Viral Myocarditis Mimicking Acute Myocardial Infarction

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Anecdotal reports have shown that myocarditis can mimic acute myocardial infarction with chest pain, electrocardiographic (ECG) abnormalities, serum creatine kinase elevation and hemodynamic instability. Thirty-four patients with clinical signs and symptoms consistent with acute myocardial infarction underwent right ventricular endomyocardial biopsy during a 6.5-year period after angiographic identification of normal coronary anatomy. Myocarditis was found on histologic study in 11 of these 34 patients. Cardiogenic shock requiring intraaortic balloon support developed within 6 h of admission in three (27%) of the patients with myocarditis.

The mean age of the group with myocarditis was 42 ± 5 years. A preceding viral illness had been present in six patients (54%). The ECG abnormalities were varied and included ST segment elevation (n = 6), T wave inversions (n = 3), ST segment depression (n = 2) and pathologic Q waves (n = 2). The ECG abnormalities were typically seen in the anterior precordial leads but were diffusely evident in three patients. Left ventricular function was normal in six patients and globally decreased in the remaining five patients, whose ejection fraction ranged from 14% to 45%. Lymphocytic myocarditis was diagnosed in 10 patients, and giant cell myocarditis was detected in the remaining patient. Four patients with impaired left ventricular function received immunosuppressive therapy with prednisone and either azathioprine (n = 2) or cyclosporine (n = 2).

All six patients whose left ventricular function was normal on admission remain alive in functional class I. Of the five patients with impaired systolic function, ejection fraction normalized in three of the four patients who received immunosuppressive therapy within 3 months of treatment and in the one patient who received only supportive therapy. All patients who required intraaortic balloon pump support survived to discharge. One death, due to progressive heart failure, occurred at 18 months in the patient with giant cell myocarditis.

Myocarditis should be clinically suspected in patients with an ischemic chest pain syndrome, particularly when ECG abnormalities are present beyond a single vascular distribution, segmental wall motion abnormalities are lacking or global left ventricular hypokinesis is present on ventriculography. The subsequent demonstration of normal coronary anatomy should prompt consideration of right ventricular endomyocardial biopsy, because those patients with myocarditis have an excellent long-term prognosis and do not require anti-ischemic therapy.

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The clinical spectrum of acute viral myocarditis ranges from asymptomatic electrocardiographic (ECG) abnormalities reported during community outbreaks of Coxsackie B virus infection to fulminant heart failure, cardiogenic shock and death. A subset of patients may have chest pain and ECG findings suggestive of acute myocardial infarction (1). Myocarditis may mimic myocardial infarction in that it is typically focal or multifocal in distribution on histologic study, segmental wall motion abnormalities may be present and associated myocyte necrosis often leads to elevation of serum creatine kinase (2,3). Furthermore, the myocyte injury and necrosis associated with inflammation seen in myocarditis may produce repolarization changes as well as temporary or permanent abnormal Q waves (4,5). Several case reports (4,5) have described myocarditis presenting as acute myocardial infarction; however, the frequency of this presentation, its clinical and ECG features and subsequent outcome have not been reported.

Methods

Study patients. The pathologic and medical records of all patients who underwent diagnostic right ventricular endomyocardial biopsy at the Massachusetts General Hospital between January 1, 1984 and June 30, 1990 were retrospectively reviewed in accordance with the hospital's Subcommittee on Human Studies guidelines. During this time, 1,149 nontransplant patients underwent biopsy; most (95%) had unexplained dilated cardiomyopathy, heart failure symptoms and clinically suspected myocarditis. Myocarditis was histologically diagnosed in 50 (4%) of these 1,149 patients.

Thirty-four patients who presented with clinically sus-

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pected acute myocardial infarction, based on the presence of both typical ischemic chest pain and ischemic ECG abnormalities, and who subsequently underwent endomyocardial biopsy when normal coronary anatomy was angiographically established, were identified from the total group of patients who underwent biopsy. Myocarditis was detected in 11 of these 34 patients; the remaining 23 had either normal myocardium or nonspecific findings (myocyte hypertrophy or interstitial fibrosis). Ischemic injury was not detected in any of the biopsy specimens. The study group consisted of the 11 patients with myocarditis whose clinical presentation suggested acute myocardial infarction. The group contained 6 men and 5 women with a mean age of 42 ± 5 years.

