

CHAPTER

11

Introduction to Clinical Myocarditis

G. William Dec, M.D.

HISTORICAL BACKGROUND

HYPERSENSITIVITY MYOCARDITIS

CLINICAL PRESENTATIONS OF LYMPHOCYTIC
MYOCARDITIS

Acute Dilated Cardiomyopathy

Myocarditis Mimicking Acute Myocardial Infarction

Sudden Cardiac Death and Ventricular Arrhythmias

DIAGNOSIS OF ACUTE MYOCARDITIS

Clinical Features and Endomyocardial Biopsy

Nuclear Imaging Techniques

Magnetic Resonance Imaging

Echocardiographic Tissue Characterization

CONCLUSION

HISTORICAL BACKGROUND

Myocarditis is simply defined as inflammation of the myocardium. The inflammation may involve the myocytes, interstitium, vascular elements, or pericardium. Despite its rather plain definition, the classification, diagnosis, and treatment of myocarditis continue to prompt considerable debate. The term “myocarditis” was initially used by Sobernheim¹ in 1837. The disease process was further clarified as “isolated idiopathic interstitial myocarditis” by Feidler² in 1899. Saphir³ proposed one of the first classification systems for myocarditis based on disease etiology. He³ was among the first to appreciate the disparity between pathologic findings and clinical presentation when he wrote “a gap between the abundance of anatomic changes in the myocardium and their apparent clinical insignificance.” Burch and Ray,⁴ in 1948, better described clinical manifestations of the disease and were the first to recognize different prognoses for acute and chronic types of myocarditis. These initial pathologic series focused on one end of the spectrum of the disease—ie, those patients who died of myocarditis. Histologic confirmation of clinical myocarditis in the living patient became possible with the advent of endomyocardial biopsy in the 1960s. The more routine use of endomyocardial biopsy has helped better define the natural history of human myocarditis and clarify clinicopathologic correlations.

Myocarditis may occur during or following a wide variety of viral, rickettsial, bacterial, and protozoal infections (Table 11-1). Infectious diseases cause myocardial injury through 3 basic mechanisms: direct invasion of the myocardium, production of a myocardial toxin (such as diphtheria), or immunologically mediated myocardial damage. Although virtually any infectious agent may produce myocardial inflammation and injury, human myocarditis is most frequently caused by viral infection.⁵ The picornavirus group, which includes coxsackievirus A and B, echovirus, and poliovirus, is most frequently associated with myocardial involvement.⁶ Less commonly implicated viral etiologies include orthomyxovirus (influenza A and B), paramyxovirus (rubeola, mumps), togavirus (rubella, dengue, yellow fever), herpesvirus (varicella zoster), Epstein-Barr virus, cytomegalovirus, and hepatitis virus (A, B, and C). Cardiac involvement in the acquired immunodeficiency syndrome (AIDS) may include infective or toxic forms of myocarditis. Cardiac involvement occurs in 25% to 45% of AIDS patients; however, it leads to clinically apparent heart disease in fewer than 10%.⁷ Myocarditis may result from opportunistic infections of the myocardium (eg, *Pneumocystis carinii*, toxoplasmosis), viral infection (cytomegalovirus, human immunodeficiency virus), or drug toxicity (antibiotics and antiretroviral drugs). Other noninfectious causes of myocarditis include myocardial toxins, autoimmune disorders, physical agents, and hypersensitivity drug reactions (Table 11-1).

The clinical manifestations of myocarditis are highly varied and are not specific enough to establish a diagnosis with certainty. Clinicians have increasingly relied on right ventricular endomyocardial biopsy for histologic confirmation of suspected inflammatory heart

Table 11-1
Etiologies of Lymphocytic Myocarditis*

Infectious causes

Viral agents

Coxsackievirus (A, B), echovirus, cytomegalovirus, adenovirus, poliovirus, influenza, hepatitis B or C, encephalomyocarditis virus, Epstein-Barr virus, rubella, retrovirus, **human immunodeficiency virus,** mumps, respiratory syncytial virus, rabies, vaccinia, varicella, yellow fever

Bacterial agents

Endocarditis-associated myocarditis; streptococcus (rheumatic or nonrheumatic), meningococcus, salmonella, diphtheriae, brucellosis, tuberculosis, staphylococcus, hemophilus

Chlamydial/atypical infectious agents

Mycoplasma, psittacosis

Rickettsial

Q fever, Rocky Mountain spotted fever, typhus

Fungal

Histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, actinomycosis, cryptococcosis, blastomycosis

Protozoal

Trypanosoma cruzi (Chagas disease), toxoplasmosis, Pneumocystis carinii, African trypanosomiasis, malaria, amebiasis

Spirochetal

Lyme disease, syphilis, leptospirosis, relapsing fever

Metazoal

Trichinosis, schistosomiasis, ascariasis, echinococcosis, cysticercosis

Autoimmune disorders

Scleroderma, lupus erythematosus

Myocardial toxins

Chemotherapeutic agents

Anthracyclines, cyclophosphamide

Antiretroviral agents

Didanosine (ddI), ddC (zalcitabine), AZT (zidovudine), ribavirin, interferon- α

Antiparasitic

Emetine, chloroquine, antimony compounds

Psychotropic agents

Phenothiazine, lithium

Metal poisoning

Mercury, arsenic

Animal toxins

Snake bite, wasp sting, spider bite, scorpion sting

Catecholamines

Cocaine, pheochromocytoma

Physical injury

Radiation

Heat stroke

Hypothermia

Hypersensitivity reaction

*Etiologies shown in **bold** are more commonly observed causes of myocarditis.

disease. Mason et al.⁸ were among the first to demonstrate evidence of myocardial inflammation by using right ventricular endomyocardial biopsies in a small group of patients with presumed idiopathic dilated cardiomyopathy. Although endomyocardial biopsy has become the standard for establishing the diagnosis, the histologic criteria used for establishing the diagnosis of myocarditis have varied considerably.

In a study designed to define quantitative criteria for the diagnosis of myocarditis, Edwards et al.⁹ reported that the presence of more than 5 lymphocytes/hpf was sufficient to diagnose active myocarditis. Tazelaar and Billingham,¹⁰ however, cautioned against the use of a focal infiltrate alone in diagnosing myocarditis because isolated lymphocyte aggregations may also be seen in idiopathic dilated cardiomyopathy. To provide more uniform criteria for the pathologic diagnosis of myocarditis, a panel of cardiac pathologists developed a disease classification known as the Dallas criteria.¹¹ These authors define myocarditis as a process characterized by an inflammatory infiltrate of the myocardium with necrosis or degeneration of adjacent myocytes (or both), not typically seen in ischemic injury. The inflammatory infiltrate is typically lymphocytic but may also include eosinophilic, neutrophilic, granulomatous, or mixed cellularity. The amount of inflammation and its distribution may be mild, moderate, or severe and focal, confluent, or diffuse, respectively. Despite the widespread adoption of this histopathologic classification, some clinicians feel that the definition is too narrow and have proposed a clinicopathologic classification that includes histologic characteristics and clinical features (Table 11-2).^{12,13} Despite its clinical appeal, this clinicopathologic approach has not been widely accepted.

Sampling error is the most critical limitation to diagnostic accuracy of endomyocardial biopsy. Hauck et al.¹⁴ analyzed hearts from autopsies in which myocarditis was determined to have contributed directly to death. Ten biopsy specimens from the apex and septum of both ventricles were evaluated for myocarditis by the Dallas criteria. Myocarditis was correctly diagnosed from all 10 specimens in 63% of the hearts. When only the first 5 right ventricular biopsy specimens from each heart were evaluated, which is the most common clinical sampling rate, the diagnosis of myocarditis could not be established in 55% of the hearts (Fig. 11-1). In a similar postmortem study of 14 hearts, 17.2 samples per heart were required to correctly diagnose myocarditis in more than 80% of the cases.¹⁵ Dec et al.¹⁶ examined the results of a repeat right and left ventricular endomyocardial biopsy in patients who were strongly suspected of having myocarditis clinically but whose initial right ventricular biopsy failed to provide histologic confirmation. Repeat biopsies detected an additional 15% incidence of myocarditis. Thus, a positive endomyocardial biopsy unequivocally establishes the diagnosis; however, the absence of histologic confirmation should not exclude consideration of myocarditis in most clinical settings.

Table 11-2
Clinicopathologic Classification of Myocarditis

Characteristic	Fulminant	Acute	Chronic active	Chronic persistent
Symptom onset	Distinct	Indistinct	Indistinct	Indistinct
Presentation	Cardiogenic shock, severe LVD	CHF, LVD	CHF, LVD	Non-CHF symptoms, normal LV function
Biopsy findings	Multiple foci of active myocarditis	Active or borderline myocarditis	Active or borderline myocarditis	Active or borderline myocarditis
Natural history	Complete recovery or death	Partial recovery or DCM	DCM	Non-CHF symptoms, normal LV function
Histologic evolution	Complete resolution	Complete resolution	Ongoing or resolving myocarditis, fibrosis, giant cells	Ongoing or resolving myocarditis
Immunosuppression	No benefit	Sometimes beneficial	No benefit	No benefit

CHF, congestive heart failure; CM, cardiomyopathy; DCM, dilated cardiomyopathy; LV, left ventricular; LVD, left ventricular dysfunction.

