

Acute Onset of Cardiogenic Shock Associated with Normal Coronary Arteries, Diffuse Myocardial Necrosis, and Rapid Clinical Recovery

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A 75-yr-old white female, with no previous history of coronary artery disease, presented with severe retrosternal chest pain of 10 hr duration. She was brought to the emergency room where a diagnosis of an acute anterior myocardial infarction was made and thrombolytic therapy was initiated.

CLINICAL HISTORY

The patient had a history of a congenital heart murmur and rheumatic fever as a child. In 1973, a diagnosis of bipolar affective disorder was made and lithium therapy was initiated. About 7 yr later, she developed hypothyroidism which was treated with replacement therapy. The patient had a 53-pack year history of cigarette smoking, however, she denied history of diabetes mellitus, hypertension, coronary artery disease, elevated cholesterol or family history of cardiac disease.

Two days prior to the onset of symptoms she flew from California to Boston for a wedding. The day before admission she noted general weakness and mild to moderate shortness of breath. At midnight, the dyspnea became severe and she experienced the onset of a left inframammary discomfort radiating to the chest and associated with nausea and dizziness. The patient stayed at home for the following 10 hr with the hope that her symptoms would improve. Due to the persistence of her symptoms, she finally sought medical advice. Upon arrival to the emer-

gency room, at 10:00 a.m., the physical examination revealed an acutely distressed, pale elderly woman with a blood pressure of 131/82 mmHg, a regular heart rate at 115 bpm and a mild fever of 100°F. The pulmonary auscultation demonstrated bibasilar rales. The cardiac examination was remarkable only for a S4 gallop and a systolic murmur grade II/VI. The admission electrocardiogram (EKG) showed a sinus rhythm with a ventricular rate of 109, a left anterior hemiblock, left atrial enlargement and ST-segment elevations of 2.0–2.5 mm in V2 through V6 (Fig. 1). Her initial plain chest radiograph (Fig. 2A) revealed an elevated right hemidiaphragm with bibasilar subsegmental atelectasis. The heart size and pulmonary vessels were normal. The hematologic work up showed a leukocytosis of 17,200 WBC/mm³ with 77% polymorphonuclears and 11% lymphocytes. The hematocrit was 40.4% and the erythrocyte sedimentation rate was 24 mm/hr. The platelet count, the prothrombin time and the partial thromboplastin time were normal. Urinalysis was slightly positive for occult blood with 5–10 RBCs by high power field probably related to an urinary catheter placement. Blood chemistry revealed hypokalemia of 3.2 mmol/liter, hypomagnesemia of 1.4 mEq/liter, SGOT of 90 U/liter, LDH of 293 U/liter and CPK of 279 U/liter with a MB isoenzyme fraction of 11.6%. The remainder of the laboratory work up was within normal limits. The patient was admitted with a diagnosis of an acute anterior myocardial infarction and at 11:20 a.m. she was treated with intravenous streptokinase. Upon admission to the Coronary Care Unit, the patient was started on heparin, 1000 u/hr (intravenous infusion), enteric-coated aspirin, 1 tablet p.o. daily, metoprolol, 100 mg p.o. b.i.d., levothyroxine, 0.1 mg p.o. daily, lithium, 300 mg p.o. daily and intravenous nitroglycerin, which was titrated as needed. She also received two doses of 40 mg of furosemide as an intravenous bolus injection and 5 mg of intravenous metoprolol.

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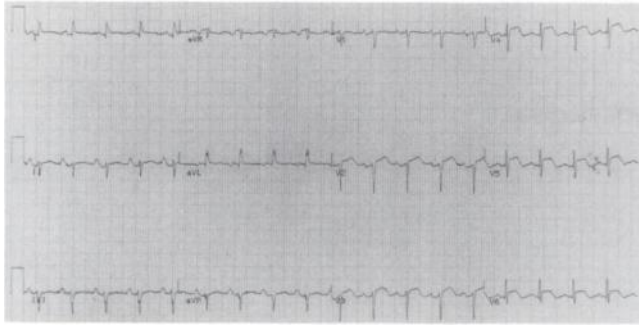


FIGURE 1. Initial electrocardiogram shows a left anterior hemiblock, ST elevations in V2 through V6 and left atrial enlargement.