Technique of transvenous endomyocardial biopsy and pathologic examination. Right heart catheterization was performed in all patients with use of a triple-lumen thermodilution catheter. At the conclusion of the procedure, right ventricular biopsy was performed with standard techniques (6). Multiple biopsy specimens (usually four to six, each measuring 2 to 3 mm in diameter) were obtained from the right ventricular septum with either a Caves-Shultz-Stanford or Cordis Bipal bioptome and were immediately fixed by immersion into buffered 10% formalin (6). All specimens were embedded in paraffin. Five-micron thick histologic sections were stained with hematoxylin-eosin and Masson trichrome stains, as previously described (6). For this study, all slides were reviewed without knowledge of the patient's clinical findings or the official pathologic diagnosis. Myocarditis was diagnosed according to the Dallas criteria (7) whenever an inflammatory cellular infiltrate was seen in association with either necrotic or degenerating myocytes.

Clinical and ventriculographic assessment. The medical records of all 11 patients with myocarditis were carefully reviewed. Each patient's clinical presentation, duration of illness, ECG findings, coronary anatomy, location and extent of left ventricular wall motion abnormalities and coronary risk factors were determined. The initial ejection fraction was determined by contrast ventriculography. Segmental wall motion abnormalities were also evaluated serially by either two-dimensional echocardiographic studies or multiple gated blood pool radioventriculography. Clinical outcome was established from a review of medical records and by a telephone survey with all surviving patients.

Immunosuppressive therapy. Four of the 11 patients in the myocarditis study received immunosuppressive therapy; all had impaired left ventricular function at initial presentation. Two received combination therapy with azathioprine and prednisone for 6 months in accordance with institutional protocol. Azathioprine was administered at a dose of 2 mg/kg body weight per day, and the dosage was decreased if leukopenia (white blood cell count <5,000) mm^3 developed. Prednisone was administered at 1 to 1.5 mg/kg per day in divided doses and tapered to 0.3 mg/kg per day by week 12. The drug was gradually withdrawn during the final 4 weeks. Two patients received prednisone and cyclosporine therapy as part of the Multicenter Myocarditis Treatment Trial. Cyclosporine was administered in an initial dosage of 10 mg/kg per day in divided doses. The dosage was then adjusted to maintain a trough level by radioimmunoassay of approximately 50 ng/ml.

Results

Clinical features. The clinical, ECG, enzymatic and histologic features of each of the 11 patients with myocarditis who presented with suspected myocardial infarction are summarized in Table 1. All patients underwent coronary arteriography either at the time of admission, because of ongoing chest pain and ECG changes, or before hospital discharge. Coronary anatomy was normal in 10 patients; 1 patient (Case 4) had a 30% stenosis of the mid-right coronary artery. No patient had received thrombolytic therapy. Results of ergonovine provocative testing were normal in the six persons in whom it was undertaken. The risk factors for myocardial ischemia or infarction at a young age included a history of smoking (n = 4), a positive family history (n = 4) and hyperlipidemia (n = 1); no risk factors were present in five patients. No patient admitted to the use of cocaine before the development of chest pain.

Clinical features at presentation included typical anginal chest pain of <12 h duration in all 11 patients. A preceding viral illness, typically upper respiratory in nature, was identified in six patients (54%). Leukocytosis was present in five patients (45%), and a pericardial friction rub was noted in three. All three patients with pericarditis also had typical anginal pain in addition to pleuritic pain on admission. Each had localized ischemic ECG abnormalities (ST segment depression in two patients) or pathologic Q waves (one patient), suggesting infarction rather than pericarditis as the primary diagnosis. Cardiogenic shock requiring temporary intraaortic balloon support developed within 6 h of admission in three patients, two of whom also had pericarditis.