From Lieberman et al.¹² By permission of the American College of Cardiology.

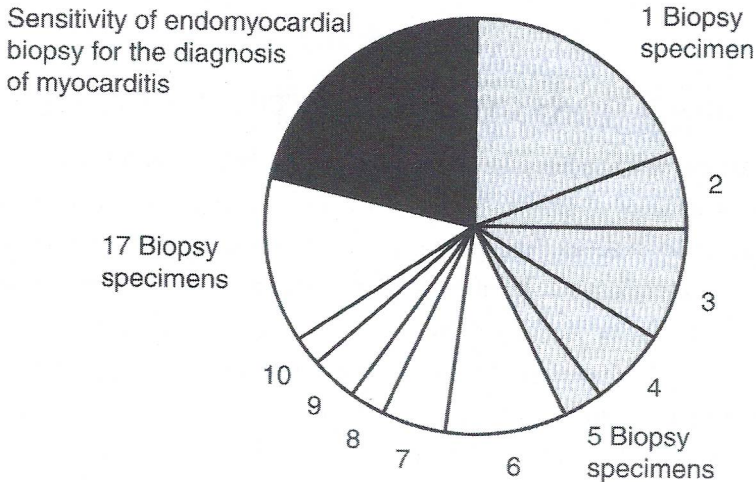


Fig. 11-1. Sensitivity of endomyocardial biopsy for detecting myocarditis in a postmortem study of 38 myocarditis hearts. Each section demonstrates the rate of detection of each additional endomyocardial biopsy specimen. One biopsy detected myocarditis in 18% of specimens. Light gray shading: 5 biopsy specimens detected myocarditis in only 43% of specimens. White: 17 biopsy specimens confirmed myocarditis in 82% of explanted hearts. Multiple biopsy specimens failed to detect known myocarditis in 18% of cases. (From Dec and Narula.⁷⁶ By permission of Edizioni Minerva Medica.)

HYPERSENSITIVITY MYOCARDITIS

Adverse effects of prescribed medications may include hypersensitivity and toxic myocarditis. Unlike toxic reactions, hypersensitivity may occur in individuals with prior uneventful exposure to the drug and is not dose related. The myocarditis is histologically characterized by a perivascular and interstitial infiltrate of the myocardium by eosinophils, leukocytes, and, rarely, multinucleated giant cells or granulomas with little or no myocyte necrosis.¹⁷ Commonly implicated drugs are sulfonamides, penicillins, methyldopa, phenytoin, and tricyclic antidepressants (Table 11-3).^{17,18} Cocaine may also rarely produce a hypersensitivity myocarditis. Unlike the hypereosinophilic syndrome, peripheral eosinophilia is typically absent.¹⁹ Prolonged continuous infusion of dobutamine has also been associated with hypersensitivity myocarditis.²⁰ Hypersensitivity myocarditis is rarely recognized clinically and is often first discovered at postmortem examination. However, it may be diagnosed by endomyocardial biopsy.¹⁷ Autopsy studies suggest that up to 50% of cases could be diagnosed by means of biopsy.¹⁸ Like most cases of myocarditis, symptoms and physical findings do not relate to the degree of cellular infiltration. Cardiac arrhythmias or unexplained sudden death are the most common clinical presentations.^{18,21} Eosinophilic myocarditis may also simulate acute myocardial infarction, with ischemic chest pain and ST-segment elevation on electrocardiography.²¹ Awareness of the condition is necessary to make the correct diagnosis. Therapy includes discontinuation of the offending medication and corticosteroids, sometimes with additional immunosuppressive agents in severe cases.^{17,22}

CLINICAL PRESENTATIONS OF LYMPHOCYTIC MYOCARDITIS

Clinical manifestations of lymphocytic myocarditis range from asymptomatic electrocardiographic abnormalities to severe heart failure and cardiogenic shock. Transient electrocardiographic abnormalities suggesting myocardial involvement have been reported during community viral epidemics. Most patients do not have clinical manifestations of heart disease.^{6,23} Typically, cardiac involvement develops 7 to 10 days after a systemic viral illness. Unrecognized myocarditis during viral infections has been supported by histologic findings obtained during routine postmortem examination.^{23,24} Subepicardial myocardial involvement has been reported frequently in patients with acute myocarditis.²⁵ The majority of patients have no specific cardiovascular complaints. Myocarditis is often inferred from ST-segment and T-wave abnormalities noted on electrocardiogram.⁶ Symptoms may include fatigue, dyspnea, palpitations, and precordial chest pain.²⁶ Chest pain usually reflects associated pericarditis but occasionally may suggest myocardial ischemia. Heart failure due to acute dilated cardiomyopathy is the most frequent manifestation of myocarditis that requires medical attention.²⁷ Myocarditis may simulate acute

Table 11-3
Common Drug Causes of Hypersensitivity Myocarditis*

Diuretics	Antituberculous	Miscellaneous
Acetazolamide	Isoniazid	Cocaine
Chlorthalidone	Paraminosalicylic acid	Dobutamine
Thiazides		Tricyclic antidepressants
Spiroinolactone	Anticonvulsants	Methyldopa
	Phenytoin	Phenothiazines
Antibiotics/antifungal	Carbamazepine	Sulfonylureas
Aminoglycosides		Tetanus toxoid
Penicillins	Anti-inflammatory	
Cephalosporins	Indomethacin	
Chloramphenicol	Phenylbutazone	
Sulfonamides		
Tetracyclines		
Streptomycin		
Amphotericin B		

*Etiologies shown in **bold** are more commonly observed causes of myocarditis.

myocardial infarction.²⁸ Ventricular arrhythmias, heart block, and sudden cardiac death are uncommon, but occasionally reported, clinical presentations.^{26,29} Most patients recover from viral myocarditis within weeks, although electrocardiographic abnormalities often persist for months. Although coxsackievirus myocarditis is only occasionally fatal in adults, neonates tend to have a more malignant course.

The clinical course of myocarditis is highly variable. In the majority of patients, the disease is self-limited and there is complete resolution of myocardial inflammation without further sequelae. Myocarditis has been reported to recur in 10% to 25% of patients after apparent resolution of the initial illness.^{27,30} There are no reliable predictors that identify patients likely to have a relapse, although one report indicated that pericarditis on initial presentation may be associated with a higher rate of recurrence.³¹ Similar to initial presentation, recurrent myocarditis may resolve spontaneously or be associated with heart failure, arrhythmias, or death.

ACUTE DILATED CARDIOMYOPATHY

Heart failure of recent onset due to acute dilated cardiomyopathy represents one of the most dramatic and clinically relevant presentations of acute lymphocytic myocarditis.^{8,32,33} Myocarditis must always be differentiated from other potentially reversible causes of acute dilated cardiomyopathy (Table 11-4). The link between clinical myocarditis and acute dilated cardiomyopathy is provided by histologic validation of acute inflammatory changes and myocyte injury. With the routine use of right ventricular endomyocardial biopsy,

Table 11-4
Reversible Causes of Acute Left Ventricular Dysfunction

Stunned myocardium following an acute ischemic insult or infarction
Sepsis-associated myocardial depression
Myocardial depression after cardiopulmonary bypass (postcardiotomy syndrome)
Acute dilated cardiomyopathies
Peripartum cardiomyopathy
Idiopathic
Toxic
Alcohol
Cobalt (beer drinker's heart)
Carbon monoxide
Cocaine
Drug-induced
Antiretroviral agents
Doxorubicin (acute response)
Interferon
Myocarditis
Lymphocytic
Giant cell
Eosinophilic
Granulomatous
Wegener granulomatosis
Cardiac sarcoidosis

histologic evidence of active myocarditis has been reported in 1% to 67% of patients presenting with dilated cardiomyopathy (Table 11-5).^{8,32,33,35,38,39,42-45}

The wide variation in reported incidence of disease has several potential explanations. Various studies have examined a heterogeneous patient mix; some series have included patients with heart failure of many years' duration whereas others have focused on those with symptoms of recent onset. In addition, the criteria for definitive diagnosis of myocarditis have varied considerably. Many series that report a biopsy incidence of myocarditis of more than 30% have used liberal definitions that included only the presence of scattered lymphocytic infiltrates. More recent series which have used the Dallas criteria have reported a substantially lower incidence of myocarditis. In the largest and most contemporary series, Mason et al.⁴² reported a biopsy incidence of myocarditis of approximately 10% in the Multicenter Myocarditis Trial. Given the multifocal nature of the inflammatory infiltrate, the frequency with which myocarditis is histologically verified probably significantly underestimates its true presence. Moreover, histologic findings may be an insensitive marker of an ongoing inflammatory process, possibly inferior to histochemical and immunologic markers. The results of enteroviral genomic detection using polymerase chain reaction techniques may ultimately establish a new diagnostic standard with higher sensitivity and specificity.

