

Cardiac Amyloidosis in a Patient with Multiple Myeloma: A Case Report and Review of Literature

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ABSTRACT: We report a case of a 52-year-old man with multiple myeloma and rapidly progressive heart failure who died unexpectedly from a probable arrhythmia. Postmortem examination revealed infiltrative amyloid cardiomyopathy, a rare cause of predominantly diastolic myocardial disease. Cardiac amyloidosis should be considered in any patient presenting with congestive heart failure, preserved systolic function, and a discrepancy between a low QRS voltage on electrocardiography and an apparent left ventricular hypertrophy on sonogram. The pattern of left ventricular diastolic dysfunction changes during the course of amyloidosis and the classically described restrictive physiology occurs only in advanced stages of the disease. © 2009 Wiley Periodicals, Inc. *J Clin Ultrasound* 37:179–184, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jcu.20552

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CASE REPORT

A 52-year-old man recently diagnosed with the immunoglobulin G multiple myeloma was admitted to the hospital complaining of progressive dyspnea with minimal exertion, orthopnea, bilateral lower extremity edema, increased abdominal girth, and lightheadedness over the preceding several weeks. He had no medical problems until 9 months before being diagnosed

with multiple myeloma. He had received several courses of chemotherapy with thalidomide at an outside facility. No data on prior cardiac workup from that institution were available.

On physical examination, the patient was afebrile and in the supine position had blood pressure of 114/76 mm Hg and a regular heart rate of 90 beats per minute. When patient stood, orthostatic changes in blood pressure and heart rate were noted. He was breathing at a rate of 19 breaths per minute. Oxygen saturation on room air was 92%.

Cardiovascular exam revealed elevated jugular venous pressure of 13 cm of water at a 30° angle and a grade 3/6 systolic ejection murmur at the left sternal border without radiation. On lung auscultation, bilateral rales in lower lung fields as well as diminished breath sounds at the left lower base were noted. The abdomen was distended and diffusely tender to deep palpation. There was bilateral lower extremity pitting edema extending to the knees.

Electrocardiogram revealed a normal sinus rhythm at a rate of 84 beats per minute and low voltage in precordial leads (Figure 1A).

A transthoracic echocardiogram (Figure 1B) revealed apparent left ventricular (LV) hypertrophy (wall thickness of the interventricular septum and posterior wall 1.5 cm each; LV mass of 256 g, or 129 g/m² using the Devereux formula,¹ bi-atrial enlargement, small pericardial effusion, and mild mitral and tricuspid valve regurgitation. On fundamental (nonharmonic) 2-dimensional imaging, the myocardium had

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52 yr Male Caucasian 190lb Loc:438
 Vent. rate 95 BPM
 PR interval 184 ms
 QRS duration 102 ms
 QT/QTc 374/470 ms
 P-R-T axes 45 -56 99
 NORMAL SINUS RHYTHM
 LEFT AXIS DEVIATION
 LOW VOLTAGE QRS, CONSIDER PULMONARY DISEASE, PERICARDIAL EFFUSION, OR NORMAL
 CANNOT RULE OUT ANTERIOR INFARCTY (CITED ON CR BEFORE 29-JUN-2002)
 ABNORMAL ECG
 WHEN COMPARED WITH ECG OF 29-JUN-2002 09:31, (UNCONFIRMED)
 QT HAS LENGTHENED