Within 6 hr of admission, the patient was free of pain, however, the physical examination showed evidence of congestive heart failure with rales in the lower one-third of the chest and jugular venous distention of 6 cm at 45°. There were a brisk carotid pulse, increased intensity of S2, a S4 gallop and a mid-systolic click followed by a systolic murmur grade III/VI at the left sternal border and apex. The murmur increased upon standing. No S3 gallop was audible. At this time, the radiographic chest evaluation (Fig. 2B) revealed moderate bilateral pleural effusions, mild enlargement of the cardiac silhouette and increased pulmonary vascular pattern. A pulmonary artery line was placed at 8:30 p.m. without any event.

Early the next morning (2:00 a.m.), the patient became hypotensive (SBP = 95 mmHg, HR = 110 bpm) with no evidence of left-to-right shunt as assessed by central venous pressure line, pulmonary artery and right atrium blood gas analysis. The second and third sets of cardiac enzymes, performed every 8 hr, showed a decline in the CPK value. Her EKG evolved to poor R-wave progression and persistent 1–2 mm ST-segment elevation in leads V1 through V3. The right heart hemodynamic evaluation revealed a central venous pressure of 13 mmHg, a pulmonary artery pressure of 45/16 mmHg, a pulmonary capillary wedge pressure of 20 mmHg and a cardiac index of 1.7 liters/min/m². An emergency coronary arteriogram was performed to investigate the possibility of potentially treatable lesions. No significant coronary artery narrowings were seen. The left ventriculogram showed akinesis of the anterolateral and apical segments with diffusely depressed global left ventricular function. An echocardiogram excluded the possibility of cardiac tamponade. At this point, the data indicated cardiogenic shock in the setting of normal coronary arteries, without any other specific identifiable causes. The patient was on a combination therapy consisting of an intra-aortic balloon counterpulsation, dobutamine, 700 µg/min (9.7 µg/kg/min), dopamine, 200 µg/min (2.7 µg/kg/min) and intravenous norepinephrine, 14 µg/min. These were slowly weaned off over the next two days.

Findings of patent coronary arteries and the fact that her left ventricular function was suppressed out of propor-