Table 11-5
Incidence of Biopsy-Proven Myocarditis in Patients With Dilated Cardiomyopathy

Series	Year	Patients screened, no.	Positive biopsies*, %
Kunkel et al. ³⁴	1978	66	6
Mason et al. ⁸	1980	400	3
Noda ³⁵	1980	52	0.5
Baandrup et al. ³⁶	1981	132	1
O'Connell et al. ³⁷	1981	68	7
Nippoldt et al. ³⁸	1982	170	5
Fenoglio et al. ³⁹	1983	135	25
Unverferth et al. ⁴⁰	1983	59	6
Parrillo et al. ³²	1984	74	26
Zee-Cheng et al. ³³	1984	35	63
Daly et al. ³⁰	1984	69	17
Bolte and Ludwig ⁴¹	1984	91	20
Dec et al. ²⁷	1985	27	67
Hosenpud et al. ²⁹	1986	38	16
Mason et al. ⁴²	1995	<u>2,233</u>	<u>10</u>
		3,649	10.3

*Histologic criteria for diagnosing myocarditis varied widely among published series. The largest and most recent series from the Multicenter Myocarditis Trial⁴² ($n = 2,233$) used the current Dallas criteria. Final mean was weighted.

It is clear that the duration of symptoms is closely related to the likelihood of detecting myocarditis on biopsy (Table 11-6). Those patients with symptoms of short duration have been found to have a higher likelihood of myocarditis or borderline myocarditis being detected.²⁷ Most studies have shown that the biopsy detection rate for myocarditis is less than 5% when heart failure symptoms have been present for more than 6 months.²⁷

Clinical signs and symptoms of active myocarditis based on community coxsackievirus outbreaks have been described in some cases of lymphocytic myocarditis.⁴⁵⁻⁴⁷ A viral-like illness (upper respiratory infection or gastrointestinal tract symptoms) is present in one-third of patients with coxsackievirus myocarditis but is a nonspecific finding. Pericarditis is associated with active myocarditis in 25% to 30% of patients.^{27,46,47} Supportive laboratory abnormalities, including increased erythrocyte sedimentation rate, leukocytosis, or increased creatine kinase concentration, are useful when present but occur in only 10% to 20% of biopsy-proven cases.^{27,48,49}

Newer laboratory markers such as serum troponin I and troponin T may be more sensitive in detecting myocardial injury and are being evaluated for diagnosis of clinical myocarditis. Thus, the classic clinical triad traditionally used to diagnose coxsackie B-induced myocarditis (ie, preceding viral illness, pericarditis, and associated laboratory abnormalities) is present in fewer than 10% of histologically proven cases.²⁷ Again, those patients with acute dilated cardiomyopathy of short duration are generally more likely to have a high clin-

Table 11-6
Relationship Among Duration of Illness, Clinical Features, Histopathologic Findings,
and Outcome for Patients Presenting With Acute Dilated Cardiomyopathy

Onset of symptoms, wk	Patients, no.	Clinical score*	Positive [†] biopsy, %	Improved [‡] , %
0-4	9	2.1	89	44
4-12	10	2.3	70	30
12-26	8	0.9	38	38

*Mean number of clinical features suggestive of myocarditis (viral syndrome by history = 1 point; pericarditis by history or examination = 1 point; supportive laboratory abnormalities [leukocytosis, increased sedimentation rate or concentration of creatine kinase] = 1 point). Score for any patient ranged from 0 to 3 points.

[†]Histologic findings confirming myocarditis or borderline myocarditis.

[‡]Improvement defined as increase in left ventricular ejection fraction > 10 units and improvement in symptoms.

Modified from Dec et al.²⁷ By permission of the Massachusetts Medical Society.

ical feature score (semiquantitatively defined as 0-3) than those with more long-standing symptoms (Table 11-6).²⁷ Therefore, a new diagnosis of acute dilated cardiomyopathy should suggest the possibility of viral myocarditis even when a prior viral illness, pericardial inflammation, or laboratory abnormalities are lacking. Conversely, the combination of one or more clinical features of coxsackie myocarditis and a subsequent substantial increase in left ventricular ejection fraction supports the clinical diagnosis of active myocarditis, even when supportive biopsy evidence is lacking.^{27,50}

A patient who has acute dilated cardiomyopathy due to myocarditis generally presents in 1 of 3 ways. Typically, the patient presents with signs and symptoms of mild (New York Heart Association [NYHA] class II) heart failure of short duration. Mild cardiomegaly is noted on chest film or an increase in left ventricular end-diastolic dimension is detected on echocardiography. Systolic function is usually only mildly impaired, with left ventricular ejection fraction in the 40% to 50% range. The vast majority of these patients have spontaneous improvement in ventricular function and normalization in heart size with conservative medical management.

A second group presents more critically ill with more prominent heart failure symptoms (NYHA class III or IV). Left ventricular size is often markedly increased, with left ventricular end-diastolic dimension greater than 70 mm on echocardiography. Likewise, systolic function is more markedly impaired; left ventricular ejection fraction is almost always less than 35%. Typically, 25% of these patients have spontaneous improvement in ventricular function, 50% develop chronic left ventricular dysfunction, and the remaining 25% progress to death or need for transplantation (personal observation). Histologic findings (ie, the extent of inflammatory infiltrate, myocyte necrosis, or interstitial fibrosis) do not correlate closely with the likelihood of improvement or deterioration in ventricular

function.^{27,51} Among the cohort of patients who have normalization of ventricular function, biopsy-proven relapses have been noted and recurrent myocarditis should be suspected if ventricular function subsequently deteriorates.²⁷

Rarely, a patient may present with fulminant myocarditis and circulatory collapse. These individuals usually have an acute onset of heart failure, severe global left ventricular function, and a minimal increase in left ventricular end-diastolic dimension.^{12,52} End-organ dysfunction is frequently present with abnormalities of hepatic and renal function. Mechanical circulatory support with an intra-aortic balloon pump or unilateral or biventricular assist devices is often necessary to bridge the time to recovery of ventricular function or heart transplantation.⁵²⁻⁵⁴ Despite the severity of their initial presentation, many patients exhibit partial or complete recovery of ventricular function with short- to intermediate-term inotropic or mechanical circulatory support.^{52,53}

Long-term outcome with histologically verified lymphocytic myocarditis has been clarified. In a single-institution study, Grogan et al.⁴³ reported a 5-year survival rate of 56% for patients presenting with lymphocytic myocarditis (Fig. 11-2). Interestingly, no difference in short- or long-term survival was noted between patients with histologically verified myocarditis and those with idiopathic dilated cardiomyopathy. Similar results have been reported for patients enrolled in the Multicenter Myocarditis Trial, with a 5-year

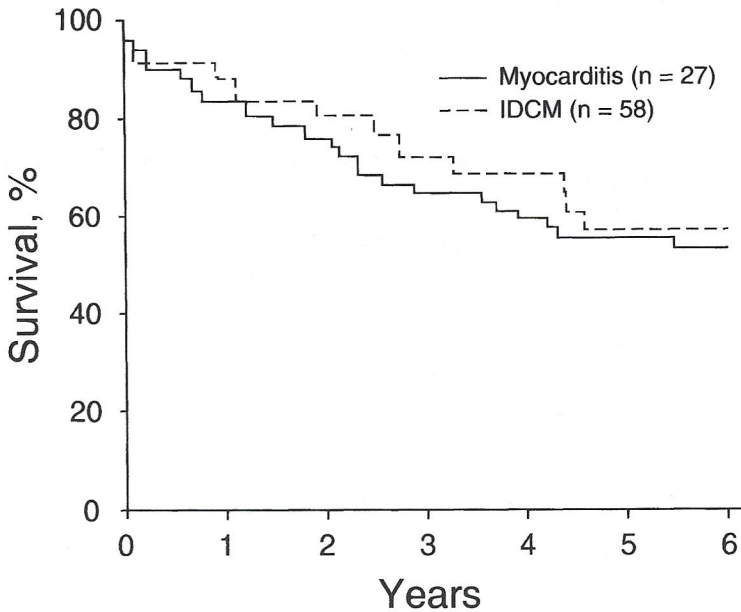


Fig. 11-2. Survival of patients with biopsy-proven myocarditis (definite or borderline by Dallas criteria) compared to that observed for patients with idiopathic dilated cardiomyopathy (*IDCM*) and negative endomyocardial biopsy findings. (From Grogan et al.⁴³ By permission of the American College of Cardiology.)

survival of 52% in patients treated with conventional medical therapy.⁴² Some investigators have suggested that patients with borderline myocarditis may respond more favorably to immunosuppressive therapy and have a better long-term outcome, but others have been unable to confirm a better long-term outcome in this group.^{51,55,56} Identification of individual patients with lymphocytic myocarditis who are at increased risk of death based on their clinical features, biopsy findings, or ventriculographic studies is not usually possible; however, the predictors of death or need for heart transplantation in two large single-center series are illustrated in Tables 11-7 and 11-8.