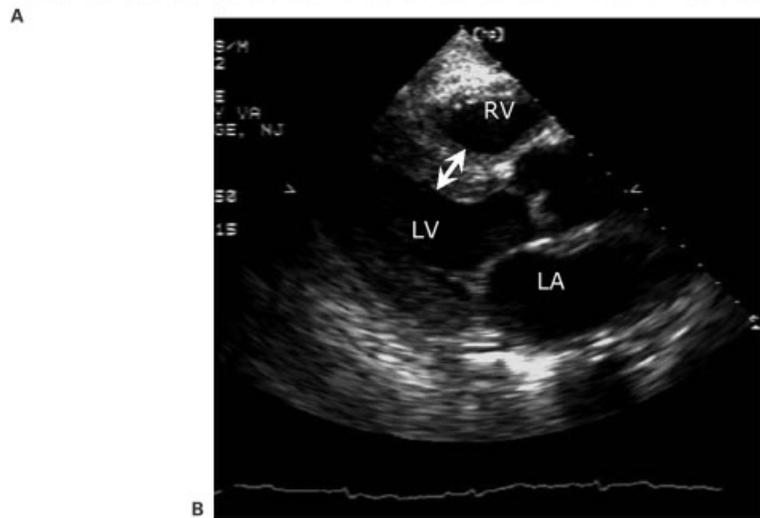
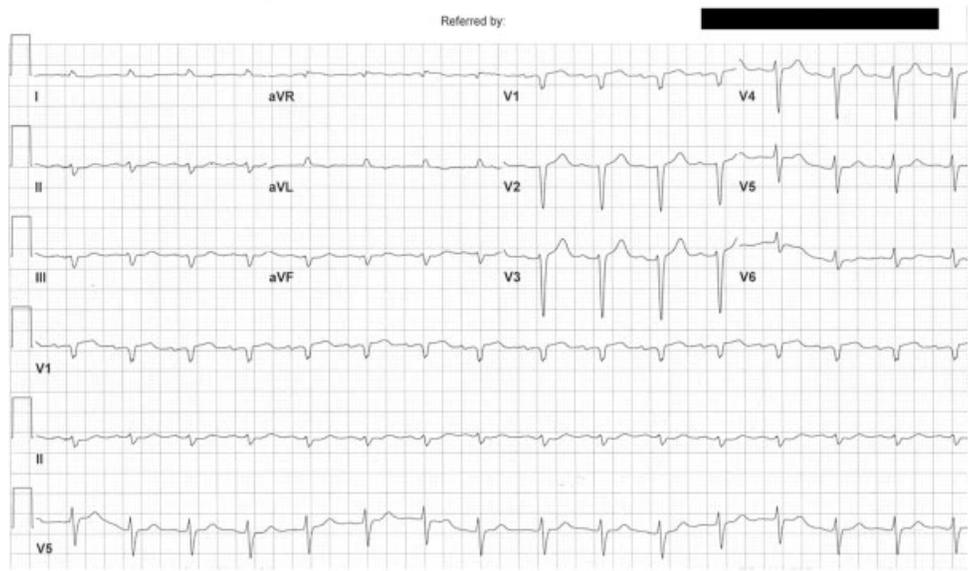


FIGURE 1. The discrepancy between the absence of electrocardiographic signs of left ventricular hypertrophy and apparent left ventricular hypertrophy on echocardiography is strongly suggestive of an infiltrative cardiomyopathy such as cardiac amyloidosis. (A) Low voltage in the limb EKG leads. (B) Transthoracic echocardiogram demonstrates thickened left ventricular walls. LA, left atrium; LV, left ventricle; RV, right ventricle; double arrow indicates the thickened interventricular septum.

“snowstorm” appearance. Left ventricular systolic function was normal (ejection fraction of 60%). In contrast, LV diastolic function was markedly abnormal as judged by severely diminished peak early diastolic velocity (E') of the medial mitral annulus on tissue Doppler imaging (Table 1 and Figure 2). Blood velocity pattern at the mitral leaflet tips and in the pulmonary veins (Figure 2) is consistent with pseudonormalization and reflective of elevated left atrial pressures. Pulmonary artery systolic pressure could not be

TABLE 1
Mitral Blood and Annular Tissue Doppler Parameters

	Mitral Blood Inflow	Medial Mitral Annulus
Isovolumic relaxation time (msec)	87	
Peak early diastolic (E) wave (cm/sec)	194	4
Peak atrial (A) wave (cm/sec)	117	7
E/A ratio	1.7	0.6
Deceleration time of E wave (msec)	204	