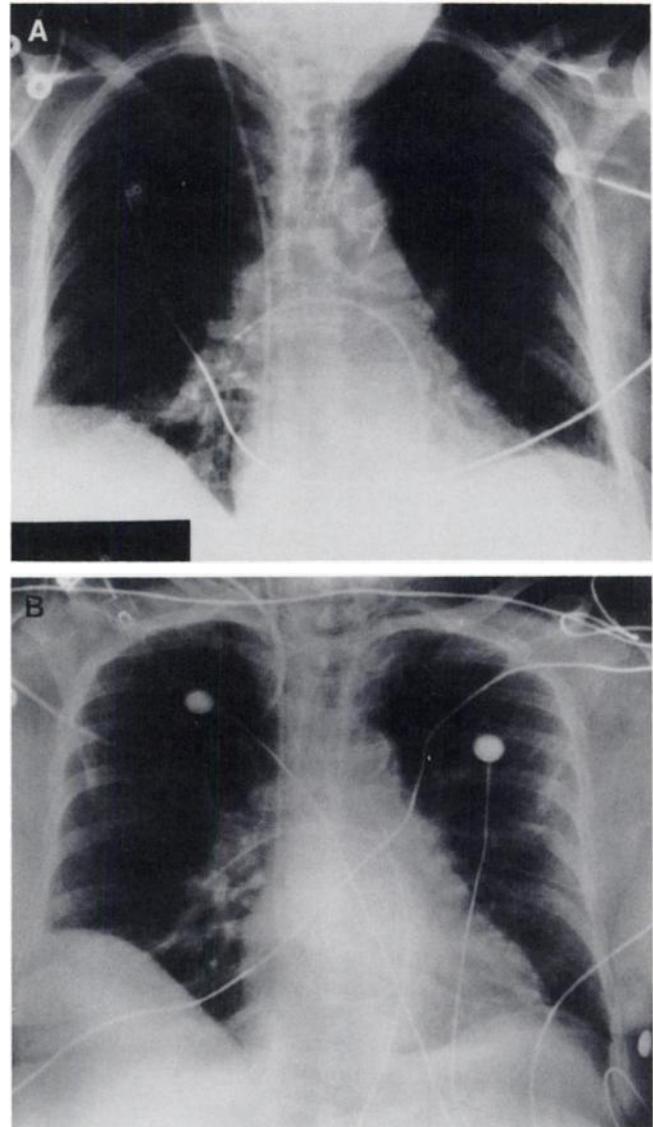


FIGURE 2. Initial chest radiograph (A) essentially shows normal lungs with right hemidiaphragm elevation. Repeated chest x-ray (B), less than 24 hr later, demonstrates cardiac enlargement, increased pulmonary vascular pattern and bilateral pleural effusions.

tion to the CPK leak resulted in a work-up for myocarditis and cardiomyopathy. A right ventricular endomyocardial biopsy on the sixth hospital day (Fig. 3, see p. 1563) was most consistent with healing ischemic necrosis of the myocardium of about 1-wk-old. One of the six fragments of endomyocardium submitted for histologic evaluation contained several foci of necrotic myocytes surrounded by a mixed inflammatory infiltrate. The immunoperoxidase stains revealed that macrophages predominated in the infiltrate, which also contained scarce T-lymphocytes and absent B-cells. An antimyosin scan (Fig. 4) obtained the same day as the biopsy, 72 hr after the intravenous administration of 67 MBq of ¹¹¹In-antimyosin, revealed diffuse positive uptake, more intense in the apex. This indicated the presence of acute myocyte necrosis. The pattern of

uptake was not consistent with an acute anterior myocardial infarction. The laboratory work-up for myocarditis showed normal values for ANA, Lyme antibody, rapid plasma reagin test, toxoplasma antibody, heterophile antibody, cold agglutinins and LDH I pattern. She also underwent evaluation for a hypercoagulable state, including protein C and protein S determinations, which were normal, and antithrombin III value, which was minimally decreased to 70% (normal range 85%–111%). The patient had positive rheumatoid factor and cytomegalovirus antibody titers. The thyroid function test revealed a low TSH with a normal T4 value consistent with her history of hypothyroidism in hormonal replacement.

The patient was placed on captopril and anticoagulant therapy. She gradually improved and was transferred from the coronary care unit to the regular medical ward in stable clinical condition. A cardiac gated blood-pool scan (Fig. 5) performed on the ninth hospital day showed a hypertrophied left ventricle with a discrete area of apical dyskinesia associated to hypokinesia of the distal anterolateral wall. There was vigorous contraction of the basal portion of the left ventricle with a normal left ventricular ejection fraction of 67%. The cardiac chambers sizes were within normal limits. A second echocardiogram (Fig. 6 A–D) showed mild mitral and tricuspid regurgitation without evidence of myocardial hypertrophy. Apical akinesis with well preserved left ventricular function and an estimated ejection fraction of 60% was demonstrated. Due to the improvement in her left ventricular function, the ACE-inhibitor was discontinued and diltiazem, for the treatment of possible coronary vasospasm, was started.

The patient was discharged to home in stable condition, 12 days after the initial event, on calcium channel blocker therapy and Coumadin. The presumptive diagnosis upon discharge was coronary vasospasm leading to an anterior