Table 11-7
Multivariate Predictors of Death or Transplantation in 109 Cases of Biopsy-Proven Lymphocytic Myocarditis From Massachusetts General Hospital

Variable	<i>P</i>	RR	CI
Syncope	0.003	8.5	2.08-34.89
BBB	0.023	2.9	1.16-7.40
EF < 40%	0.05	2.9	1.01-8.49
Borderline histologic results	0.018	0.07	0.01-0.64

BBB, bundle branch block; EF, ejection fraction.

From Goldberg LR, Suk HJ, Patton KK, Semigran MJ, Dec GW, DiSalvo TG. Predictors of adverse outcome in biopsy-proven myocarditis (abstract). *J Am Coll Cardiol* 1999;33 Suppl A:505A. By permission of the American College of Cardiology.

Table 11-8
Multivariate Predictors of Death or Transplantation in 147 Patients With Lymphocytic Myocarditis Diagnosed by Biopsy at Johns Hopkins Hospital

Variable*	Adjusted hazard ratio for death or transplantation (95% CI)	<i>P</i> value
Fulminant myocarditis at presentation	0.10 (0.01-0.88)	0.04
Increased mean pulmonary artery pressure (for each increment of 5 mm Hg)	1.50 (1.1-2.1)	0.01
Increased cardiac output (for each increment of 1 L/min)	0.75 (0.59-0.96)	0.02

*Nonsignificant predictors were age, histopathologic findings (borderline myocarditis or active myocarditis), heart rate, mean arterial pressure, mean right atrial pressure, and mean pulmonary-capillary wedge pressure. Mean pulmonary-artery pressure and cardiac output were evaluated as continuous variables. CI denotes confidence interval.

From McCarthy et al.⁵¹ By permission of the Massachusetts Medical Society.

MYOCARDITIS MIMICKING ACUTE MYOCARDIAL INFARCTION

Myocarditis is not infrequently associated with chest pain, which is typically pleuritic in nature and related to accompanying pericardial inflammation. Patients with myocarditis may also present with angina-like chest discomfort, despite the absence of epicardial coronary artery disease. Myocarditis has been reported at autopsy in patients who presented with acute myocardial infarction, normal coronary anatomy, and documented coxsackie B viral disease.⁵⁷ Because myocarditis is associated with focal or multifocal myocardial inflammation and necrosis, it is not surprising that it may be associated with increased serum concentration of creatine kinase, electrocardiographic repolarization abnormalities, abnormal QS waves, and segmental wall motion abnormalities on left ventriculography.⁵⁷⁻⁶¹

At our institution, 34 patients with clinical signs and symptoms of acute myocardial infarction underwent right ventricular endomyocardial biopsy during a 6.5-year period after angiographic identification of normal coronary anatomy.⁶² Myocarditis was confirmed on biopsy in 11 of these patients (32%). Cardiogenic shock requiring transient intra-aortic balloon support developed within 6 hours of admission in 3 of these patients. Electrocardiographic abnormalities were noted, including ST-segment elevation in 2 or more contiguous leads (54%), widespread T-wave inversions (27%), ST depression (18%), and pathologic Q waves (18%) (Fig. 11-3). A clear-cut viral illness had been present in 54% of these patients. Electrocardiographic abnormalities were typically observed in the anterior precordial leads in this series; other reports confirmed abnormalities in the inferior and lateral distributions.⁵⁸⁻⁶⁰ Left ventricular function was normal in 55% of patients at presentation and globally decreased in the remaining patients. Ejection fraction ranged from 17% to 45%. Diffuse, rather than segmental, wall motion abnormalities were present in this series. Ventricular function remained normal in all patients who presented with normal contractility; left ventricular ejection fraction normalized in 4 of the 5 patients in whom it was impaired at presentation. All patients who required transient intra-aortic balloon support survived to dismissal. One death due to progressive heart failure occurred 18 months after presentation in the only patient in the series with giant cell myocarditis on biopsy. Thus, acute myocarditis that mimics myocardial infarction is generally associated with an excellent long-term prognosis. The electrocardiographic abnormalities, including pathologic Q waves, typically resolved during the first 12 months. Likewise, reversible impairment in ventricular contractile function was evident within 3 to 6 months. Ischemic chest pain did not recur in any patient.

Clinicians should consider acute myocarditis in patients who present with ischemic chest pain syndromes when electrocardiographic abnormalities extend beyond a single vascular distribution, segmental wall motion abnormalities are lacking on echocardiography or left ventriculography in the distribution of myocardial injury, or global left ventricular hypokinesis is noted. The subsequent demonstration of normal coronary anatomy should

prompt consideration of this diagnosis. Although histologic confirmation by endomyocardial biopsy is of theoretical interest, it is seldom clinically indicated because spontaneous improvement in electrocardiographic and ventriculographic abnormalities is quite likely. Biopsy should be considered for individuals who do not demonstrate a typical clinical course of recovery to exclude the possibility of giant cell myocarditis, which has a substantially poorer prognosis.⁶²⁻⁶⁴

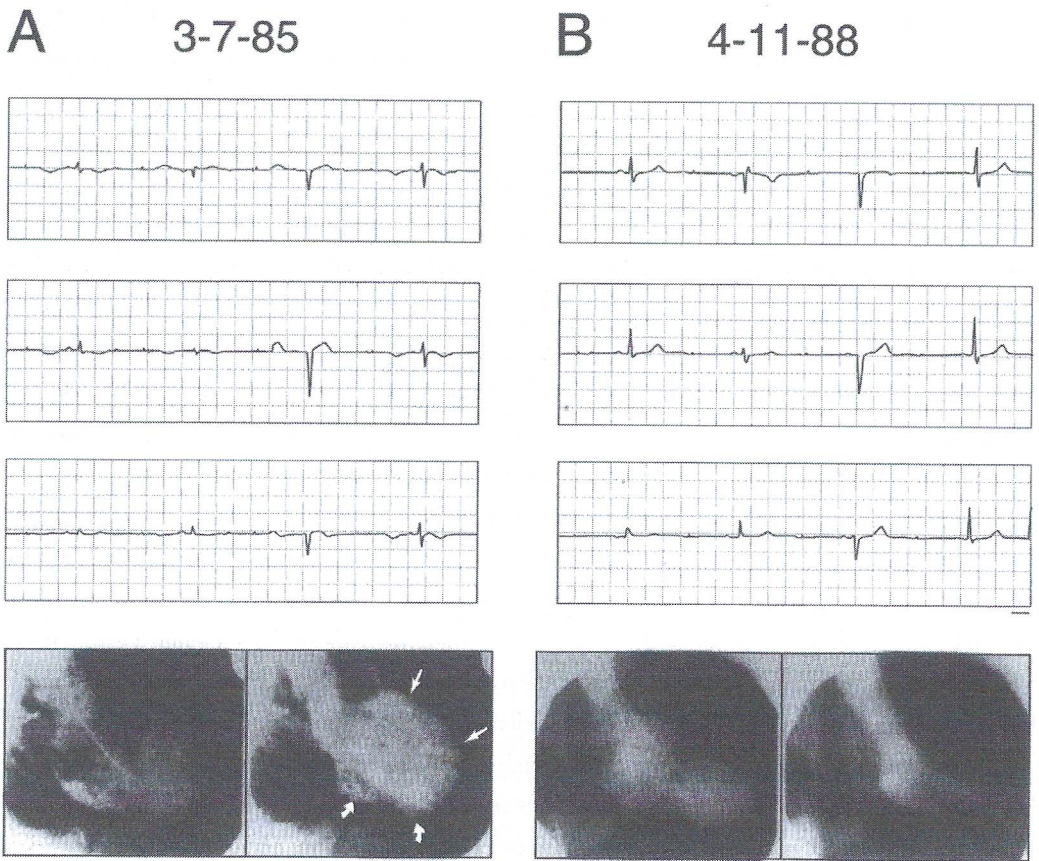


Fig. 11-3. *A*, Admission electrocardiogram (ECG) and left anterior oblique ventriculogram of a patient with biopsy-proven lymphocytic myocarditis. The ECG shows QS waves in leads V₁ and V₂ with diffuse T-wave inversions. End-diastolic (*Bottom left*) and end-systolic (*Bottom right*) frames of the ventriculogram demonstrate anteroapical and lateral akinesis (*top arrows*) and marked inferior hypokinesis (*bottom arrows*). The overall left ventricular ejection fraction was calculated at 34%. *B*, At 3-year follow-up, the ECG shows improvement in R-wave progression and resolution of the repolarization abnormalities. End-diastolic (*Bottom left*) and end-systolic (*Bottom right*) frames of the left ventriculogram demonstrate normal contractile function and an ejection fraction of 62%. Repeat right ventricular biopsy revealed healed myocarditis. (From Dec et al.⁶² By permission of the American College of Cardiology.)