AMYLOID CARDIOMYOPATHY

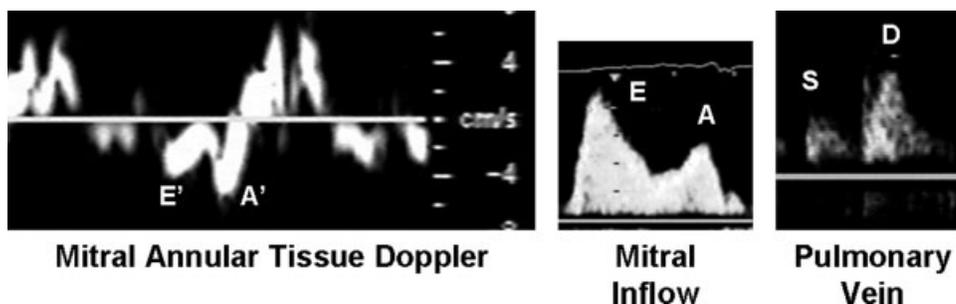


FIGURE 2. Doppler recordings of our patient with multiple myeloma demonstrating low mitral annular tissue Doppler E' velocity indicative of diminished left ventricular relaxation, as well as the pseudonormal filling pattern in the mitral and pulmonary venous flow velocity tracings indicative of elevated left atrial pressure. E, peak early diastolic flow velocity; A, peak diastolic flow velocity with atrial contraction; E', myocardial velocity during early filling; A', myocardial velocity during filling produced by atrial contraction; S, systolic pulmonary vein velocity; D, diastolic pulmonary vein velocity

estimated because there was not sufficient tricuspid regurgitant jet.

The patient was admitted to the coronary care unit with a diagnosis of new-onset diastolic heart failure. He was treated with intravenous furosemide and an angiotensin-converting enzyme inhibitor with marked improvement in symptoms during the next few days.

Several days later, he developed severe abdominal pain. While awaiting surgical consultation for possible large bowel obstruction, he became pulseless as a result of asystole. Despite all resuscitative efforts, he expired.

The postmortem exam revealed extensive systemic amyloidosis involving the heart (Figure 3), blood vessels, and smooth muscle of various organs. The pericardial cavity was smooth and contained 15 milliliters of clear yellow fluid. The serosal surface of heart revealed no abnormalities. The heart was enlarged and dilated; it weighed 600 grams. The left and right ventricles were hypertrophied, and their walls measured 2.1 cm and 0.9 cm, respectively, in thickness. The myocardium was waxy and pale with a few areas of fibrosis. All valves were normal in dimension with thin leaflets. The coronary arteries had mild atherosclerotic disease.

DISCUSSION

Amyloidosis is a systemic or organ-limited disease in which insoluble homomeric amyloid fibrils that are composed of a variety of serum proteins gradually replace normal tissue in various body organs. Despite the array of proteins that can give rise to amyloid deposits, all amyloid fibrils share the same structural feature of antiparallel beta-pleated sheets seen on electron microscopy.²

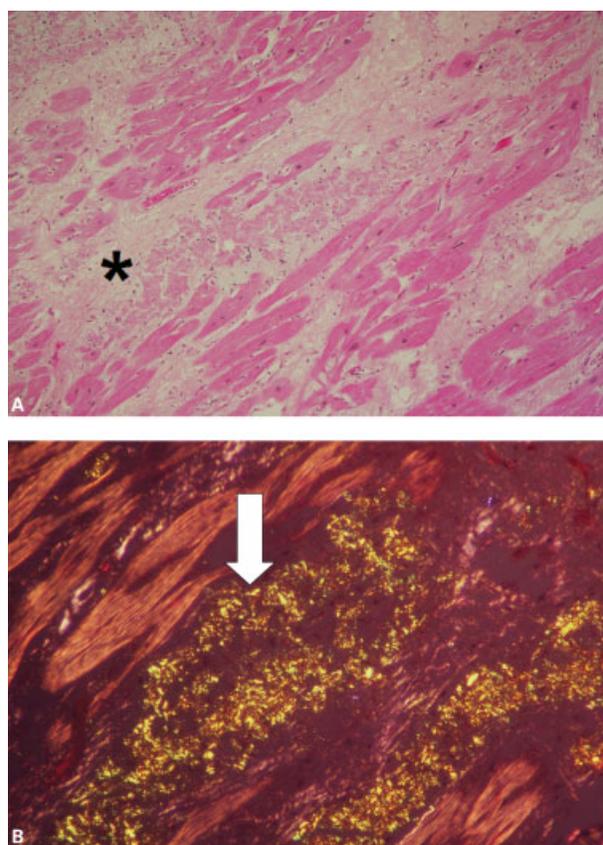


FIGURE 3. (A) Hematoxylin and eosin-stained section of the heart shows extracellular deposits of pale eosinophilic homogenous material (asterisk) consistent with amyloid. Original magnification, 200 \times . (B) Congo red-stained cardiac tissue shows patchy areas of bright apple-green birefringency under polarization, which is diagnostic of amyloidosis. Original magnification, 200 \times .

