive studies of ventricular function remain normal despite unequivocal histologic evidence of ongoing myocardial inflammation. The myocardial infiltrate does not appear to be improved by immunosuppressive therapy.

Discussion

The Dallas criteria (16) provide a histologic classification of myocarditis; we propose a clinical classification in which four distinct subgroups are identified. The spectrum of

myocarditis exhibited by patients with fulminant, acute, chronic active and chronic persistent myocarditis is similar to that in previous descriptions of viral hepatitis (19,20) and, as in hepatitis, classification of an individual patient into one of these subgroups has important prognostic and therapeutic implications.

Endomyocardial biopsy: histologic findings. The endomyocardial biopsy retains a fundamental role in this clinical classification and only patients with biopsy-documented active or borderline myocarditis have been included. In addition, some histologic features of the biopsy that are not addressed by the Dallas criteria are associated with the clinical subgroups in this patient series. Fulminant myocarditis is distinguished by an active inflammatory infiltrate and multiple foci of myocyte necrosis. The initial endomyocardial biopsy in those patients who develop acute, chronic active and chronic persistent myocarditis all appear similar with less severe infiltration and, when present, fewer foci of myocyte necrosis. Those patients who develop chronic active disease progressively develop interstitial and replacement fibrosis and giant cells. The myocarditis in those patients with chronic active myocarditis proved refractory to immunosuppressive therapy and inexorably progressed to end-stage dilated cardiomyopathy. It is remarkable that two of these patients had Dallas criteria of "borderline myocarditis" on initial endomyocardial biopsy. We find the presence of giant cells and the persistence of myocarditis to be more important than the distinction between active and borderline myocarditis. Patients in this series with giant cells on endomyocardial biopsy tend to have a chronic, progressive disease and a poor prognosis.

Giant cell myocarditis. Giant cell myocarditis is a rare histologic form of myocarditis that is characterized by the finding of multinucleated giant cells in the heart and the absence of extracardiac involvement. It is frequently confused with sarcoidosis; however, ultrastructural studies demonstrating the transition of apparently normal myocytes to multinucleated variants support the concept that this is a distinct illness (25,26). Giant cell myocarditis has been recognized to carry a dismal prognosis with progression to death within 18 months of diagnosis (26) in many patients. Immunosuppression has failed to alter the course of the disease (26,27). Although a few reported patients (25) with fulminant myocarditis demonstrate giant cells, the clustering of our cases of giant cell myocarditis under the chronic active myocarditis category suggests that the development of giant cell myocarditis may be associated with chronic progressive disease. The association of giant cell myocarditis with numerous autoimmune diseases (28) highlights the significant role of the host's immune response in the disease expression.

Davidoff et al. (29) recently compared the course of 10 patients with giant cell myocarditis with the course of 36 patients with lymphocytic myocarditis. They confirmed the greater decline in systolic function and worse prognosis of patients with giant cell versus lymphocytic myocarditis. In addition, the giant cell group had a higher incidence of ventricular tachycardia (9 of 10) and AV block requiring pacemaker insertion (6 of 10) than did their lymphocytic myocarditis control patients. As opposed to the Davidoff group (29), we did not include patients with giant cells demonstrated by endomyocardial biopsy and known sarcoidosis or other diseases known to be associated with a giant cell myocardial reaction. Therefore, the giant cell myocarditis category remains controversial and ill defined. We have demonstrated that ongoing chronic myocardial inflammation can lead to giant cell myocarditis and implies a poor outcome.

Animal myocarditis: pathophysiology. Although some cases of myocarditis may be the consequence of a direct cytopathic viral effect, increasing evidence implicates immune mediation of myocardial inflammation. The rarity of human myocarditis makes studies of its pathogenesis difficult; therefore, several murine models of myocarditis have been developed. These models indicate that the clinical spectrum of human disease may reflect patient to patient variations in the host's cell-mediated or humoral immune responses. Alternatively, infection with different viruses may produce different disease phenotypes.

Several years ago, members of our group (30,31) undertook an investigation to determine which genetic factors control the response of mice to coxsackievirus B3 infection. Two-week old animals of a variety of strains were infected with a myocarditic coxsackie B3 variant and subsequently examined for pathologic and immunologic responses as well as for recovery of infectious virus from blood and tissues. These studies clearly demonstrated that coxsackie B3-induced myocarditis can be separated into two phases. The earliest histologic abnormalities were seen 5 days after viral inoculation and were characterized by focal zones of myocyte necrosis and polymorphonuclear and monocytic infiltration (32). In agreement with the reports of other investigators (33), virus was isolated from the heart on postinoculation day 3 and peaked on day 5. By day 15 after infection, no infectious virus was detected in any of the strains examined (34). Most mice did not show signs of ongoing inflammation after day 7. In a few mouse strains, a second phase of myocarditis became evident 9 days after infection. Although no infectious virus was present, heart-specific autoantibodies could be detected in these animals (35). The cardiac lesions during this later phase were more diffuse than in the earlier stage and were characterized by a different, interstitial mononuclear infiltrate. Therefore, genetic susceptibility to both early and late phase myocarditis induced by the same viral agent differed among various host mouse strains.