SUDDEN CARDIAC DEATH AND VENTRICULAR ARRHYTHMIAS

Myocarditis is a significant cause of sudden, unexpected death in adults younger than age 40 years and elite young athletes.^{65,66} In these presumably healthy individuals, autopsy findings have revealed myocarditis in up to 20% of cases.^{65,66} The diagnosis is now often made before death through the routine use of endomyocardial biopsy. Although heart failure, cardiomyopathy, and myocardial mimicry are more common clinical presentations, patients with myocarditis can also occasionally present with syncope or sudden cardiac death.

Several series have examined the frequency of myocarditis among patients evaluated for life-threatening ventricular arrhythmias that occurred in the absence of structural heart disease.^{64,67-69} These patients tended to be young (younger than 50 years) and to have normal or near-normal left ventricular systolic function. The frequency of syncope or cardiac arrest as reported has ranged from 8% to 61%.^{68,69} Biopsy evidence of myocarditis among patients without structural heart disease has ranged from 8% to 50% (Table 11-9). At our institution, granulomatous myocarditis has been associated more frequently with life-threatening ventricular arrhythmias, syncope, and high-grade atrioventricular block requiring temporary or permanent ventricular pacing than has lymphocytic myocarditis.⁶⁴

Management of patients with ventricular arrhythmias due to lymphocytic or granulomatous myocarditis remains problematic. Electrophysiologic testing fails to provoke inducible monomorphic ventricular tachycardia or ventricular fibrillation in more than two-thirds of patients who undergo testing.^{21,67,68} Many investigators use short-term immunosuppressive therapy to decrease myocardial inflammation and injury and to control ventricular tachyarrhythmias. Friedman et al.⁷⁰ reported persistent complex ventricular arrhythmias after apparent resolution of myocarditis in children and young adults. Patients with life-threatening arrhythmias generally require long-term antiarrhythmic therapy. For those with out-of-hospital cardiac arrest, an implantable defibrillator is often preferable to pharmacologic treatment. Patients with histologically documented granulomatous myocarditis and those with cardiac sarcoidosis are at particularly high risk for life-threatening

Table 11-9
Incidence of Biopsy-Proven Myocarditis in Patients
Presenting With Ventricular Arrhythmias

Series	Year	Patients, no.	Sudden death/ syncope, %	Myocarditis, %
Strain et al. ⁶⁹	1983	18	61	17
Sugrue et al. ⁶⁸	1984	12	8	8
Vignola et al. ⁶⁷	1984	12	33	50
Hosenpud et al. ²⁹	1986	12	33	33

ventricular tachyarrhythmias.^{64,71,72} Control studies have not evaluated the success of immunosuppressive strategies, pharmacologic antiarrhythmic suppression, or implantable cardioverter-defibrillator treatment. Nonetheless, many clinicians recommend placement of an implantable cardioverter-defibrillator in such high-risk individuals.

DIAGNOSIS OF ACUTE MYOCARDITIS

CLINICAL FEATURES AND ENDOMYOCARDIAL BIOPSY

Myocarditis may be diagnosed with a moderate degree of certainty when a constellation of clinical features is present: a preceding viral illness, acute onset of symptoms, fever, pericardial inflammation, supportive laboratory abnormalities (increased erythrocyte sedimentation rate, leukocytosis, increased concentration of creatine kinase), and electrocardiographic abnormalities. As previously discussed, however, fewer than 10% of patients present with 2 or more of these supportive clinical features. Further, endomyocardial biopsy, while serving as the most appropriate way to confirm the clinically suspected diagnosis, also has substantial problems as a diagnostic tool. It is invasive, costly, and samples only a tiny portion of the myocardium. Given the focal or multifocal nature of myocarditis, it is not surprising that substantial sampling error exists. Clinicians are increasingly reluctant to recommend routine endomyocardial biopsy, even when myocarditis is clinically strongly suspected.

A noninvasive technique that possesses high sensitivity and specificity has been sought to identify those patients in whom right ventricular biopsy has a high probability of yielding a histologic diagnosis of myocarditis. Creatine kinase or its isoform is not useful as a noninvasive screening method because of low predictive value.^{27,49} Recently, cardiac troponin T has been shown in a moderate-sized single center study to be useful in establishing the diagnosis. Lauer et al.⁴⁸ reported an increased serum concentration of troponin T (> 0.1 ng/mL) was associated with a sensitivity for detecting myocarditis (histologically verified by Dallas criteria, by immunohistochemical techniques, or both) of 53%; its specificity was 94%; its positive predictive value, 93%; and the negative predictive value, 56%. Additional confirmatory studies are necessary to verify the utility of this simple serologic method.

NUCLEAR IMAGING TECHNIQUES

Gallium-67 cardiac scintigraphic imaging has been used to evaluate conditions that result in myocardial inflammation. It is currently seldom performed at most centers. However, at centers with extensive experience in the technique, gallium-67 imaging has been reported to be useful as a screening tool and in predicting response to treatment.^{37,73} O'Connell et al.,⁷³

who studied this methodology most extensively, reported a sensitivity of 36% and a specificity of 98% for histologic detection of myocarditis.

Indium-labeled monoclonal antibody fragments of antimyosin antibodies (directed against heavy chain myosin) bind to cardiac myocytes that have lost the integrity of their sarcolemma membranes and have exposed intracellular myosin to the extracellular fluid space.⁷⁴ Unlike gallium-67, which detects extent of myocardial *inflammation*, antimyosin uptake reflects the extent of myocyte *necrosis*. Because both elements are present in myocarditis, the 2 imaging modalities should provide similar or complementary information. Unfortunately, no studies have been performed that directly examine the utility of these radionuclide techniques when combined or when compared with one another. Nonetheless, published sensitivities and specificities suggest that antimyosin has a higher negative predictive value than gallium-67 scintigraphy.

Dec et al.⁷⁵ studied the utility of antimyosin imaging in 82 patients with clinically suspected myocarditis. Symptoms at presentation included congestive heart failure and cardiomyopathy (92%), chest pain mimicking myocardial infarction (6%), and life-threatening ventricular tachyarrhythmias (2%). All patients underwent planar and single photon emission computed tomographic cardiac imaging 48 hours after injection of indium-111-labeled antimyosin antibody fragments (Fig. 11-4). Right ventricular biopsy was performed within 48 hours after imaging. On the basis of right ventricular histologic

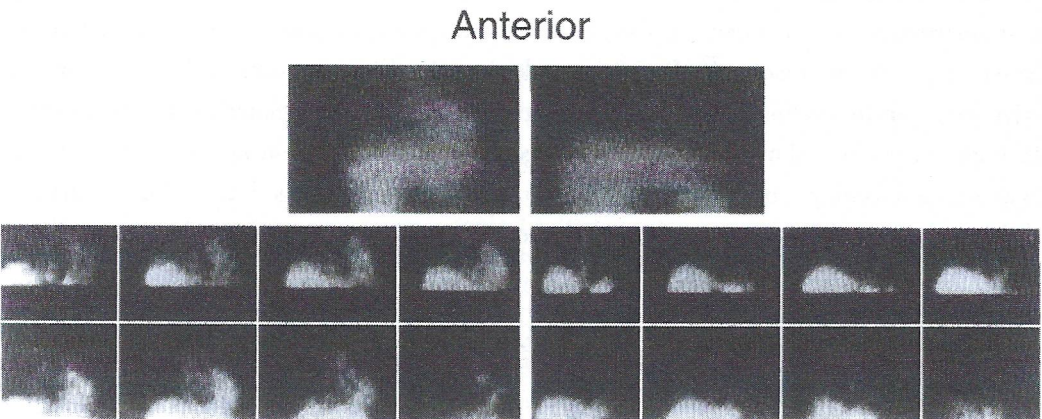


Fig. 11-4. A positive antimyosin image demonstrates diffuse tracer uptake in the cardiac region on both the anterior planar image (*Upper left*) and in all coronal tomographic reconstructions (*Bottom left*). Biopsy showed multifocal lymphocytic myocarditis. Antimyosin imaging was repeated after 6 months of immunosuppressive therapy. Biopsy showed healed myocarditis. No antimyosin uptake is visible on either the planar (*Top right*) or tomographic reconstructions (*Bottom right*). (From Dec and Narula.⁷⁶ By permission of Edizioni Minerva Medica.)

features, antimyosin was highly sensitive but moderately specific for detecting myocardial necrosis (Table 11-10).⁷⁵ The sensitivity was 83%; specificity, 53%; and predictive value of a negative scan, 92%.