myocardial infarction and a discrete apical aneurysm. Her first post-hospitalization follow-up visit, 5 days after discharge, was remarkable for the development of bilateral 3 plus nonpitting edema of the lower extremities. The patient was started on diuretic therapy. After this examination, she returned to California. Approximately 6 wk after discharge, the patient was readmitted to a hospital in California with substernal discomfort and EKG changes consisting of symmetric T-wave inversions in leads I, AVL and V3 through V6, without ST-segment elevations. The total CPK value was 20 U/liter. A diagnosis of post-myocardial infarction pericarditis (Dressler's syndrome) was presumed on the basis of a small pericardial effusion demonstrated by echocardiogram. This examination also revealed apical hypokinesis to akinesis with compensatory hypercontractile septum and a left ventricular ejection fraction of 87%. An exercise test using a modified Bruce protocol was attempted, but the patient stopped at 1.5 min due to severe dyspnea. The test was nondiagnostic. Coumadin was discontinued and upon discharge a regimen of moderate physical exercise and a low cholesterol diet was started. She remained clinically stable on medical therapy consisting of diltiazem SR, 90 mg p.o. b.i.d., and nitrates, without any further intervention.

DISCUSSION

This patient presents a difficult diagnostic dilemma. Her initial presentation was consistent with coronary artery disease that caused an anterior wall myocardial infarction

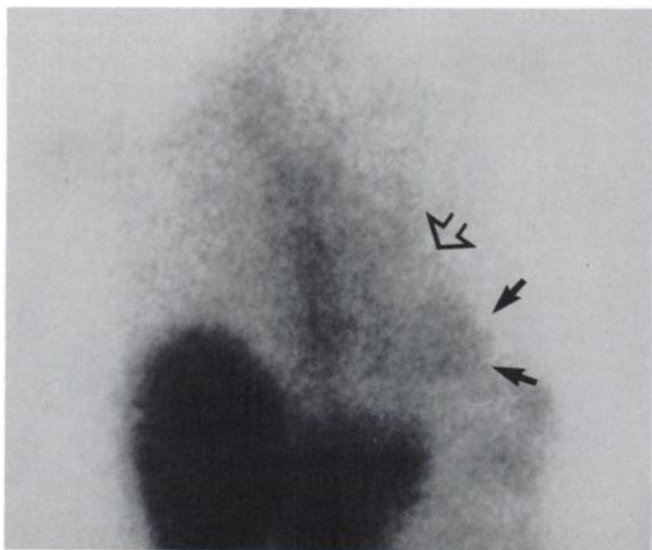


FIGURE 4. Anterior projection of the antimyosin scan showing intense myocardial uptake in the mid to distal left ventricle (two black arrows) and less intense uptake in the base (white arrow).

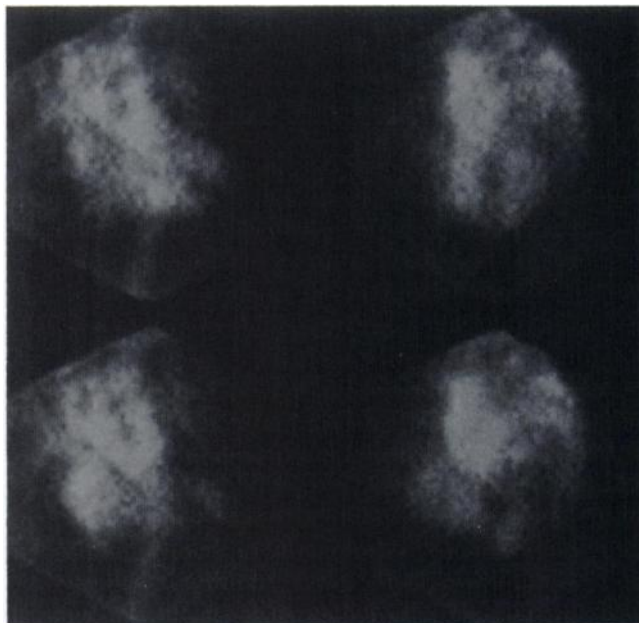


FIGURE 5. Diastolic frames (upper panel) and systolic frames (lower panel) of the gated blood-pool scan. Left pictures show anterior views and the pictures on the right represent LAO 45° views of the heart. The size of the cardiac chambers and the overall left ventricular contraction are within normal limits. There is a suggestion of distal anterolateral wall and apical hypokinesis present.

