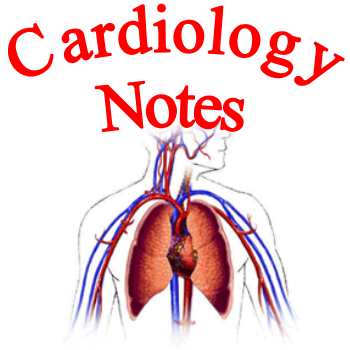

An Unusual Cardiac Manifestation of Multiple Myeloma

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Introduction

Amyloidosis is a systemic or organ-limited disease in which there is extracellular deposition of amyloid fibrils that gradually replace normal tissue in various organs in different pathological states, leading to loss of normal tissue architecture.[1] The extent and location of amyloid deposition is directly responsible for the degree of cardiac failure.[1,2]

Usually 25% of the myocardium is replaced by amyloid deposition for symptoms to appear with congestive heart failure being the most common presentation of cardiac amyloidosis. In the clinical workup of patients with diastolic heart failure and myocardial hypertrophy, cardiac amyloidosis is an important differential diagnosis. Once congestive heart failure occurs, the median survival is less than six months in untreated patients, and is the most common cause of death.[2]

Case Report

A 57-year-old female with a history of hypertension, diabetes mellitus, paroxysmal atrial fibrillation, morbid obesity, and multiple myeloma presented for recurrent episodes of shortness of air for the past six months. The initial echocardiogram revealed normal left ventricular systolic function, moderate tricuspid and mitral valve regurgitation, severe diastolic dysfunction, and a “speckled-like" pattern suggestive of possible amyloid disease. She underwent multiple fat biopsies without any conclusive evidence of amyloidosis. Cardiac MRI also was performed and was non-conclusive for the diagnosis of cardiac amyloid. Meanwhile, she had worsening dyspnea and interval increase in her pericardial effusion size along with worsening tricuspid and mitral valve regurgitation.

Her physical exam was positive for a 3/6 systolic murmur at the level of the mitral valve radiating to the axillary region and bilateral lower extremities edema. Chest x-ray revealed only mild cardiomegaly. Her electrocardiogram obtained at rest is shown below in Figure 1. She underwent elective pericardiocentesis and pericardial fluid analysis revealed only chronic inflammatory pattern with modest improvement in her symptoms. She was started on diuretic therapy with good response and significant improvement in her symptoms. She underwent a right heart catheterization and a right ventricular biopsy revealing a positive Congo red staining consistent with cardiac amyloidosis.

Discussion

Cardiac amyloidosis is an invariably progressive infiltrative cardiomyopathy that carries a grave prognosis. Cardiac involvement may be present in up to one-third of patients with primary amyloidosis (designated AL) resulting from plasma cell dyscrasias.[1,2] Although only 10% of the