Perhaps more important than the correlation between cardiac antimyosin uptake and histologic findings, improvement in left ventricular function within 6 months of treatment occurred in 54% of patients with a positive antimyosin scan but in only 18% of those with a negative scan.⁷⁵ Because spontaneous improvement in ventricular function is a well-recognized feature of acute lymphocytic myocarditis, it is suspected that several patients who were scan-positive but biopsy-negative may have, in fact, had myocarditis.^{27,76} A small cohort of patients who had a negative initial antimyosin scan returned 6 to 12 months later for a second study. All showed no evidence for antimyosin uptake.⁷⁵ Repeat antimyosin imaging among 17 patients whose initial scan was positive showed persistent uptake in 9 individuals and resolution of uptake in the remaining 8 patients. No correlation could be found between ongoing myocarditis on repeat biopsy and clinical improvement.⁷⁵

Narula et al.⁶¹ also evaluated the role of antimyosin imaging among patients who presented with chest pain mimicking acute myocardial infarction despite normal coronary anatomy. Antimyosin uptake was global in 7 of the 8 patients with confirmed myocarditis on biopsy and equivocal in the 8th patient. Antimyosin uptake was segmental in patients with acute myocardial infarction and almost always confined to the territory of the infarct-related vessel. Thus, antimyosin uptake may be useful in differentiating unstable coronary syndromes from myocarditis.

The low specificity of cardiac antimyosin uptake results from its exquisite affinity with necrotic myocytes. Antimyosin uptake has been reported in systemic diseases that affect the heart such as Lyme disease.⁷⁷ Positive uptake has also been reported in heart transplant rejection,⁷⁸ anthracycline-induced cardiomyopathy,⁷⁹ and alcohol-related cardiomyopathy.⁸⁰ Its high sensitivity and modest specificity suggest that antimyosin scintigraphy may be useful as an initial screening tool to determine which patients should undergo biopsy. Unfortunately, this imaging agent is not currently available commercially and is restricted to research.

MAGNETIC RESONANCE IMAGING

Prior studies that demonstrated the reliability of magnetic resonance imaging (MRI) in tissue characterization of cardiac allograft rejection suggested that this technique might be useful in diagnosing acute myocarditis, which has similar histologic findings. Cardiac MRI has been shown to be effective in detecting myocardial edema. A preliminary study by Chandraratna et al.⁸¹ detected localized myocardial edema in regions of hypokinesis or akinesis on echocardiography in 2 patients with clinically diagnosed myocarditis. After improvement in ventricular function, repeat MRI demonstrated resolution of myocardial edema.⁸¹

Gagliardi et al.⁸² evaluated MRI and endomyocardial biopsy results in 11 consecutive children (age, 9 months to 9 years) with clinically suspected myocarditis. Tissue characterization was obtained in regions of interest of the right and left ventricles by using T1 and T2 spin-echo sequences. The myocardial/skeletal muscle signal intensity ratio was able to accurately identify all patients with histologically confirmed myocarditis (Table 11-10). While encouraging, these results were obtained in a small number of patients. Further, myocarditis in children is often associated with more prominent interstitial edema than that observed in adults. Additional MRI studies in adults are needed.

Contrast-enhanced MRI has also been evaluated.⁸⁴ Nineteen patients with clinically suspected myocarditis and the combination of electrocardiographic abnormalities, impaired left ventricular function, increased creatine kinase concentration, positive troponin T values, and positive results of antimyosin cardiac scintigraphy underwent sequential contrast-enhanced MRI. Electrocardiographic-triggered, T1-weighted images were obtained before and after administration of 0.1 mmol/kg of gadolinium. Global relative signal enhancement of the left ventricular myocardium relative to skeletal muscle was obtained and compared with measurements obtained in 18 volunteers. Global left ventricular enhancement was substantially higher in the myocarditis patients than in controls on days 2, 7, 14, and 28 after onset of acute symptoms. Although enhancement was generally focal during the initial studies, global enhancement was noted during the later times. Histologic verification of myocarditis was not obtained in any of these published studies. More importantly, the ability of this technique to differentiate viral myocarditis from other causes of acute dilated cardiomyopathy was not investigated. If additional studies confirm these findings, longitudinal follow-up of the same patient will become possible and will allow reexamination for recurrent disease or persistent myocarditis.

Table 11-10
Sensitivity, Specificity, and Predictive Value of Noninvasive
Techniques for Diagnosing Myocarditis

Technique	No.	Sen, %	Spec, %	+PV, %	-PV, %	Author	Year
Troponin T	80	53	96	93	56	Lauer et al. ⁴⁸	1997
Gallium-67	71	87	86	36	98	O'Connell et al. ⁷³	1984
Antimyosin	82	83	53	33	92	Dec et al. ⁷⁵	1990
MRI	11	100	100	100	100	Gagliardi et al. ⁸²	1991
Echo	106	100	91	---	---	Leiback et al. ⁸³	1996

Echo, echocardiographic tissue characterization; MRI, magnetic resonance imaging; +PV, positive predictive value; -PV, negative predictive value; sen, sensitivity; spec, specificity.

ECHOCARDIOGRAPHIC TISSUE CHARACTERIZATION

Similar to MRI, echocardiography may provide precise visualization of tissue characterization and has been reported to be useful in establishing the diagnosis of myocarditis. Tissue characterization seeks to define the nature of the tissue from changes that occur in sound waves during their physical interaction with the myocardium. Quantitative approaches have used backscatter to define tissue characteristics. Backscatter is generally measured as the reflected ultrasound power at each frequency over the bandwidth of the transducer. Backscatter, like attenuation, characteristically increases with frequency. Significant increases in backscatter were described for rabbit myocardium exposed to doxorubicin.⁸⁵ Longitudinal studies of Syrian hamster cardiomyopathy revealed increasing values of backscatter as myocardial fibrosis progresses.⁸⁶ Leiback et al.⁸³ compared backscatter measurements among patients with persistent ($n = 12$), healed ($n = 9$), or healed myocarditis with fibrosis ($n = 17$) to measurements obtained in 35 cases of chronic dilated cardiomyopathy and 8 normal controls. Mean gray scale values were substantially higher in patients with cardiomyopathy than in normal controls. Sensitivity was 100% and specificity, 91% (Table 11-8). However, this technique was unable to differentiate myocarditis patients from those with other causes of cardiomyopathy.

CONCLUSION

Myocarditis has a wide variety of clinical presentations for the clinician to ponder. Although most cases are associated with viral pericarditis and are self-limited, the spectrum of abnormalities may include chest pain mimicking myocardial infarction, unexplained ventricular tachyarrhythmias, acute or chronic dilated cardiomyopathy, and cardiogenic shock. Awareness is necessary because characteristic clinical features (pleuritic chest pain or pericardial rub; fever; increased sedimentation rate or concentration of creatine kinase or troponin I) are lacking in the majority of patients with biopsy-proven disease. Noninvasive imaging modalities, including antimyosin cardiac scintigraphy, echocardiographic tissue characterization, and MRI, all possess sufficient sensitivity and specificity to serve as initial screening tools. Endomyocardial biopsy remains the procedure of choice for unequivocally establishing the diagnosis. It is especially useful in differentiating lymphocytic myocarditis with its more favorable prognosis from giant cell myocarditis. Clinical trials of immunosuppressive therapy or immunomodulatory therapy have failed to demonstrate a beneficial effect in this disorder. Spontaneous improvement may occur in more than 30% of patients with lymphocytic disease but is rarely, if ever, observed with granulomatous myocarditis. Effective forms of treatment are urgently needed because the 5-year mortality in patients with dilated cardiomyopathy due to myocarditis exceeds 50%. Better understanding of the

cellular and immunologic abnormalities that characterize the disease process and more complete understanding of the natural history of the various subtypes of myocarditis (acute lymphocytic, fulminant, borderline) should help clinicians plan more effective therapy in the future.