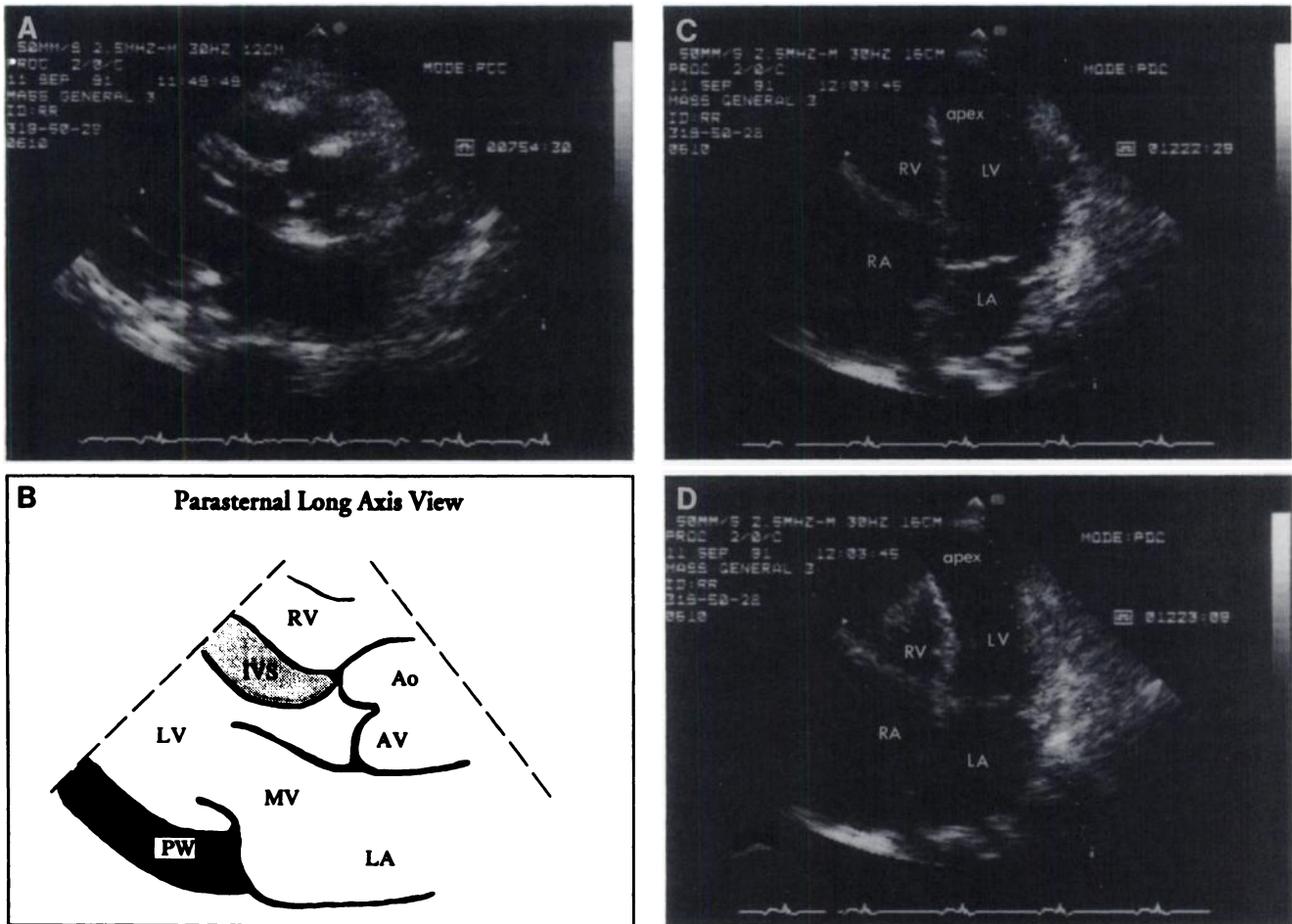


FIGURE 6. End-diastolic parasternal long-axis view (A) and schematic diagram (B) demonstrate normal septal thickness (11 mm). Diastolic (C) and systolic (D) four chamber apical views show apical akinesis with normal basal contraction. The estimated LVEF is 60%. (RV = right ventricle; RA = right atrium; LV = left ventricle; LA = left atrium; IVS = intraventricular septum; Ao = aorta; PW = posterior wall; AV = aortic valve; MV = mitral valve; a segment of the broken line represents approximately 1 cm).