Multiple types of amyloidosis have been identified based on the biochemical composition of fibrillar subunits.³ In the clinical setting, major forms of amyloidosis that affect the heart can be classified into 6 subtypes: (1) AL or primary amyloidosis in which the amyloid protein is composed of monoclonal immunoglobulin light chains

produced in excess by plasma cell tumor; (2) AA or secondary amyloidosis resulting from deposits of the so-called serum amyloid protein that is secreted in chronic inflammatory diseases such as rheumatoid arthritis; (3) familial (hereditary) amyloidosis of which the most common form is the result of mutations in gene for transthyretin (prealbumin); (4) senile systemic amyloidosis, also known as wild-type transthyretin, which is seen almost exclusively in elderly men; (5) isolated atrial amyloidosis, which can increase the risk of atrial fibrillation; and (6) hemodialysis-related amyloidosis resulting from accumulation of beta-2 microglobulin.

Signs and symptoms of amyloidosis, such as fatigue, purpura, peripheral neuropathy, and atypical chest pain, are nonspecific, which makes achieving a correct clinical diagnosis of cardiac amyloidosis a difficult and lengthy process.

Clinical evidence of cardiac involvement occurs in up to 50% of patients with AL amyloidosis but only in 10% of individuals with AA amyloidosis and less than 5% with familial syndromes.⁴ It is important to emphasize that although only 10% of the patients with multiple myeloma develop systemic light-chain amyloid disease, their prognosis is very poor, especially in the presence of cardiac amyloidosis. Because cardiac involvement in amyloidosis is associated with a rapidly progressive course and high mortality, a rapid and accurate diagnosis is essential to aid in the selection of therapy.

Amyloid depositions occur mainly in the interstitium of contractile myocardium but may also involve the pericardium, the endocardium (resulting in valvular leaflet thickening),⁵ and the conduction system (giving rise to abnormalities in impulse formation, impulse conduction, stress-precipitated syncope, atrial fibrillation, and sudden cardiac death).⁶ Coronary angiography in patients with cardiac amyloidosis and angina is often normal because amyloid fibrils are deposited in the small intramural vessels sparing the epicardial arteries.^{7,8} This small vessel disease leads to decreased myocardial flow reserve and persistent elevation of cardiac markers, which often lead to costly noninvasive and invasive cardiac testing.⁹ Plasma levels of B-natriuretic peptide are also elevated, likely the result of elevated ventricular filling pressures and possibly the result of direct damage to myocytes caused by amyloid deposition.¹⁰

Accumulation of electrically inert amyloid protein in the extracellular matrix of the myocardium leads to an increase in ventricular wall thickness and a false impression of ventricular

hypertrophy on sonography. On the electrocardiogram, however, there are no signs of LV hypertrophy and the recorded voltage is low (<5 mm in limb leads and <10 mm in precordial leads).¹¹ Indeed, the cardinal feature of amyloidosis is the pronounced discrepancy between low EKG voltage and increased ventricular mass on sonography. Therefore, the most sensitive and specific test for detecting cardiac amyloidosis is a low voltage-to-mass ratio.¹²

The ventricular myocardium in amyloidosis may have a "snowstorm" or "sparkling" appearance on sonographic images. However, this supposedly distinctive pattern has a low sensitivity and specificity and is primarily seen on fundamental rather than harmonic imaging.¹³ A thickened interatrial septum, which is rarely present even in the later stages of the disease process, has been shown to have a 100% specificity.

The diagnosis of cardiac amyloidosis can be ascertained by either (1) a positive biopsy from a noncardiac tissue in addition to sonographic evidence of amyloidosis, which includes a mean LV wall thickness of greater than 12 mm in the absence of other causes of LV hypertrophy, or (2) an endomyocardial biopsy illustrating amyloid deposition in addition to laboratory and clinical evidence of organ involvement.¹⁴ In patients with cardiac involvement, endomyocardial biopsy is a relatively safe procedure in experienced hands with 100% sensitivity in diagnosis of cardiac amyloidosis.¹⁵

Biopsy specimen from the involved organ, such as the heart or from the abdominal fat pad, exhibits a red or pink color under light microscopy after chemical staining with Congo red and a dramatic apple-green birefringence under polarized light. A large variety of special immunohistochemical staining has been used to identify and classify amyloid deposits. However, with an increasing number of amyloid proteins discovered, this process can be costly and time consuming. In addition, prolonged fixation of the specimen may decrease or abolish adequate staining, leading to a false negative result.