REFERENCES

1. Sobernheim JF. Diagnostik der inneren Krankheiten mit vorzuegleicher Ruecksicht auf pathologische. Anatomie. Berlin: Hirschwald, 1837:1-43.
2. Feidler A. Ueber akute intestielle Myokarditis. In: Festschrift des Standtkrankenhauses. Dresden: Friedrichstadt, 1899:1-10.
3. Saphir O. Myocarditis: a general review, with an analysis of two hundred and forty cases. *Arch Pathol* 1941;32:1000-1051; 1942;33:88-137.
4. Burch G, Ray T. Myocarditis and myocardial degeneration. *Bull Tulane Med Faculty* 1948;8:1-3.
5. Reyes MP, Lerner AM. Coxsackievirus myocarditis—with special reference to acute and chronic effects. *Prog Cardiovasc Dis* 1985;27:373-394.
6. Grist NR, Bell EJ. Coxsackie viruses and the heart (editorial). *Am Heart J* 1969;77:295-300.
7. Blanchard DG, Hagenhoff C, Chow LC, McCann HA, Dittrich HC. Reversibility of cardiac abnormalities in human immunodeficiency virus (HIV)-infected individuals: a serial echocardiographic study. *J Am Coll Cardiol* 1991;17:1270-1276.
8. Mason JW, Billingham ME, Ricci DR. Treatment of acute inflammatory myocarditis assisted by endomyocardial biopsy. *Am J Cardiol* 1980;45:1037-1044.
9. Edwards WD, Holmes DR Jr, Reeder GS. Diagnosis of active lymphocytic myocarditis by endomyocardial biopsy: quantitative criteria for light microscopy. *Mayo Clin Proc* 1982;57:419-425.
10. Tazelaar HD, Billingham ME. Leukocytic infiltrates in idiopathic dilated cardiomyopathy. A source of confusion with active myocarditis. *Am J Surg Pathol* 1986;10:405-412.
11. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, Olsen EG, Schoen FJ. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987;1:3-14.
12. Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. *J Am Coll Cardiol* 1991;18:1617-1626.
13. Waller BF, Slack JD, Orr CD, Adlam JH, Bournique VM. "Flaming," "smoldering" and "burned out": the fireside saga of myocarditis. *J Am Coll Cardiol* 1991;18:1627-1630.
14. Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. *Mayo Clin Proc* 1989;64:1235-1245.
15. Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. *J Am Coll Cardiol* 1989;14:915-920.
16. Dec GW, Fallon JT, Southern JF, Palacios I. "Borderline" myocarditis: an indication for repeat endomyocardial biopsy. *J Am Coll Cardiol* 1990;15:283-289.
17. Kounis NG, Zavras GM, Soufras GD, Kitrou MP. Hypersensitivity myocarditis. *Ann Allergy* 1989;62:71-74.
18. Burke AP, Saenger J, Mullick F, Virmani R. Hypersensitivity myocarditis. *Arch Pathol Lab Med* 1991;115:764-769.
19. Isner JM, Chokshi SK. Cardiovascular complications of cocaine. *Curr Probl Cardiol* 1991;16:89-123.

20. Spear GS. Eosinophilic explant carditis with eosinophilia: ? hypersensitivity to dobutamine infusion. *J Heart Lung Transplant* 1995;14:755-760.
21. Galiuto L, Enriquez-Sarano M, Reeder GS, Tazelaar HD, Li JT, Miller FA Jr, Gleich GJ. Eosinophilic myocarditis manifesting as myocardial infarction: early diagnosis and successful treatment. *Mayo Clin Proc* 1997;72:603-610.
22. Taliercio CB, Olney BA, Lie JT. Myocarditis related to drug hypersensitivity. *Mayo Clin Proc* 1985;60:463-468.
23. Weinstein C, Fenoglio JJ. Myocarditis. *Hum Pathol* 1987;18:613-618.
24. Abelman WH. Viral myocarditis and its sequelae. *Annu Rev Med* 1973;24:145-152.
25. Karjalainen J, Heikkila J. "Acute pericarditis": myocardial enzyme release as evidence for myocarditis. *Am Heart J* 1986;111:546-552.
26. Marboe CC, Fenoglio JJ Jr. Pathology and natural history of human myocarditis. *Pathol Immunopathol Res* 1988;7:226-239.
27. Dec GW Jr, Palacios IF, Fallon JT, Aretz HT, Mills J, Lee DC-S, Johnson RA. Active myocarditis in the spectrum of acute dilated cardiomyopathies. Clinical features, histologic correlates, and clinical outcome. *N Engl J Med* 1985;312:885-890.
28. Narula J, Khaw BA, Dec GW Jr, Palacios IF, Southern JE, Fallon JT, Strauss HW, Haber E, Yasuda T. Recognition of acute myocarditis masquerading as acute myocardial infarction. *N Engl J Med* 1993;328:100-104.
29. Hosenpud JD, McAnulty JH, Niles NR. Unexpected myocardial disease in patients with life threatening arrhythmias. *Br Heart J* 1986;56:55-61.
30. Daly K, Richardson PJ, Olsen EG, Morgan-Capner P, McSorley C, Jackson G, Jewitt DE. Acute myocarditis. Role of histological and virological examination in the diagnosis and assessment of immunosuppressive treatment. *Br Heart J* 1984;51:30-35.
31. Fowler NO, Manitsas GT. Infectious pericarditis. *Prog Cardiovasc Dis* 1973;16:323-336.
32. Parrillo JE, Aretz HT, Palacios I, Fallon JT, Block PC. The results of transvenous endomyocardial biopsy can frequently be used to diagnose myocardial diseases in patients with idiopathic heart failure. Endomyocardial biopsies in 100 consecutive patients revealed a substantial incidence of myocarditis. *Circulation* 1984;69:93-101.
33. Zee-Cheng CS, Tsai CC, Palmer DC, Codd JE, Pennington DG, Williams GA. High incidence of myocarditis by endomyocardial biopsy in patients with idiopathic congestive cardiomyopathy. *J Am Coll Cardiol* 1984;3:63-70.
34. Kunkel B, Lapp G, Kober G, et al. Light microscopic evaluation of myocardial biopsies. In: Kaltenbach M, Loogen F, Olsen EGJ, eds. *Cardiomyopathy and myocardial biopsy*. Berlin: Springer-Verlag, 1978:62-70.
35. Noda S. Histopathology of endomyocardial biopsies from patients with idiopathic cardiomyopathy; quantitative evaluation based on multivariate statistical analysis. *Jpn Circ J* 1980;44:95-116.
36. Baandrup U, Florio RA, Rehahn M, Richardson PJ, Olsen EGJ. Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy. II. Comparison of histology and clinical/haemodynamic information. *Br Heart J* 1981;45:487-493.
37. O'Connell JB, Robinson JA, Henkin RE, Gunnar RM. Immunosuppressive therapy in patients with congestive cardiomyopathy and myocardial uptake of gallium-67. *Circulation* 1981;64:780-786.
38. Nippoldt TB, Edwards WD, Holmes DR Jr, Reeder GS, Hartzler GO, Smith HC. Right ventricular endomyocardial biopsy: clinicopathologic correlates in 100 consecutive patients. *Mayo Clin Proc* 1982;57:407-418.
39. Fenoglio JJ Jr, Ursell PC, Kellogg CF, Drusin RE, Weiss MB. Diagnosis and classification of myocarditis by endomyocardial biopsy. *N Engl J Med* 1983;308:12-18.

40. Unverferth DV, Fetters JK, Unverferth BJ, Leier CV, Magorien RD, Arn AR, Baker PB. Human myocardial histologic characteristics in congestive heart failure. *Circulation* 1983;68:1194-1200.
41. Bolte HD, Ludwig B. Viral myocarditis: symptomatology, clinical diagnosis, and hemodynamics. In: Bolte H-D, ed. *Viral heart disease*. Berlin: Springer-Verlag, 1984:177-187.
42. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, Moon TE, the Myocarditis Treatment Trial Investigators. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med* 1995;333:269-275.
43. Grogan M, Redfield MM, Bailey KR, Reeder GS, Gersh BJ, Edwards WD, Rodeheffer RJ. Long-term outcome of patients with biopsy-proved myocarditis: comparison with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1995;26:80-84.
44. Chow LC, Dittrich HC, Shabetai R. Endomyocardial biopsy in patients with unexplained congestive heart failure. *Ann Intern Med* 1988;109:535-539.
45. Smith WG. Coxsackie B myopericarditis in adults. *Am Heart J* 1970;80:34-46.
46. Sainani GS, Krompotic E, Slodki SJ. Adult heart disease due to the Coxsackie virus B infection. *Medicine (Baltimore)* 1968;47:133-147.
47. Gardiner AJ, Short D. Four faces of acute myopericarditis. *Br Heart J* 1973;35:433-442.
48. Lauer B, Niederau C, Kühl U, Schannwell M, Pauschinger M, Strauer B-E, Schultheiss H-P. Cardiac troponin T in patients with clinically suspected myocarditis. *J Am Coll Cardiol* 1997;30:1354-1359.
49. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis: experimental and clinical correlates. *Circulation* 1997;95:163-168.
50. Narula J, Khaw BA, Dec GW, Palacios IF, Newell JB, Southern JF, Fallon JT, Strauss HW, Haber E, Yasuda T. Diagnostic accuracy of antimyosin scintigraphy in suspected myocarditis. *J Nucl Cardiol* 1996;3:371-381.
51. McCarthy RE III, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK, Hare JM, Baughman KL. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med* 2000;342:690-695.
52. Kesler KA, Pruitt AL, Turrentine MW, Heimansohn DA, Brown JW. Temporary left-sided mechanical cardiac support during acute myocarditis. *J Heart Lung Transplant* 1994;13:268-270.
53. Jett GK, Miller A, Savino D, Gonwa T. Reversal of acute fulminant lymphocytic myocarditis with combined technology of OKT3 monoclonal antibody and mechanical circulatory support. *J Heart Lung Transplant* 1992;11:733-738.
54. Rockman HA, Adamson RM, Dembitsky WP, Bonar JW, Jaski BE. Acute fulminant myocarditis: long-term follow-up after circulatory support with left ventricular assist device. *Am Heart J* 1991;121:922-926.
55. Dec GW Jr, Fallon JT, Southern JF, Palacios IF. Relation between histological findings on early repeat right ventricular biopsy and ventricular function in patients with myocarditis. *Br Heart J* 1988;60:332-337.
56. Jones SR, Herskowitz A, Hutchins GM, Baughman KL. Effects of immunosuppressive therapy in biopsy-proved myocarditis and borderline myocarditis on left ventricular function. *Am J Cardiol* 1991;68:370-376.
57. Saffitz JE, Schwartz DJ, Southworth W, Murphree S, Rodriguez ER, Ferrans VJ, Roberts WC. Coxsackie viral myocarditis causing transmural right and left ventricular infarction without coronary narrowing. *Am J Cardiol* 1983;52:644, 646-647.
58. Miklozek CL, Crumpacker CS, Royal HD, Come PC, Sullivan JL, Abelmann WH. Myocarditis presenting as acute myocardial infarction. *Am Heart J* 1988;115:768-776.
59. Costanzo-Nordin MR, O'Connell JB, Subramanian R, Robinson JA, Scanlon PJ. Myocarditis confirmed by biopsy presenting as acute myocardial infarction. *Br Heart J* 1985;53:25-29.

