

CASE OF THE MONTH

A Young Woman with an Acute Illness and Chest Pain

Paul Karagiannis, M.D.; Barry H. Trachtenberg, M.D.

Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, Houston, Texas

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PRESENTATION

A 45-year-old woman presented to the emergency department with several weeks of progressive malaise and fatigue and vague chest pressure for the past 2-3 days. The pain was constant, unrelated to activity or change in body position, and non-pleuritic. She denied dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or edema. A review of systems was positive for paresthesia in her right hand and intermittent diarrhea and nausea, both of a few weeks duration. Her medical history was notable for hysterectomy one year ago for severe menorrhagia, with an uncomplicated perioperative course. Family history was pertinent for sarcoidosis in her mother. She was married with 4 children and did not smoke or consume alcohol or illicit drugs.

On examination, the patient appeared in no acute distress. She was normotensive (110/70 mm Hg) and afebrile with a pulse rate of 90 beats/min and a respiratory rate of 12 breaths/min, saturating well on room air. Her neck was supple with jugular venous distension in the supine position, lungs were clear to auscultation, heart had a normal PMI and regular rhythm without murmurs or gallop, abdomen was soft but with mild epigastric tenderness, bowel sounds were present, and there was no peripheral edema.

LAB TESTS AND RESULTS

Laboratory results revealed a hemoglobin of 11.1 g/dL, normal white cell and platelet counts, a BUN of 17 mg/dL with a creatinine of 1.1 mg/dL, and mild hyponatremia (132 mmol/L) and hypokalemia (3.2 mmol/L). There was marked elevation of troponin I with her initial laboratories (15.64 ng/mL) and a BNP of 513 pg/mL. A lipid panel revealed a total cholesterol of 191 mg/dL with an HDL of 37mg/dL and LDL of 120 mg/dL. A 12-lead electrocardiogram (Figure 1) showed sinus tachycardia, vertical frontal axis, mild ST elevation in V1-2 with poor R wave progression, and inferolateral ST segment depression.

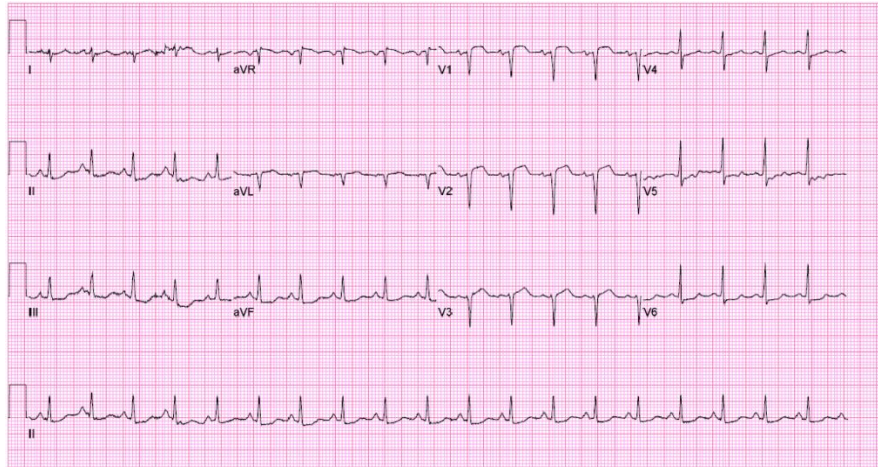


Figure 1. A 12-lead electrocardiogram shows sinus tachycardia, vertical frontal axis, mild ST elevation in V1-2 with poor R wave progression, and inferolateral ST segment depression

QUESTION 1: Which of the following would you do next?

- a) Repeat the ECG
- b) Coronary angiography with PCI, if appropriate
- c) Repeat the cardiac enzymes
- d) A transthoracic echocardiogram

ANSWER

B: Coronary angiography with PCI, if appropriate

Although the presenting symptoms were atypical for acute myocardial infarction, given a female patient (known to have more atypical symptoms than men) with the noted ECG findings and the troponin elevation, it would be appropriate to take the patient immediately for coronary catheterization to localize a culprit lesion and intervene. A transthoracic echocardiogram (TTE) would be valuable in assessing global and regional left ventricular (LV) function given the elevated BNP, but it could wait until after completion of the catheterization.