Electrocardiographic, enzymatic and ventriculographic findings. The ECG findings on admission (Table 1) were varied and included ST segment elevation in two or more contiguous leads (n = 6), T wave inversions (n = 3) and ischemic ST segment depression (n = 2). Pathologic Q waves were evident in two patients at presentation (Fig. 1). The ECG changes were seen diffusely (n = 3), anteriorly (n = 7) or inferiorly (n = 1). No PR depression was seen in the three patients with pericarditis, nor was diffuse ST segment elevation noted. Ventricular tachycardia was evident on the initial ECG in two patients, and a new right bundle branch block pattern was observed in three. The ECG abnormalities did not evolve during the hospital period and returned to normal in seven patients between 2 and 23 months after discharge; two patients had a persistent right bundle branch block and anterior T wave inversions were persistent in the remaining two.

The peak creatine kinase (CK) elevation was modest, averaging only 405 ± 132 (normal <85). An elevation in total CK was detected in eight patients, and the CK MB isoen-

Table 1. Summary of Clinical Findings in 11 Patients

Pt No.	Age (yr)/ Gender	ECG Findings	Peak CK	LV Function	Myocarditis Histology	Long-Term Outcome	
						NYHA Class	Follow-Up (mo)
1	24/M	ST↑ $V_3 \rightarrow V_6$; TWI $V_4 \rightarrow V_6$, II,III, aVF; RBBB	532	Normal (LVEF 70%)	Lymphocytic	I	44.5
2	56/F	ST↑ II,III, aVF; TWI $V_3 \rightarrow V_6$	719	Normal (LVEF 72%)	Lymphocytic	I	21
3	27/M	ST↑ $V_2 \rightarrow V_6$; VT, RBBB	80	Global hypokinesia (LVEF 14%)	Giant cell	Died (CHF)	18
4	44/M	TWI I, aVL, $V_3 \rightarrow V_6$, II,III, aVF	269	Global hypokinesia (LVEF 43%)	Lymphocytic	I	77
5	53/F	ST↑ $V_2 \rightarrow V_4$; TWI I, aVL, $V_1 \rightarrow V_6$	81	RV hypokinesia (LVEF 70%)	Lymphocytic	I	27.5
6	62/M	ST↑ I, aVL, $V_3 \rightarrow V_6$	30	Normal (LVEF 65%)	Lymphocytic	I	5
7	25/M	TWI II,III aVF, $V_3 \rightarrow V_6$	256	Normal (LVEF 61%)	Lymphocytic	I	24
8	31/M	ST↑ I, aVL, $V_1 \rightarrow V_6$	1,518	Normal (LVEF 48%)	Lymphocytic	II	12
9	35/F	ST↓ I, aVL, $V_2 \rightarrow V_6$	248	Posteroseptal hypokinesia (LVEF <45%)	Lymphocytic	III	48
10	31/M	ST↑ $V_1 \rightarrow V_6$; RBBB	627	Mild global hypokinesia (LVEF 40%)	Lymphocytic	I	14
11	70/F	TWI II,III, aVF, $V_1 \rightarrow V_6$; VT	100	Global hypokinesia (LVEF 46%)	Lymphocytic	I	14

CHF = congestive heart failure; CK = creatine kinase; ECG = electrocardiographic; F = female; LV = left ventricular; LVEF = left ventricular ejection fraction; M = male; NYHA = New York Heart Association; Pt = patient; RBBB = right bundle branch block; RV = right ventricular; ST↓ = ST segment depression; ST↑ = ST segment elevation; TWI = T wave inversion; VT = ventricular tachycardia.

zyme fraction was >6% in all eight. The rise and fall in serum enzymes followed the typical pattern for acute infarction in all patients.

Assessment of left ventricular size and function at rest by either left ventriculography or gated blood pool imaging revealed normal systolic function in six patients, two of whom had mild left ventricular dilation despite preserved systolic function. A global decrease in left ventricular contractility at rest was seen in five patients whose ejection fractions ranged from 14% to 45%. Discordance was frequently noted between ECG findings and ventriculographic wall motion abnormalities. Despite ECG changes that were localized in eight patients and suggested either anterior or inferior myocardial ischemia or infarction, impaired *segmental* left ventricular wall motion was detected in only one person. The only death in this series occurred in this patient, who died 18 months after the onset of symptoms. The remaining 10 patients had either global hypokinesia or normal systolic function despite localized ECG findings. Right ventricular dilation and dysfunction were evident in 3 of the 11 patients.