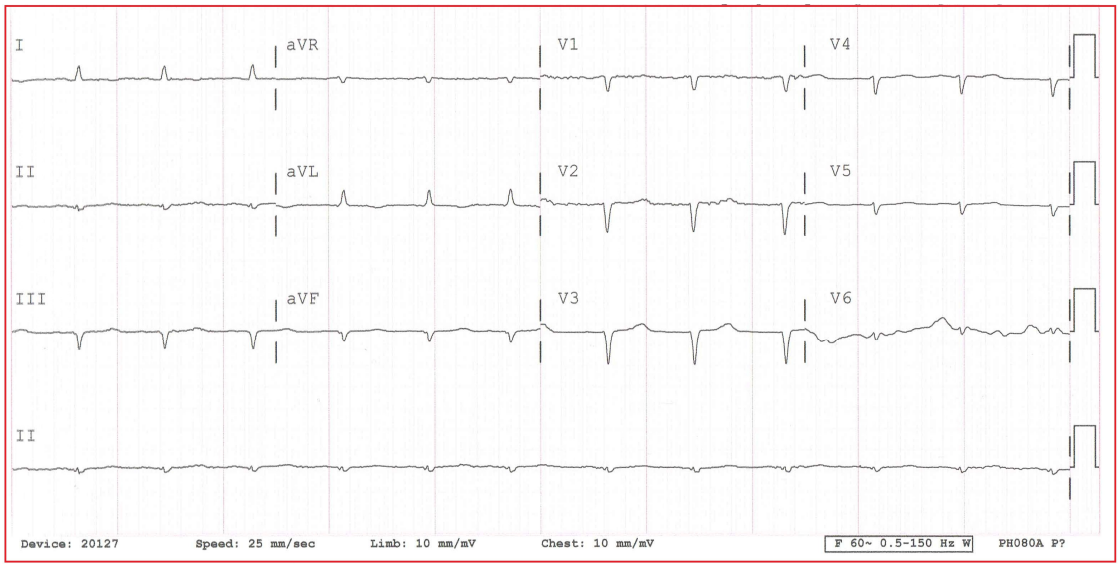

Figure 1. ECG revealing normal sinus rhythm with left axis deviation. Note the low voltage findings, anterior wall infarct (pseudo-infarct pattern), absent R wave in precordial leads, and possible inferior wall infarct. Artifacts noted in lead V6.

patients with multiple myeloma develop systemic light-chain amyloid disease, their prognosis is very poor, especially in the presence of cardiac amyloidosis.[3] Myocardial infiltration tends to be less with secondary amyloidosis (designated AA), in which the AA protein deposits tend to be smaller and more perivascular in location, thus less likely to produce myocardial dysfunction.[2,4] Other forms include familial and senile amyloidosis.[2]

The term amyloidosis means "starch-like." The heart infiltrated with amyloid appears tan and waxy and is rubbery in consistency. The atria also are enlarged significantly. Histologically, amyloid deposits can be detected with Congo red or Sirius red staining and are present between cardiac myocytes.[2,5]

There are four overlapping syndromes that may occur with cardiovascular involvement of amyloidosis, including restrictive cardiomyopathy, systolic heart failure, orthostatic hypotension, and presentation with conduction system disease. Most commonly, patients with cardiac amyloidosis present with signs of congestive heart failure with preserved systolic and abnormal diastolic function.[2,4]

Cardiomegaly may be present on chest roentgenography. The electrocardiogram most often reveals low QRS voltage, and bundle branch block and abnormal axis are also common. A pattern of old anterior myocardial infarction may be simulated by diminutive or absent R waves in the right precordial leads, or by an old inferior infarction by inferior Q-waves (pseudo-infarct pattern).[2,6] Amyloid infiltration of the atrium predisposes to atrial fibrillation, and ventricular arrhythmias are also common. Atrioventricular conduction defects are common and electro-physiological testing is usually necessary to detect significant intrahisian block. Sinus node dysfunction is also common and the ECG may show sick sinus syndrome.[6]

Echocardiography is quite valuable and reveals increased ventricular wall thickness with small intracavitary chambers, enlarged atria, and a thickened interatrial septum. The walls of the ventricles often reveal a distinctive appearance with a sparkling and granular texture, most likely resulting from the amyloid deposition itself. Pericardial effusions may be present, but usually do not

advance to tamponade. Doppler echocardiography is valuable to evaluate diastolic dysfunction, the degree of which offers prognostic information.[3,6,7] Cardiac MRI has a very high sensitivity for the detection of cardiac amyloid, and also may be valuable in measuring the extent of amyloid deposition in the heart, a significant prognostic factor.[8,9]

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 left ventricular 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. In patients with cardiac involvement, endomyocardial biopsy is a relatively safe procedure in experienced hands with 100% sensitivity in diagnosis of cardiac amyloidosis. 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.[2,5,6]

Patients with cardiac amyloidosis have few treatment options, although there are ongoing attempts to modify the severe natural history of this disorder.[10] Approaches for patients with AL amyloidosis involve chemotherapy with alkylating agents alone or in combination with autologous bone marrow stem cell transplantation and heart transplantation.[2,11] In terms of conventional cardiac medications, the use of digitalis glycosides requires additional vigilance because patients with cardiac amyloidosis have increased sensitivity to digitalis preparations. Calcium-channel antagonists also require caution because their negative inotropic effect has the potential to exacerbate heart failure. Pacemakers are frequently indicated for conduction system disturbances, and implantable cardioverter-defibrillators may be considered. The mainstay of symptom relief in volume overloaded patients is the judicious use of diuretics, which requires very careful titration, in combination with rigorous fluid restriction.[10]

Conclusion

In summary, cardiac amyloidosis is a progressively infiltrative cardiomyopathy that should be suspected in patients with multiple myeloma and worsening dyspnea. It carries a poor prognosis even with aggressive therapy. A cardiac screening in all patients with multiple myeloma should include at least an electrocardiogram and complete cardiac sonography.

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