CONTINUED

The patient was taken to the catheterization laboratory and coronary angiography revealed patent normal arteries without dissection and a right-dominant system. Figure 2 illustrates a recording of the LV pressure on a scale of 0-40 mm Hg. Note the elevated early diastolic pressure (green arrow) as well as end-diastolic pressure (red arrow), both implying elevated filling pressure, and significant abnormalities in diastolic function.

A TTE was performed (Videos 1 and 2, Figure 3). The study was interpreted as showing a small LV cavity with severely increased LV wall thickness, diffuse hypokinesia with an ejection fraction measured at 36%, and right ventricular hypertrophy (RVH) with moderate RV systolic dysfunction. A trivial pericardial effusion was also noted. There were no valvular abnormalities. The left atrium was at the upper normal limit in size. Transmitral velocity and tissue Doppler annular velocities were consistent with severe LV

relaxation abnormality. Figure 4 shows the longitudinal strain bullseye obtained with speckle tracking technology.

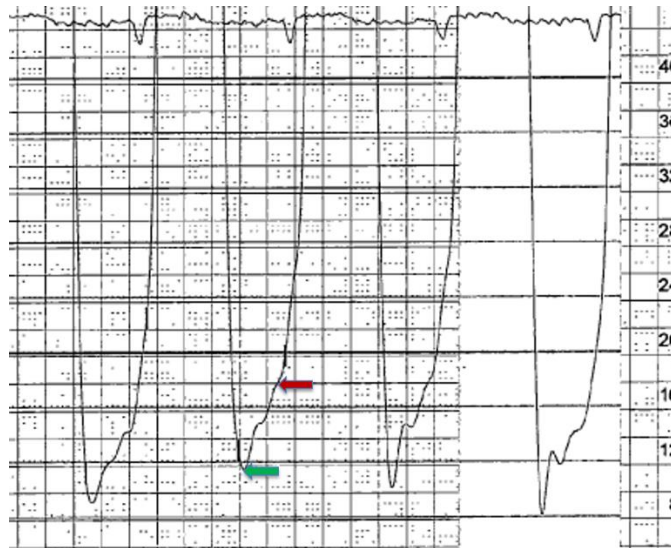


Figure 2. Recording of the LV pressure on a scale of 0-40 mm Hg. Note the elevated early diastolic pressure (green arrow) as well as end-diastolic pressure (red arrow), both implying elevated filling pressure, and significant abnormalities in diastolic function.