The primary manifestation of amyloid cardiomyopathy is congestive heart failure with preserved systolic and abnormal diastolic function. Classically, amyloidosis was described as a form of restrictive cardiomyopathy based on the so-called restrictive mitral inflow pattern on spectral Doppler imaging. However, this severe form of LV diastolic dysfunction occurs only in the late stage of the disease.

Early in the process, diastolic dysfunction is only mild and is characterized by the Doppler pattern of abnormal relaxation (the ratio of early

[E] to late [A] peak blood velocity of diastolic mitral inflow [E/A ratio] < 1; S-dominant pattern in pulmonary veins). This same pattern of mild diastolic dysfunction occurs frequently in normal middle-aged and elderly individuals and should not be used in isolation to diagnose cardiac amyloidosis. Subsequently, the mitral inflow pattern progresses to moderate (pseudonormal pattern) and finally to the classic severe diastolic dysfunction (restrictive pattern).

Our patient falls into the moderate diastolic dysfunction group as judged by both mitral inflow parameters (E/A ratio < 2, deceleration time of E wave > 150 msec) and the pulmonary venous flow (D-dominant pattern). The pseudonormal pattern has been shown to be associated with an elevated mean left atrial pressure in the range of 15–22 mm Hg.

More recently, pulsed tissue Doppler imaging (TDI) has been used to detect the presence of diastolic dysfunction in patients with cardiac amyloidosis who have mild abnormalities on 2-dimensional sonography or nondiagnostic Doppler pattern of diastolic filling or who have suboptimal pulmonary venous flow recordings.^{16,17} Early in the course of the disease, the pulsed TDI of the myocardium is associated with an early impairment of diastolic function (E') without affecting the late diastolic function (A') or the systolic function (S). As the disease progresses and the patient develops signs of heart failure, the early systolic function and the late diastolic function remains unchanged, but the systolic function diminishes. Strain and strain rate imaging are able to detect impairment in longitudinal contraction even earlier than TDI. On cardiac magnetic resonance imaging diffuse myocardial amyloid deposits lead to a decreased tissue signal intensity along with a specific pattern of global late subendocardial tissue enhancement.¹⁸

Aside from the treatment of the underlying cause of amyloid deposition, the treatment of symptomatic cardiac amyloidosis is primarily supportive. Preload and afterload reduction using diuretics alone or in combination with vasodilators, or long-acting nitroglycerin preparations, may be helpful. However, hemodynamic deterioration after nifedipine¹⁹ and verapamil has been reported.²⁰

Digital glycosides may reduce the symptoms of congestive failure, but dysrhythmia and sudden death have been reported following their use. Although the use of mechanical LV assistance devices has not been studied in patients with cardiac amyloidosis, it may be offered to patients with end-stage heart failure as a palliative measure.²¹

Untreated patients with AL amyloidosis and heart failure have a median survival of 6–9 months.²² A number of studies indicate that some patients benefit from chemotherapy with long-term melphalan and prednisone that suppresses the underlying plasma-cell dyscrasia, which prevents further amyloid deposition and gradual amyloid regression.^{23,24} Cardiac transplantation may be a lifesaving measure for those patients with preserved extracardiac organ function who are also fit to undergo subsequent chemotherapy.²⁵ Successful post-transplantation chemotherapy has been shown to greatly improve the longevity of the patient, possibly leading to a survival of up to 10 years. A more aggressive approach, such as autologous stem cell transplantation, may offer patients long-term survival.²⁶

In summary, a cardiac screening in all patients with multiple myeloma should include at least an EKG and complete cardiac sonography. Sonographic findings in cardiac amyloidosis are not specific for this disease because they can also be present in other disease states. The pattern of LV diastolic dysfunction changes during the course of amyloidosis and is not limited to the classically described restrictive physiology. Even though there is no single noninvasive test that can accurately diagnose cardiac amyloidosis, the consolation of heart failure symptoms, sonographic findings, and low-voltage EKG are highly suggestive of disease. This further underscores the importance of early and accurate bioptic diagnosis of the disease.

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