and subsequent cardiogenic shock. Normal coronary angiographic findings and the severe global left ventricular dysfunction were discordant with the magnitude of her cardiac enzyme leak. This necessitated further diagnostic evaluation to elucidate the etiology of her peculiar clinical course. While the right ventricular endomyocardial biopsy was most consistent with ischemic necrosis and failed to demonstrate a significant interstitial inflammatory lymphocytic infiltration, the antimyosin scintigraphic study revealed diffuse left ventricular uptake indicating myocardial necrosis in a pattern not compatible with an acute anterior myocardial infarction. The echocardiographic evaluation showed a normal thickness of the septum and posterior wall without evidence of a left ventricular outflow tract pressure gradient or abnormal systolic anterior movement of the mitral valve, making concentric or asymmetric left ventricular hypertrophy a less likely diagnosis. Although during the first 48 hr of admission the patient was critically ill and in cardiogenic shock, a condition which is fatal in more than 90% of the patients if associated with anterior myocardial infarction (1,2), her recovery was rapid and steady.

It has been estimated that 1%–3% of all myocardial infarctions occur without demonstrable evidence of significant coronary atherosclerosis (3,4). This number can increase up to 17% in younger patients less than 36 yr old (5). In the following discussion, we review the different possible mechanisms for the development of acute myocardial necrosis with cardiogenic shock in the setting of normal coronary arteries.

Acute Coronary Thrombosis and Coronary Vasospasm

Acute coronary thrombus formation with rapid and spontaneous resolution has been implicated in the etiology of myocardial infarction in patients with angiographically normal coronary arteries (6–9). Thrombosis rarely occurs, however, without pre-existing atherosclerotic coronary disease (10). Acute coronary thrombosis often are single and in the majority of the patients are located in the major extramural arteries. The initiation of thrombus formation is usually associated with plaque ulceration, hemorrhage and rupture (11–16). A coronary thrombus is found to be associated with a transmural infarction in 60%–90% of

patients compared to 20%–30% in patients with subendocardial injury. In the setting of cardiogenic shock, the probability of finding a coronary thrombotic event as the cause of acute infarction is three to four times greater than in patients without this postinfarction complication (17–21).

The role of coronary vasospasm in the etiology of acute myocardial infarction is still unclear (15,22). Coronary artery spasm is often encountered in patients with concomitant atherosclerotic heart disease. A patent artery supplying the area of necrosis is found in about 35% of patients studied within 6 mo of transmural infarction (23,24). In those patients, coronary spasm may play an important role in the genesis of ischemia. Nevertheless, resolution of a previously formed thrombus is another consideration that is a more likely explanation. The incidence of coronary spasm related to acute myocardial injury is higher in inferior wall myocardial infarction when compared to anterior infarction and is often demonstrable in the early phase of the ischemic insult (less than 6 hr) (25–27).

Coronary thrombosis and coronary vasospasm are not two independent mechanisms for vessel occlusion in the initiation of an acute myocardial infarction. Although it is possible to have isolated coronary artery spasm leading to myocardial necrosis, spasm is usually associated with thrombosis or atherosclerotic disease (15). Coronary spasm can occur superimposed on a plaque, thus causing infarction without thrombosis. In some patients it can precede the onset of thrombus formation and facilitate platelet aggregation and disruption of an sclerotic plaque. A nonocclusive thrombotic event can also occur first followed by coronary spasm and subsequent occlusion. In all instances, these mechanisms are modulated by the presence of vasoactive substances that may facilitate the triggering of vasospasm or the initiation of platelet aggregation (21,28–31). The exact interaction between acute thrombosis, coronary artery spasm, atherosclerotic plaque, platelet function and endothelial mediators for the initiation of an acute myocardial infarction is a matter for further investigation (15).

