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Cardiac Amyloidosis Diagnosed by Endomyocardial Biopsy

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A 56-year-old male patient who had a history of syncopal attack was diagnosed as having cardiac amyloidosis. His ECG finding showed a pattern of inferior and anteroseptal wall infarction with Wenckebach AV block.

Echocardiographic examination revealed that the LV posterior wall and interventricular septum were markedly thickened with granular sparkling.

We demonstrated the amyloid deposit in the myocardium by endomyocardial biopsy.

Pathology showed a green white birefringence by polarizing illumination and amyloid fibril in electron microscopic study.

Key Words: *Amyloid deposit, Endomyocardial biopsy*

INTRODUCTION

Amyloidosis is a rare disease that results from the deposition of unique twisted β-pleated sheet fibrils formed from various proteins in one or several organs. This deposition may be local or systemic, and frequently involved sites are kidneys, liver, heart, GI tract, skin, joints, peripheral nerves and muscle. The clinical diagnosis of amyloidosis is very difficult because of its variable manifestation. In Korea, several cases of amyloidosis of skin and kidneys have been reported, and there have been 2 case reports of systemic amyloidosis in which heart involvement was suggested on echocardiographic grounds. But a case of cardiac amyloidosis diagnosed by demonstration of the characteristic deposits in the myocardium has never been reported in Korea. The following is a report of a case of cardiac amyloidosis in which the diagnosis was made by endomyocardial biopsy.

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CASE REPORT

The Patient was a 56-year-old man who presented with the chief complaint of loss of consciousness.

This patient felt dyspneic on exertion and dizzy about 4 and 8 months before admission. On the day of admission, while climbing stairs, he again felt dyspneic and dizzy and, after a while, lost consciousness for about 20 to 30 minutes.

The patient's past medical history indicated that he had suffered from left facial palsy for the past 6 years and paraparesis of his right arm for 1 year before admission. Both of these gradually improved after the attacks. He was a heavy smoker (50 to 60 pack·year).

His family history revealed that his parents died suddenly and the cause of deaths was not known, and his younger brother died of hypertension and cerebrovascular accident at the age of 46.

On physical examination at admission his blood pressure was 110/80 mmHg, pulse rate 75 beats/min, and body temperature 36.3°C. Jugular venous pressure was elevated to 10 cm above the sternal angle. A grade II systolic murmur with irregular heart beat was heard on auscultation. The lung sounds were clear. Firm liver was palpable 3

cm blow the right costal margin. Otherwise the physical findings were not remarkable.

Laboratory tests for blood chemistry, showed that total protein was 6.5 mg/dl, albumin 3.3 mg/dl, BUN 15 mg/dl and creatinine 1.0 mg/dl. GOT was 15 IU/L, GPT 14 IU/L, and serum alkaline phosphatase 40 IU/L, CK was 58 IU/L and LDH 262 IU/L. In a serum PEP study, α-globulin fraction was elevated and the serum IEP finding was normal (Table 1). Urinalysis showed normal findings except (++)- proteinuria and the urine Benes-Jones protein was absent. In a 24-hour urine collection, the excreted protein amount was 829mg/dl and urine PEP showed elevated albumin- and β-fractions (Table 1). The chest X-ray film showed a slightly enlarged cardiac silhouette and the C/T ratio was 0.6, and there was no pulmonary congestion.

ECG findings showed the pattern of inferior and anteroseptal infarction, first degree AV block and type I second degree AV block (Fig. 1).

The echocardiogram revealed a thickened IVS and LV posterior wall (Fig. 2). Both LV dimension and ejection fraction were within normal limits.

Cardiac catheterization was performed (Table 2). Pulmonary wedge pressure and LVEDP were elevated.

The left ventriculogram showed a thickened LV wall with normal wall motion (Fig. 3).

In electrophysiologic study, the corrected SNRT was increased to 1000 msec and AH block was developed at the cycle length of 750 msec. VT or SVT was not induced by rapid atrial or ventricular pacing.

An endomyocardial bioptome was inserted via the right femoral vein, and a biopsy was done at the RV apex and interventricular septum.

Pathologic examination of the myocardial tissue showed endocardial and myocardial infiltration of an amyloid substance. A H&E stained section faintly revealed an eosinophilic, homogeneous amyloid substance at the subendocardium, interstitial space of the myocardium and the walls of blood vessels. The amyloid substance was negatively stained by PAS stain and was a homogeneous violet-blue color by Masson's trichrome stain. Congo red stain revealed a light brown color by day light illumination, and green white birefringince by polarizing illumination (Fig. 4). Amyloid deposits in the subendocardial, interestitial space and vessel walls showed a coarse lattice-like arrangement. Electron microscopy revealed nonbranching, homogeneously slender and long amyloid fibrils arranged in random directions, and scattered fine particular substances (Fig. 5). The amyloid mass abutted on the sarcolemma and basement membranes of the endocardial cells and capillary endothelial cells. The width of fibrils measured by high magnification ranged from 7.1 to 10.7 nm.