Myocarditis: From Bench to Bedside

60. Desai'Neto A, Bullington JD, Bullington RH, Desser KB, Benchimol A. Coxsackie B5 heart disease. Demonstration of inferolateral wall myocardial necrosis. *Am J Med* 1980;68:295-298.
61. Narula J, Southern JF, Abraham S, Pieri P, Khaw BA. Myocarditis simulating myocardial infarction. *J Nucl Med* 1991;32:312-318.
62. Dec GW Jr, Waldman H, Southern J, Fallon JT, Hutter AM Jr, Palacios I. Viral myocarditis mimicking acute myocardial infarction. *J Am Coll Cardiol* 1992;20:85-89.
63. Cooper LT Jr, Berry GJ, Shabetai R, Multicenter Giant Cell Myocarditis Study Group Investigators. Idiopathic giant-cell myocarditis—natural history and treatment. *N Engl J Med* 1997;336:1860-1866.
64. Davidoff R, Palacios I, Southern J, Fallon JT, Newell J, Dec GW. Giant cell versus lymphocytic myocarditis. A comparison of their clinical features and long-term outcomes. *Circulation* 1991;83:953-961.
65. Drory Y, Turetz Y, Hiss Y, Lev B, Fisman EZ, Pines A, Kramer MR. Sudden unexpected death in persons less than 40 years of age. *Am J Cardiol* 1991;68:1388-1392.
66. Wesslen L, Pahlson C, Lindquist O, Hjelm E, Gnarpe J, Larsson E, Baandrup U, Eriksson L, Fohlman J, Engstrand L, Linglof T, Nystrom-Rosander C, Gnarpe H, Magnus L, Rolf C, Friman G. An increase in sudden unexpected cardiac deaths among young Swedish orienteers during 1979-1992. *Eur Heart J* 1996;17:902-910.
67. Vignola PA, Aonuma K, Swaye PS, Rozanski JJ, Blankstein RL, Benson J, Gosselin AJ, Lister JW. Lymphocytic myocarditis presenting as unexplained ventricular arrhythmias: diagnosis with endomyocardial biopsy and response to immunosuppression. *J Am Coll Cardiol* 1984;4:812-819.
68. Sugrue DD, Holmes DR Jr, Gersh BJ, Edwards WD, McLaran CJ, Wood DL, Osborn MJ, Hammill SC. Cardiac histologic findings in patients with life-threatening ventricular arrhythmias of unknown origin. *J Am Coll Cardiol* 1984;4:952-957.
69. Strain JE, Grose RM, Factor SM, Fisher JD. Results of endomyocardial biopsy in patients with spontaneous ventricular tachycardia but without apparent structural heart disease. *Circulation* 1983;68:1171-1181.
70. Friedman RA, Kearney DL, Moak JP, Fenrich AL, Perry JC. Persistence of ventricular arrhythmia after resolution of occult myocarditis in children and young adults. *J Am Coll Cardiol* 1994;24:780-783.
71. Sekiguchi M, Yazaki Y, Isobe M, Hiroe M. Cardiac sarcoidosis: diagnostic, prognostic, and therapeutic considerations. *Cardiovasc Drugs Ther* 1996;10:495-510.
72. Fleming HA, Bailey SM. Sarcoid heart disease. *J R Coll Physicians Lond* 1981;15:245-253.
73. O'Connell JB, Henkin RE, Robinson JA, Subramanian R, Scanlon PJ, Gunnar RM. Gallium-67 imaging in patients with dilated cardiomyopathy and biopsy-proven myocarditis. *Circulation* 1984;70:58-62.
74. Khaw BA, Beller GA, Haber E, Smith TW. Localization of cardiac myosin-specific antibody in myocardial infarction. *J Clin Invest* 1976;58:439-446.
75. Dec GW, Palacios I, Yasuda T, Fallon JT, Khaw BA, Strauss HW, Haber E. Antimyosin antibody cardiac imaging: its role in the diagnosis of myocarditis. *J Am Coll Cardiol* 1990;16:97-104.
76. Dec GW, Narula J. Antimyosin imaging for noninvasive recognition of myocarditis. *Q J Nucl Med* 1997;41 Suppl 1:128-139.
77. Casans I, Villar A, Almenar V, Blanes A. Lyme myocarditis diagnosed by indium-111-antimyosin antibody scintigraphy. *Eur J Nucl Med* 1989;15:330-331.
78. Ballester M, Obrador D, Carrió I, Moya C, Augè JM, Bordes R, Martí V, Bosch I, Bernà-Roqueta L, Estorch M, Pons-Lladó G, Cámara ML, Padró JM, Arís A, Caralps-Riera JM. Early postoperative reduction of monoclonal antimyosin antibody uptake is associated with absent rejection-related complications after heart transplantation. *Circulation* 1992;85:61-68.

79. Carrio I, Lopez-Pousa A, Estorch M, Duncker D, Berna L, Torres G, de Andres L. Detection of doxorubicin cardiotoxicity in patients with sarcomas by indium-111-antimyosin monoclonal antibody studies. *J Nucl Med* 1993;34:1503-1507.
80. Ballester M, Marti V, Carrio I, Obrador D, Moya C, Pons-Llado G, Berna L, Lamich R, Aymat MR, Barbanj M, Guardia J, Carreras F, Udina C, Auge JM, Marrugat J, Permanyer G, Caralps-Riera JM. Spectrum of alcohol-induced myocardial damage detected by indium-111-labeled monoclonal antimyosin antibodies. *J Am Coll Cardiol* 1997;29:160-167.
81. Chandraratna PA, Bradley WG, Kortman KE, Minagoe S, Delvicario M, Rahimtoola SH. Detection of acute myocarditis using nuclear magnetic resonance imaging. *Am J Med* 1987;83:1144-1146.
82. Gagliardi MG, Bevilacqua M, Di Renzi P, Picardo S, Passariello R, Marcelletti C. Usefulness of magnetic resonance imaging for diagnosis of acute myocarditis in infants and children, and comparison with endomyocardial biopsy. *Am J Cardiol* 1991;68:1089-1091.
83. Leiback E, Hardouin I, Meyer R, Bellach J, Hetzer R. Clinical value of echocardiographic tissue characterization in the diagnosis of myocarditis. *Eur Heart J* 1996;17:135-142.
84. Friedrich MG, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. *Circulation* 1998;97:1802-1809.
85. Mimbs JW, O'Donnell M, Miller JG, Sobel BE. Detection of cardiomyopathic changes induced by doxorubicin based on quantitative analysis of ultrasonic backscatter. *Am J Cardiol* 1981;47:1056-1060.
86. Perez JE, Barzilai B, Madaras EI, Glueck RM, Saffitz JE, Johnston P, Miller JG, Sobel BE. Applicability of ultrasonic tissue characterization for longitudinal assessment and differentiation of calcification and fibrosis in cardiomyopathy. *J Am Coll Cardiol* 1984;4:88-95.