Case Report

CARDIAC AMYLOIDOSIS AS A COMPLICATION OF MULTIPLE MYELOMA

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ABSTRACT

Restrictive cardiomyopathy due to cardiac amyloid deposition is not an uncommon complication of multiple myeloma. Most cases of cardiac amyloidosis reported in early series were diagnosed postmortem at autopsy(1,2).

The following is a report of a case with antemortem diagnosis of cardiac amyloidosis as a complication of multiple myeloma. We described the clinical features and diagnostic approaches by review of the literature.

Key Words : Cardiac amyloidosis, Multiple myeloma, Restrictive cardiomyopathy

INTRODUCTION

Cardiac involvement is common in amyloidosis associated with multiple myeloma. In one-third of the patients clinical heart disease is present, although pathological involvement is apparent in all cases (1). Common presentations of cardiac amyloidosis are restrictive cardiomyopathy, congestive heart failure, orthostatic hypotension, and conduction disturbances. The most characteristic feature seen in the electrocardiogram is diffuse low-voltage. The findings simulating myocardial infarction (loss of R wave progression in precordial leads, Q waves in the inferior leads) are also usually observed (2). Echocardiography demonstrates increased wall thickness and decreased diameters of ventricles, atrial enlargement, and thickened interatrial septum. The granular sparkling appearence of cardiac walls due to the amyloid deposit on two-dimensional echocardiography is distinctive (1,3). Doppler ultrasonography reveals abnormalities in global cardiac function and is a useful predictor of clinical outcome (4,5). Definitive diagnosis is made by endomyocardial biopsy of right or left ventricles if the abdominal fat aspirate is negative , which also indicates the degree of myocyte damage and atrophy (6.)

CASE REPORT

A fifty-nine year old man was admitted to the hospital with a one year history of progressive exertional dyspnea, peripheral edema, and easy fatigue. There was no history of rheumatic fever, angina pectoris, or hypertension.

On examination, the patient appeared pale with normal vital signs. The neck veins were flat. Moist rales were heard in both lung bases. The heart size was normal by percussion. No murmurs were noted. Extremities showed moderate pitting edema . The peripheral pulses were palpable and bilaterally equal. Neurological examination was essentially normal.

Results of laboratory tests were as follows : hemoglobin, 11.9 g/dl, hematocrit, 36%, leukocytes, 6.600 / mm^3 with normal differential count. The erythrocyte sedimentation rate was rapid (80 mm/h). Peripheral blood film revealed normochromic, normocytic red cells with rouleaux formation. The serum electrolytes, BUN, and creatinine were within normal limits. The total serum protein was 7.4 g/dl, with an albumin level of 3.2 g /dl. Urine analysis revealed a specific gravity of 1.020; had a negative reaction for protein; negative sediment. Protein electrophoresis revealed a peak in the gamma zone that was identified as monoclonal IgG by immunoelectrophoresis. The serum IgG level was 3140 mg/dL (normal value is 70 to 150 mg/dL). Bence Jones protein was found in the urine. Bone marrow aspiration revealed hypercellularity with increase in plasma cells (%22) in various stages of maturation and containing two or three nuclei. A diagnosis of multiple myeloma with bone-marrow involvement was made. An X-ray survey of the skeleton as a further evaluation

disclosed no lytic lesions. Treatment with prednisone (2mg/kg/d) and melphalan (0.25 mg/kg/d) was initiated.

During follow-ups , the patient developed progressive dyspnea and orthopnea with increasing edema despite biochemical improvement. A chest film revealed moderate cardiomegaly with pulmonary congestion and right-sided pleural effusion. The electrocardiogram showed poor R wave progression , and T wave negativity across the precordium. Electrocardiographic voltage was measured as the sum of S in V_1 and R in V_5 and was 15 mm. An echocardiogram revealed enlarged left atrium (43mm) (normal, <40mm) and ventricule, (57 mm) (normal <55 mm), 1 (+) mitral regurgitation, increased thickness of the interventricular septum (1,5 cm) and posterior wall of the left ventricule (1,6 cm). The left ventricular dimension (R) and thickness (Th) was measured at end-diastole from the M-mode echocardiogram. The cross-sectional area of the LV wall corrected for body surface area (bsa, m^2) $[(R+Th)^2 - R^2/bsa,]$, as an indicator of LV mass, was 11.7 cm^2/m^2. Voltage/mass ratio was 1.28. Ejection fraction was decreased (29%) with diffuse hypokinesia. Coronary angiography revealed patent coronary arteries.