Histology, treatment and outcome. Lymphocytic myocarditis was diagnosed in 10 patients; the inflammatory infiltrate was diffuse in 2 patients and focal or multifocal in the remaining 8. One patient presented with diffuse giant cell myocarditis, anterior ECG changes and cardiogenic shock.

The prognosis for this presentation of myocarditis was generally excellent; 10 of the 11 patients were alive at a mean follow-up interval of 28 ± 6 months (range 5 to 77). All six patients whose initial left ventricular function was normal remain alive and are in New York Heart Association functional class I. Of the five patients with impaired systolic function on admission, ejection fraction normalized in three and improved in one; one patient died. Left ventricular function normalized within 3 months in three of the four patients treated with prednisone and either azathioprine or cyclosporine immunosuppression. All three patients who required temporary intraaortic balloon support for cardiogenic shock survived and were discharged. One of the three patients demonstrated rapid normalization of systolic function; one remains alive with mild impairment of left ventricular function and the third, who had giant cell myocarditis, died of progressive heart failure after 18 months.

Discussion

Clinical features. The clinical features that suggested myocarditis in these patients included the young age at presentation (six patients were <35 years old), the paucity of conventional risk factors for accelerated atherosclerosis and the presence of normal coronary anatomy despite clinical signs, symptoms and ECG findings that were highly suggestive of acute myocardial ischemia or infarction. These clinical features are similar to those recently reported by Paillard et al. (8) in a series of patients with suspected myocarditis not verified by biopsy. Several important differences were evident in our study group and included a greater prevalence of anterior ECG findings, a lower degree of CK elevation,

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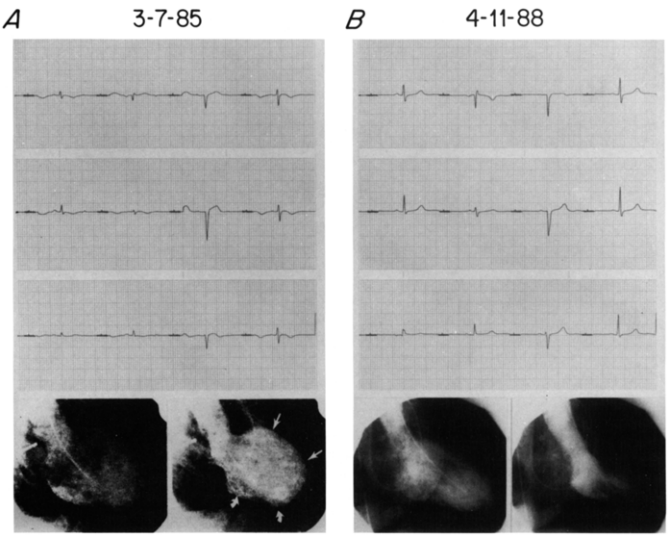

Figure 1. **A,** Admission electrocardiogram (ECG) and left anterior oblique ventriculogram of a patient with histologically verified myocarditis. The ECG shows Q waves in leads V_1 and V_2 with diffuse T wave inversions. A comparison of end-diastolic (**bottom left**) and end-systolic frames (**bottom right**) of the left anterior oblique ventriculogram illustrates anteroapical and lateral akinesia (**top arrows**), marked inferior hypokinesia (**bottom arrows**) and an overall left ventricular ejection fraction (LVEF) of 34%. (B), At the time of repeat evaluation 3 years later, the ECG demonstrates improvement in R wave development and resolution of the repolarization abnormalities. A comparison of end-diastolic (**bottom left**) and end-systolic (**bottom right**) frames of the left anterior oblique ventriculogram demonstrates normal contractile function and a left ventricular ejection fraction of 62%. Repeat right ventricular biopsy (RV Bx) revealed healed myocarditis after a short course of prednisone and azathioprine.

fewer segmental wall motion abnormalities and a lower incidence of temporary bundle branch block. Despite the localized ECG abnormalities and the focal appearance of the myocardial inflammatory process, segmental wall motion abnormalities were rare in this series. When present, depression of left ventricular function was typically global in nature; normal systolic function was the more common finding.