Video 1. https://youtu.be/p_lbhEtrXYo

Video 2. <https://youtu.be/ZDGy8ROkNwc>

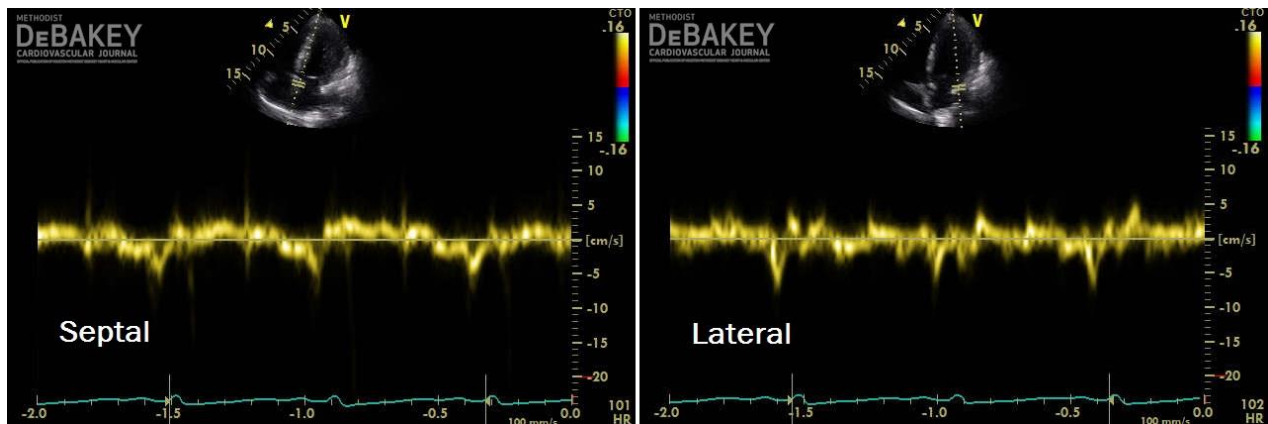


Figure 3. Septal and lateral TTE views.

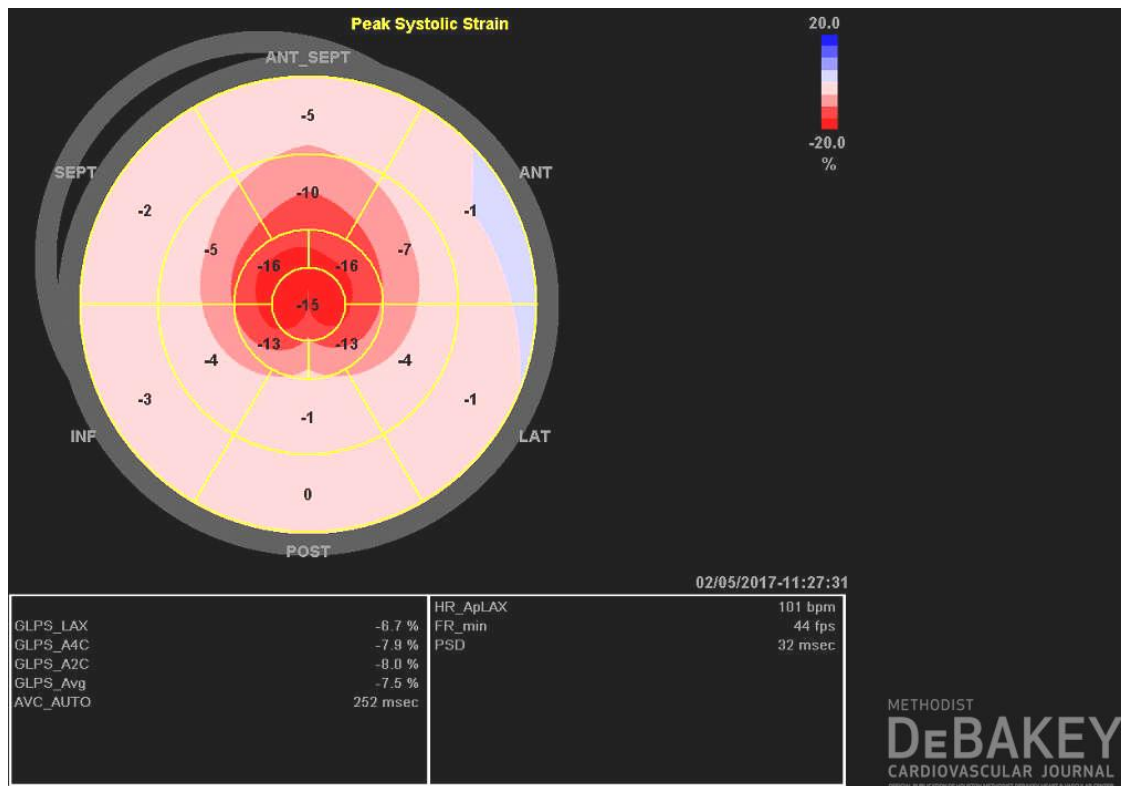


Figure 4. Longitudinal strain bullseye obtained with speckle tracking technology.

QUESTION 2: Which of the following diagnoses is least likely in this patient?