Huber and coworkers (36,37) have demonstrated an immunologic correlate to these two phases of histologic and serologic abnormalities. They found that two populations of cytotoxic T lymphocytes are produced when Balb/c mice are infected with coxsackievirus B3. Initially, one population of virus-specific effector cells arises and preferentially lyses

infected myocytes. A second "autoreactive" population arises 3 to 6 days after infection and preferentially lyses uninfected myocytes. When these separated T cell populations are adoptively transferred into T cell-deficient, virus-infected mice, myocarditis subsequently develops. Myocarditis is not observed in the presence of viral infection before the lymphocytes are adoptively transferred. Therefore, the clinical spectrum of murine myocarditis may be due to strain-related differences in the genetic control of this immune response to infection.

Genetically determined immune response factors are responsible for the variety of clinical presentations of human myocarditis. Several investigators have retrospectively identified immune response abnormalities such as circulating antiheart antibodies (38), in vitro suppressor cell defects (39,40), and associations with certain histocompatability antigen (HLA) types (41) in patients with active myocarditis or dilated cardiomyopathy. Similar abnormalities have been identified in patients with other chronic inflammatory diseases (30,42–44) and suggest a common autoimmune mechanism. Murine models of myocarditis utilizing different viral genera indicate that the different genera are associated with varying clinical outcomes. Myocarditis produced in inbred strains of Balb/c (45) and DBA/Z (46) mice by encephalomyocarditis virus produced a severe myocarditis that progressed to dilated cardiomyopathy; this murine model parallels human chronic active myocarditis. Coxsackievirus A9 causes a self-limited disease whereas coxsackievirus B3 induces a severe myocarditis associated with high mortality (33). Indeed, different variant strains of the same genus may exhibit different myocarditic capabilities.

The capacity of coxsackievirus B3 variants to induce acute and chronic myocarditis in mice was examined in detail by Gauntt et al. (47,48). Two prototypic variants of the well studied Nancy strain were found to be antigenically identical. However, when the myocarditic variant, coxsackievirus $B3_0$ was compared with the myocarditic coxsackievirus strain, $B3_M$, a difference in their infectivity was found. Furthermore, comparison of the variants in vitro showed that cytotoxic T cells induced by coxsackie $B3_M$ infection lysed monocytes of mice infected with coxsackievirus $B3_M$ and not with coxsackievirus $B3_0$.

Human myocarditis. If the murine models adequately reflect the pathogenesis of human myocarditis, one would expect that conflicting descriptions of the human illness would appear in the published medical reports. Although improvement in left ventricular function in patients with dilated cardiomyopathy (1,49), the progression of active myocarditis to a dilated hypocontractile heart (1,6,13) and the spontaneous resolution of histologic myocarditis (6,11) have been noted in prior reports, this is the first classification of myocarditis that categorizes the clinical spectrum of disease.

In 1983, Fenoglio et al. (4) characterized myocarditis as either acute, rapidly progressive or chronic based on examination of endomyocardial biopsy specimens. They concluded that the biopsy provided clinically relevant prognostic information. Our classification differs from that of Fenoglio et al. (4) in several ways. First, we rely on clinical as well as histologic data. Second, we include the first reports of chronic persistent myocarditis, an active myocarditis that does not impair left ventricular function. Finally, our classification parallels that of another viral disease, viral hepatitis, in which autoimmune mechanisms produce different clinical expressions of infection.

The Dallas criteria (16) established exacting histologic criteria for the presence or absence of myocarditis and have been useful to pathologists and clinicians. Features defined by the Dallas criteria do not provide prognostic information when considered in isolation from the clinical data. We recommend the continued utilization of the Dallas criteria; however, we recommend the clinical modification of the classification to include the four categories identified.

Conclusions The majority of patients with either active or borderline myocarditis have significant left ventricular dysfunction. Patients with the fulminant form of myocarditis can be clinically distinguished by their history of rapid hemodynamic deterioration and histologic evidence of severe active myocarditis. Patients with either acute or chronic active forms of myocarditis cannot initially be separated clinically or histologically. However, the chronic active form is characterized by recurrent episodes of clinical deterioration, decline in ventricular function and histologic persistence of myocardial inflammation associated with the appearance of giant cells, making this category distinct and recognizable. In addition, a minority of the patients with myocarditis appear to have persistent myocardial inflammation with normal ventricular function, categorized as chronic persistent myocarditis. Our experience with this small number of patients suggests that immunosuppressive therapy appears to be of benefit exclusively in patients with active myocarditis.

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