The diffuse uptake of antimyosin antibody in our patient suggests that myocyte necrosis appeared to have taken place in the entire heart. This also does fit the clinical feature of severe left ventricular dysfunction. The suddenness of the illness suggests acute thrombosis or spasm. It is difficult to imagine that all three vessels were thrombosed simultaneously. Even when a minimal decrease in the antithrombin III value was documented in this patient, it probably was not clinically significant to postulate a hypercoagulable state with spontaneous thrombus formation. A spasm, however, is possible.

Diagnosis of Myocarditis: Endomyocardial Biopsy and Antimyosin Scan

One of the clinical entities that can resemble acute myocardial infarction with cardiogenic shock is myocar-

ditis (32–34). Patients with myocarditis and normal coronary angiograms can present with left ventricular systolic and diastolic dysfunction, cardiac arrhythmias and symptoms of chest discomfort (35,36). According to the most widely used histologic criteria for myocarditis, the Dallas Criteria (37), the diagnosis requires the presence of an “inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease.” Once detected, the inflammatory infiltrate is further classified in terms of cell type and the amount and distribution of the infiltrate itself and the associated fibrosis if present.

The sensitivity of the endomyocardial biopsy for the diagnosis of myocarditis has been a matter of great controversy (37–41). The reported frequency of endomyocardial biopsy showing lymphocytic infiltration in patients with the clinical diagnosis of myocarditis and acute onset of unexplained heart failure range from 0 to 67% in different series (42–44). The great variability in the reported sensitivity of the right ventricular endomyocardial biopsy for the detection of myocarditis is probably related to the focal nature of this disease and the small amount of histologic material available using this diagnostic approach. Despite the potential for sampling errors, the right ventricular endomyocardial biopsy is still the most accepted standard method for the diagnosis of myocarditis.

Indium-111-antimyosin antibodies that bind to exposed myosin which migrates to the extracellular space after disruption of the cell membrane integrity has been successfully used in the diagnosis of myocyte damage in acute myocardial infarction (45,46). Its role in the setting of acute myocarditis has also been investigated (35,47,48). The sensitivity of the antimyosin scan has been found to be as high as 83%, while the negative predictive value of a normal scan has been 92% (35). Antimyosin antibody imaging is probably an appropriate noninvasive procedure for the selection of patients for an endomyocardial biopsies (35,47). Despite a positive antimyosin scan suggestive of diffuse myocardial necrosis, endomyocardial biopsy in our patient failed to demonstrate the inflammatory response typical of myocarditis.

Hypertrophic Cardiomyopathy and Ischemia

The incidence rate of angina pectoris in patients in whom hypertrophic cardiomyopathy (HCM) has been diagnosed is estimated to be around 76%–83% (49). It is interesting that the reported incidence of significant coronary artery disease in the same population of patients is only 15% (49). Necropsy reports indicate that 15% of patients with HCM and without significant coronary atherosclerosis had at least one episode of a transmural myocardial infarction (50). The occurrence of cardiac ischemia in patients with the diagnosis of HCM and normal coronary arteries is probably related to an imbalance between oxygen supply and demand as a consequence of increased

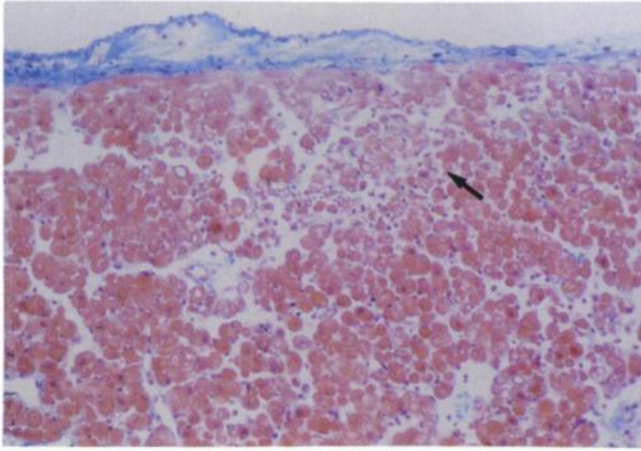


FIGURE 3. Right ventricular endomyocardial biopsy revealed scattered foci of healing myocardial ischemic necrosis. The arrow is pointing to a focus of necrotic myocytes.