- a) Acute myocarditis
- b) Cardiac amyloidosis
- c) Takotsubo cardiomyopathy
- d) Cardiac hemochromatosis

ANSWER

C: Takotsubo cardiomyopathy

Of the choices given, Takotsubo cardiomyopathy is the least likely given that this condition is usually accompanied by regional wall motion abnormalities, most frequently apical akinesis. To summarize, the patient had a nonischemic cardiomyopathy with evidence of biventricular hypertrophy, systolic dysfunction without dilation, elevated filling pressures, and evidence of cardiomyocytolysis. The differential diagnosis included acute myocarditis, inflammatory cardiomyopathies, and infiltrative cardiomyopathies. Tachycardia-induced cardiomyopathy and peripartum cardiomyopathy were unlikely, and the patient had not been exposed to chemotherapeutic agents, illicit substances, or alcohol. Laboratories were obtained as part of the initial workup, and notable results included the following:

- Sed rate: normal
- Antinuclear Antibodies: negative

- Ferritin: 39 ng/mL [30-400 ng/mL]
- Kappa light chain: 135 mg/L [3-19.4 ng/mL]
- Lambda light chain: 8 mg/L [5.7-26.3 mg/L]
- k/l: 2.11 [26-1.65]

QUESTION 3: Which test would you perform next?

- a) Transesophageal echocardiography (TEE)
- b) Cardiac computed tomography (CT)
- c) Cardiac magnetic resonance imaging (CMR)
- d) Endomyocardial biopsy (EMB)

ANSWER

C: Cardiac magnetic resonance imaging (CMR)

The echocardiographic and laboratory findings, particularly the elevation in light chain ratio, suggest an acute presentation of cardiac light chain amyloidosis as the leading diagnosis. While we cannot exclude acute myocarditis or sarcoidosis with these findings alone, the combination of the abnormal k:l ratio and apical sparing on strain echocardiography are very suggestive of cardiac amyloidosis. Hemochromatosis is eliminated by a normal ferritin.

At this juncture, further testing was necessary. The relative reduction in QRS voltage on the ECG despite significant concentric LVH by echocardiography further supported a diagnosis of amyloidosis, as did the pattern of “apical sparing” seen by speckle tracking (Figure 4), which has been commonly observed in amyloidosis. Although tissue diagnosis will ultimately be necessary, unless hemodynamic instability exists, CMR should be considered first since the pattern of late gadolinium enhancement will provide additional diagnostic information. However, if clinical suspicion for amyloid is already high, one could consider pursuing bone marrow biopsy (if k:l abnormal) or EMB as the next test. Neither TEE nor cardiac CT provide additional information to establish a diagnosis or guide therapy.

CMR was performed the day following catheterization and echocardiography. It confirmed many of the echocardiographic findings including the RV dysfunction (ejection fraction: 40%). Gadolinium enhancement (Figure 5) was present (red arrows) and was described as: “diffuse non-CAD scarring throughout the myocardium (worse in the septum) concerning for an infiltrative disorder (e.g., cardiac amyloid).”

On the third day of hospitalization and while awaiting EMB, the patient collapsed in the bathroom and was found without a pulse. Telemetry tracings leading to the arrest (Figure 6) demonstrated bradycardia evolving to pulseless electrical activity (PEA). An intraaortic balloon pump was placed at bedside, and CPR was performed for an hour without success. Permission for an autopsy was not granted by her family.