Being refractory to treatment with digitalis and diuretics, we suspected the diagnosis of cardiac amyloidosis complicating multiple myeloma, and thus the patient underwent cardiac catheterization. A right ventricular endomyocardial biopsy specimen was obtained. Amyloid deposit was identified on light microscopy by positive staining reaction with Congo red.

DISCUSSION

Cardiac amyloidosis is a frequent and well-known complication of multiple myeloma. Clinical heart disease is present in one-third of patients with primary amyloidosis (AL) associated with a plasma cell dyscrasia . It is more common in men than in women, and is rare before the age of 30 years . AL cardiac amyloidosis due to multiple myeloma is often accompanied with other organ dysfunctions, such as, heavy proteinuria and findings of malabsorption. However, heart involvement represents the worst prognostic indicator with a median survival from diagnosis of 1year, falling to 0.75 years with the onset of heart failure (1,2).

Cardiac amyloidosis mostly presents as restrictive cardiomyopathy(1,3). Fatigue and weakness are the commonest presenting symptoms reported in the literature in patients with AL amyloidosis with heart involvement. Another common presentation is congestive heart failure due to systolic dysfunction, and patients commonly complain of exertional dyspnea and orthopnea (1,2,4). Schattner et al (5), on the other hand, demonstrated a case of multiple myeloma presenting as a diastolic heart failure without evidence of amyloidosis. In that case endomyocardial biopsy showed myocardial infiltration by intercellular fibrillar tissue which was not amyloid . Our patient presented with fatigue and progressive exertional dyspnea that fits well with the findings reported in the literature. Other modes of presentation are as orthostatic hypotension occurring in about 10 % of cases which is possibly due to amyloid infiltration of the autonomic nervous system or of blood vessels , as conduction disturbances ,and as pericardial effusion which may cause cardiac tamponade (1,6).

The documentation of cardiac involvement is important prognostically among patients with primary systemic amyloidosis because in 30 to 40 % of these patients the leading cause of death is congestive heart failure and arrythmia (1,2,7). Reisinger et al (8) determined certain electrophysiologic abnormalities in patients with cardiac involvement due to AL amyloidosis, and demonstrated infra-His (HV) conduction prolongation in 92% of patients. They also noted that patients with cardiac amyloidosis were prone to sudden death due to lethal ventricular arrhytmias or electromechanical dissociation. Among 42 patients with biopsy-proved amyloidosis followed by Brandt et al (9), 60% of primary amyloidosis patients and 40% of multiple myeloma group developed signs of congestive heart failure. They also observed that treatment of heart failure was complicated by increased sensitivity to digitalis and calcium channel blockers.

The diagnosis of cardiac amyloidosis has, in general, been deduced from the clinical course of the patient with biopsy-proved amyloidosis elsewhere in the body, or is made at postmortem examination (1,2,4,10). However, in the presence of a definable cause of amyloidosis such as multiple myeloma, familial Mediterranean fever and chronic inflammatory diseases, the index of suspicion of cardiac involvement is very high.The development of intractable congestive heart failure, or atrial fibrillation in the absence of significant coronary atherosclerosis or valvular disease, and orthostatic hypotension should prompt the diagnosis of amyloid heart in these patients (1). Our patient fits this clinical profile closely.

Recognition of cardiac amyloidosis is difficult because of its variable presentation. It is particularly important to distinguish patients with surgically correctable lesions - for example, constrictive pericarditis, valvular disease - from those with cardiac amyloid in whom

cardiac surgery is of no value and may result in a fatal outcome (7). For these reasons, there have been numerous attempts to identify reliable indicators of cardiac involvement.