Acute myocardial infarction and normal coronary arteries. Myocardial infarction at <40 years of age has received much attention over the past decade and remains a relatively uncommon occurrence. Although coronary atherosclerosis accounts for the majority of such cases, a significant number of younger patients have nonatherosclerotic causes, including coronary artery anomalies, coronary embolism (septic or bland), cocaine usage and coronary vasculitis (9,10). The incidence of normal coronary arteries in all patients who present with acute myocardial infarction has been estimated to be <3%. This figure rises dramatically to 17% to 20% when only patients <35 years old are considered (9,11,12). Conventional coronary risk factors are distinctly less common and coronary vasospasm may be a more likely precipitating cause of infarction in this age group (12). A limited number of case reports (1,13) have linked myocarditis and myocardial infarction in patients with normal coronary arteries, but this association has almost always relied entirely on a clinical diagnosis of myocarditis, an assumption that has frequently been shown to be inaccurate. This series is the first to use right ventricular endomyocardial biopsy in a sizable number of patients (n = 34) with suspected myocardial infarction and angiographically normal coronary arteries. Histologically verified myocarditis was detected in an unexpectedly high proportion of this group. Although the

majority of patients were <40 years old, myocarditis presenting as acute myocardial infarction may also occur in older persons. Four patients were >50 years old at presentation.

Role of thrombolytic therapy. Although no patient in the present study received thrombolytic therapy, it can be expected that in the future the majority of patients with signs and symptoms that are highly suggestive of acute myocardial infarction will be treated with such agents. Myocarditis should be strongly considered in the differential diagnosis in those patients whose echocardiographic abnormalities and symptoms fail to resolve after thrombolytic therapy and who subsequently are found to have normal coronary anatomy on coronary angiography. This group will certainly represent only a tiny minority of patients admitted with suspected infarction.

Prognosis. Acute myocarditis that mimics acute myocardial infarction is associated with an excellent long-term prognosis. The ECG abnormalities, including pathologic Q waves, typically resolve during the 1st year, and impairment in left ventricular function may also demonstrate a reversible component. Even the presence of cardiogenic shock requiring hemodynamic support may demonstrate rapid recovery of ventricular function. A recent study (14) of patients whose systolic function normalizes after acute dilated cardiomyopathy secondary to myocarditis has shown normal exercise performance and unimpaired diastolic function.

Limitations of the study. Although this series is the largest yet reported of patients with ischemic symptoms and normal coronary anatomy to undergo right ventricular biopsy, the sample size is small and the true incidence of myocarditis detected by biopsy remains uncertain. Although the majority of our patients with normal coronary arteries did undergo biopsy during this time, the decision to undertake a biopsy in the presence of normal coronary arteries and suspected infarction was left to the referring physician. It is possible that patients with more severe disease, as manifested by widespread ECG changes, impaired left ventricular function or clinical instability, may have been preferentially selected to undergo diagnostic biopsy. Although myocarditis was detected histologically, associated coronary vasospasm or thrombosis with spontaneous lysis may have also occurred in a subgroup of these patients.

Conclusions. These findings document that myocarditis can mimic acute myocardial infarction but do not define the frequency of this uncommon presentation. This diagnosis should be sought in persons who present with an ischemic chest pain syndrome despite minimal coronary risk factors, particularly when ischemia or infarction is seen beyond a single vascular distribution on the admission ECG. Additional supportive evidence for myocarditis rather than acute infarction frequently includes the absence of segmental wall motion abnormalities or the presence of global left ventricular hypokinesia on echocardiography, suggestive of a primarily myopathic process. Frequently, patients who have widespread ischemic ECG changes undergo cardiac catheterization. The finding of normal coronary arteries should suggest the diagnosis of myocarditis and prompt consideration of right ventricular biopsy. Such patients generally have an excellent long-term prognosis, may demonstrate rapid resolution of abnormal ventricular function and do not require anti-ischemic medical therapy.

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