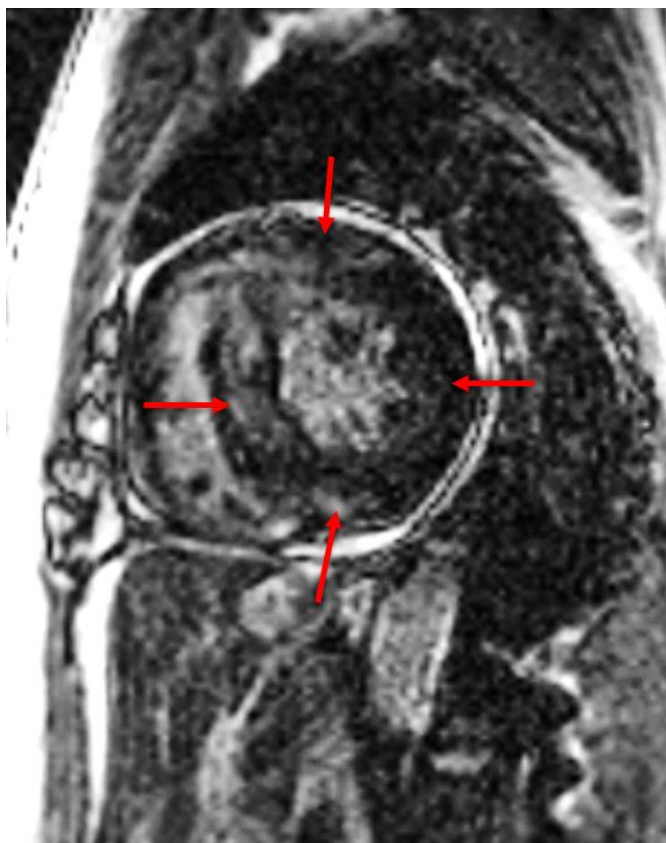


Figure 5. CMR with gadolinium enhancement (red arrows) shows diffuse non-CAD scarring throughout the myocardium (worse in the septum) concerning for an infiltrative disorder.

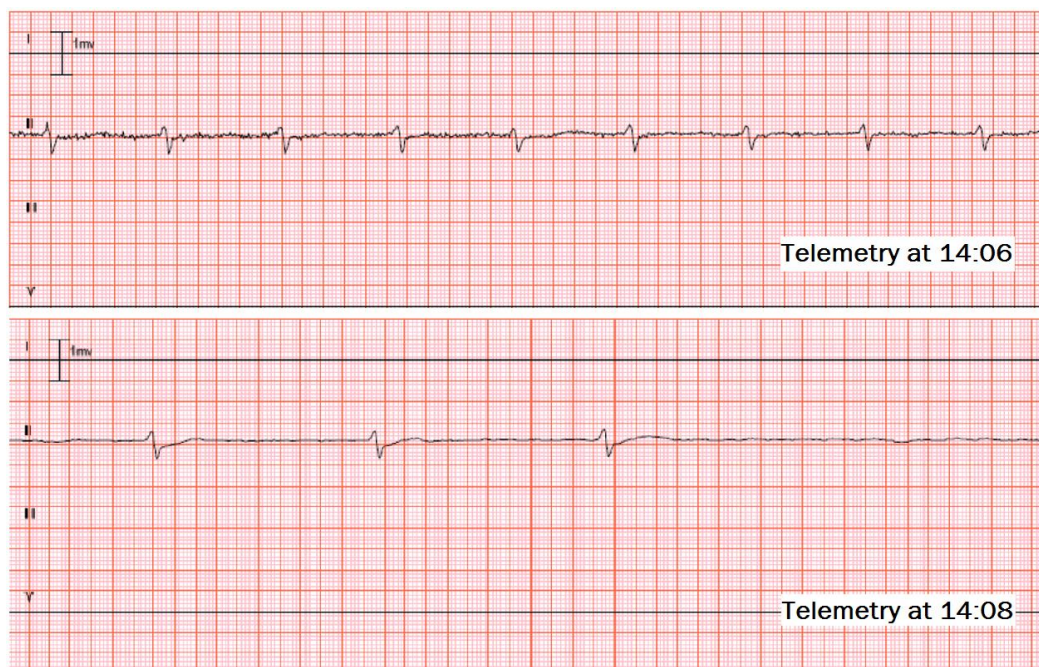


Figure 6. Telemetry tracings leading to the arrest demonstrated bradycardia evolving to pulseless electrical activity.