myocardial mass (51), septal perforator arterial compression (52), abnormalities of the intramural arteries (53) and disturbance of left ventricular relaxation (54,55). Coronary vasospasm and embolic events have also been implicated in the pathogenesis of ischemia in patients with HCM (56). Cardiogenic shock in these patients has been associated with fluid depletion causing decreased intracardiac volume and accentuation of the left ventricular outflow tract gradient. This situation can potentially lead to severe hypotension and decreased coronary perfusion pressure and culminate in myocardial ischemia (56). Functional myocardial impairment in HCM has been evaluated by ^{99m}Tc gated cardiac blood-pool scintigraphy (57,58), magnetic resonance imaging (59,60) and ^{201}Tl cardiac imaging (61–63). Assessment of active myocardial damage in HCM using antimyosin antibody scintigraphy (64) and positron emission tomography (65) has been recently reported.

The gated cardiac blood-pool scan in our patient was suggestive of left ventricular hypertrophy. She presented, however, with normal septal and posterior wall thickness and no evidence of left ventricular pressure gradient or systolic anterior movement of the mitral valve by echocardiographic evaluation. An apical segmental motion abnormality was detected with both imaging procedures. It is of interest that Webb et al. (66) evaluated a group of 26 patients with asymmetric myocardial hypertrophy confined to the apex, an entity associated with “giant T-wave” inversion, which was initially described in Japan by Sakamoto et al. (67) and Yamaguchi et al. (68). Webb found that the population he studied had a normal septal and posterior wall thickness, none of them presented with left ventricular outflow tract gradient or systolic anterior movement and one of the patients, with no history of angina and in whom normal coronary arteries were documented, sustained an apical infarction with the formation of an apical aneurysm and loss of the “giant T-wave” inversion.

Rare Causes of Myocardial Necrosis in the Setting of Normal Coronary Arteries

Myocardial infarction with reversible ischemia and cardiogenic shock following excess thyroid administration in a patient with normal coronary arteries was described by Bergeron et al. (69). The thyroid function tests in our patient were within normal limits for an individual undergoing thyroid hormone replacement. Moreover, a thyrotoxic state was never documented during the hospitalization period.

Sources of coronary emboli include thrombotic endocarditis of infective or nonpyogenic origin, either in relation to native or prosthetic valves, cardiac tumors, thromboembolic event during cardiac invasive procedures or surgery, and atrial or ventricular mural thrombi. None of these conditions were detected in our patient.

Myocardial infarction and/or cardiogenic shock have been less commonly associated to coronary arteritis as in Kawasaki disease (70) and rheumatoid arthritis (71), blunt chest trauma (72), a hypercoagulable state causing a thrombotic event (73), acute myocardiotoxicity (74) and to an electrocution event (75). In addition, other reported causes of myocardial infarction has been related to inborn errors of metabolism leading to an accumulation of exogenous substances in the arterial wall with subsequent narrowing of the coronary lumen and congenital anomalies regarding the origin of the coronary arteries. Recently, Nader et al. (76) described an extremely rare cause of acute fatal myocardial infarction associated with aortic degenerative changes. In that reported case, cystic medial necrosis and elastin fragmentation were documented as promoters of thrombus formation. Nader et al. postulated that transient occlusion of the main coronary ostium by the aortic thrombus was the triggering event in the initiation of the myocardial ischemia. These unusual circumstances leading to myocardial necrosis were not documented in our patient.

CONCLUSION

This patient’s unusual clinical presentation and inconsistent first results make the diagnosis uncertain. The pathological findings obtained from the right ventricular endomyocardial biopsy were consistent with ischemic necrosis. In addition, a follow-up echocardiogram did not show improvement of the apical “infarction.” The circumstantial evidence, however, suggests that our patient sustained an ischemic event, regardless of its cause.

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