Electrocardiographic abnormalities frequently noted in cardiac amyloidosis are low voltage QRS (< 0.5 mV or the sum of S in V_1 and R in V_5 or V_6<23), bundle-branch blocks, nonspecific ST-T changes, and poor progression of the R waves across precordial derivations. (11,12) The literature range of low-voltage electrocardiographic pattern in patients with primary cardiac amyloidosis is between 54% and 67% (1,2,4,13). Decreased progression of R waves across precordial derivations simulating old anterior myocardial infarction seen in our patient who has patent coronary arteries is also a characteristic feature of an amyloid heart (14).

Although electrocardiographic abnormalities are commonly present, these are nonspecific. Echocardiography has been widely used to evaluate the presence and extent of cardiac involvement, and it is the most useful diagnostic procedure. Typical features include thickened ventricular walls, reduced global left ventricular function, symmetric thickening of interventricular septum and posterior wall of left ventricle, atrial enlargement, pericardial effusion , and "granular" appearence of the myocardium (1,2,4,13,15,16). Garcia et al (17) showed that echocardiography can confirm the progression of amyloid infiltration of the heart within a relatively short period. Serial echocardiographic changes may detect progressive amyloid infiltration, and be helpful in the assessment of patients with clinical deterioration. Their observations also indicated that mild to moderate amyloid infiltration of the heart may not be detected by clinical or electrocardiographic evaluations.This early asymptomatic phase may be detected by two-dimensional echocardiography as a mild to moderate increase in left ventricular or right ventricular wall thickness as the sole abnormality. With increasing grades of interstitial amyloid, there is a trend toward an increase in thickness of the ventricular septum and a decrease in ejection fraction. From this standpoint, recognized findings in our patient indicate a more advanced stage of amyloid heart.

The ratio of electrocardiographically demonstrated voltage to mass indicated as left ventricular cross-sectional area measured from echocardiographically demonstrated left ventricular thickness is characteristic of myocardial amyloid infiltration (11,12). Falk et al (11) showed that a ratio of less than 1.5 was 82% sensitive and 83% specific for cardiac amyloid, and useful in distinguishing patients with left ventricular hypertrophy due to causes other than amyloidosis. Mean voltage/mass ratio for patients with amyloid was 1.01±0.45 compared to 1.96±0.55 for control subjects in their study (11). The case presented had a ratio of 1.28, and met the criteria described for cardiac amyloidosis.

Doppler ultrasonography and radionuclide ventriculography demonstrate systolic and diastolic dysfunctions, and predict the outcome by estimating the extent of cardiac involvement (1,15,16). Tei C et al (15) determined the clinical value of a Doppler-derived index, defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time, measured from left ventricular outflow and mitral inflow Doppler velocity profiles during echocardiography. They found that isovolumetric contraction and relaxation times were prolonged and ejection time was shortened in patients with cardiac amyloidosis.

Although echocardiography is extremely helpful in differentiation of cardiac amyloidosis from constrictive pericarditis, and/or hypertrophic obstructive cardiomyopathy, definitive diagnosis requires histologic confirmation. In patients with clinically unexplained cardiac disease and who have echocardiograms showing the typical features of cardiac amyloidosis but without demonstrated tissue-proved amyloidosis, transvenous endomyocardial biopsy is both easy to perform and safe. Biopsy specimens can be stained by Congo red, thioflavine T, and the sulfated alcian blue to demonstrate amyloid. Amyloid can be identified as a characteristic fibrillary protein deposited as pericellular, vascular, nodular and mixed patterns (1,10,18,19).

Our patient who had clinical, electrocardiographic,and echocardiographic features suggestive of amyloid cardiomyopathy, underwent cardiac catheterization. Transvenous right endomyocardial biopsy demonstrated amyloid material with Congo red stain.

The case presented provides an example of antemortem diagnosis of cardiac amyloidosis due to multiple myeloma and is presented to elucidate clinical, laboratory findings of cardiac amyloidosis and to demonstrate the reliability and safety of transvenous endomyocardial biopsy in definitive diagnosis.

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