CASE DISCUSSION

Cardiac amyloidosis is a relatively uncommon disorder, characterized by vague symptoms, subtle imaging findings, and an often unrelenting course in those diagnosed late in the disease process. Traditional pearls such as low voltage on ECG are not very sensitive when studied prospectively;¹ the same can be said for the “sparkling or scintillating myocardium” seen on echocardiography. Significant increased LV wall thickness in a patient without hypertension should raise clinical suspicion but is itself nondiagnostic and should prompt further testing. While cardiac amyloidosis is a tissue diagnosis, CMR has emerged as a noninvasive tool to help in diagnosis due to a characteristic subendocardial late gadolinium enhancement pattern that does not follow a coronary distribution.² The clinical constellation of small LV chamber size with severe biventricular hypertrophy, characteristic CMR findings, and abnormal light chain levels were highly supportive of the diagnosis of light chain cardiac amyloidosis in our patient.

Amyloidosis is caused by the deposition of abnormally-folded serum proteins. Although several proteins can misfold and lead to amyloidosis, the majority of clinical disease is caused by misfolded transthyretin or immunoglobulin light chains. These misfolded proteins aggregate into amyloid fibrils that can deposit throughout the body and within the heart where they accumulate in the myocardium, conduction system, and valves. Infiltration leads to a restrictive cardiomyopathy, and the fibrils have a direct toxic effect on cardiomyocytes, with apoptosis leading to troponin leak without ischemia and marked natriuretic protein elevation.³

Light chain amyloidosis (AL amyloidosis) arises from a plasma cell dyscrasia. Although the abnormal light chains can accumulate in any tissue, the prognosis of this malignancy is, in fact, related to cardiac involvement. Unfortunately, the majority of patients have cardiac amyloidosis at the time of diagnosis, often at an advanced stage. The 2012 Mayo Classification System risk-stratifies patients by troponin and NT-pro-BNP elevation and by free-light-chain difference, ranging from patients with zero risk factors to stage IV patients with all three positive. Median survival from the time of diagnosis is 6 months in patients with stage IV disease due to rapidly progressive pump failure and sudden cardiac death (SCD).⁴ In fact, SCD accounts for a significant proportion of mortality, and unfortunately, implantable cardioverter-defibrillators have not been shown to benefit this population given the high burden of asystole.⁵ An uncertain but nontrivial number of patients have SCD as their presenting complaint.

A serum free light chain assay with ratio is recommended to screen patients for AL amyloidosis and is confirmed with serum and urine immunofixation, which demonstrates the existence of a plasma cell clone. A biopsy demonstrating tissue involvement is necessary to complete the diagnosis, with endomyocardial biopsy carrying nearly 100% sensitivity; peripheral fat-pad aspiration is much less reliable.⁴

Aggregation of abnormal transthyretin leads to ATTR amyloidosis, a subtype of that produces a similar pattern of echocardiographic and CMR findings to AL amyloidosis. Unlike in AL amyloidosis, a noninvasive radiotracer-labeled pyrophosphate scintigraphy (99mTc-PYP) study can reliably diagnose ATTR amyloidosis. Recent work suggests that ATTR cardiac amyloidosis may be more prevalent than

previously thought,⁴ with some studies suggesting that nearly 15% of patients with symptomatic heart failure with preserved ejection fraction having undiagnosed ATTR amyloidosis.³

Although current treatment paradigms are outside the scope of this case, the most important intervention for a patient with cardiac amyloidosis is timely diagnosis and referral to a center specialized in the treatment of this unusual and serious disease.

TAKE-HOME MESSAGES

- Cardiac amyloidosis is a relatively uncommon disorder with vague symptoms and subtle imaging findings, requiring a high index of suspicion for prompt diagnosis
- Concentric LV hypertrophy in a patient without hypertension in association with elevated troponin and beta natriuretic peptide should raise suspicion for cardiac amyloidosis
- Cardiac MRI has emerged as a noninvasive tool to help in diagnosis due to a characteristic noncoronary subendocardial late gadolinium enhancement pattern.
- A serum free light chain assay with ratio is recommended to screen patients for AL amyloidosis
- The most important intervention for a patient with cardiac amyloidosis is timely diagnosis and referral to a center specialized in the treatment of this unusual and serious disease

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