Isolated particular substances were ring or doughnut shaped, however, pentagonality was not conspicuous. The particles (p-component) measured

Table 1. Paper Electrophoresis of Serum and Urine

Fraction	Normal (serum) (%)	Serum (%)	Urine (%)
Albumin	50-60	51.1	57.5
a1-globulin	4.2-7.2	4.2	1.7
a2-globulin	6.8-12	14.1	1.7
B-globulin	9.3-15	14.4	7.0
r-globulin	13-23	16.2	2.1

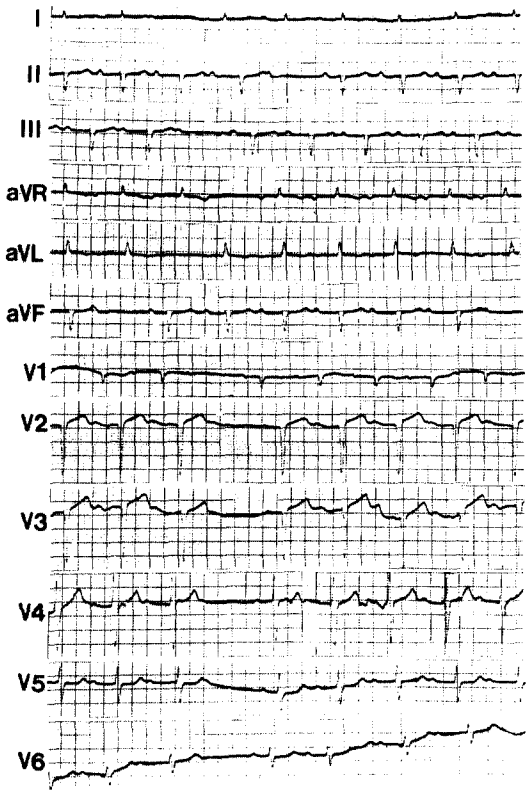

Fig. 1. *ECG in a patient with cardiac amyloidosis showing the pattern of inferior and anteroseptal infarction, and 1st degree and type I 2nd degree AV block.*

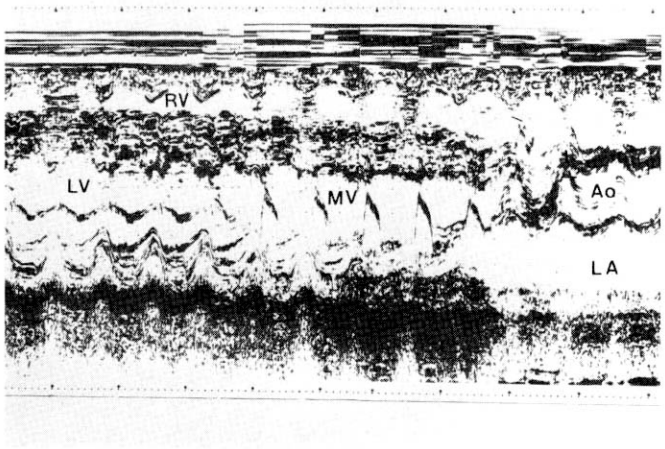

Fig. 2. *Echocardiogram in a patient with cardiac amyloidosis showing a thickened IVS and LV posterior Wall. IVS thickness was measured as 20mm in systole and 15mm in distole, and LV posterior wall thickness 21mm in systole and 13mm in diastole. LV dimension was measured 29mm in systole and 48mm in diastole. Ejection fraction was 78%. LV: left ventricle, RV: right ventricle, LA: left atrium, Ao: aorta, MV: mitral valve.*

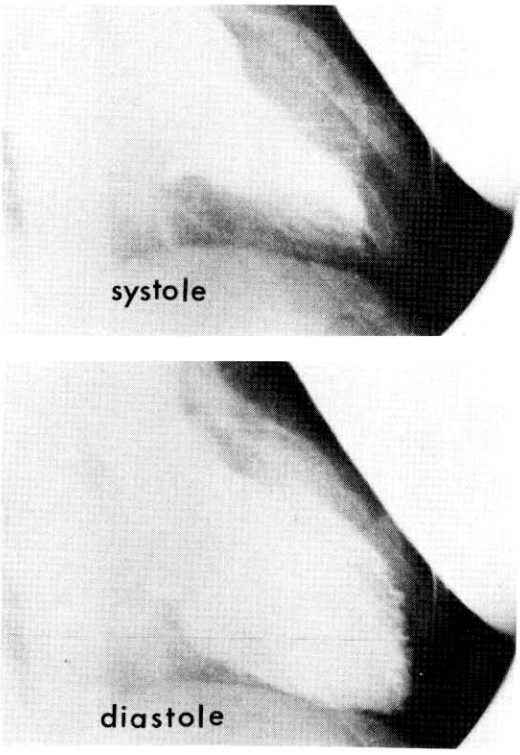

Fig. 3. *Left ventriculogram of cadiac amyloidosis shows hypertrophied LV wall with normal wall motion.*

Table 2. Cardiac Catheterization Findings

Site	Pressure (s/d/m) (mmHg)	02 Saturation (%)
PW	a=13/v=22/m=13	
PA	30/10/18	68
RV	28/ 0/ 7 (ED)	
RA	a=7/v=9/m=6	
LV	90/ 0/13 (ED)	
Ao	95/55/75	90

PW=pulmonary wedge, PA=pulmonary artery, RV=right ventricle, RA=right atrium, LV=left ventricle, Ao=aorta, ED=end diastolic.

10 nm in external diameter.

DISCUSSION

Cardiac amyloidosis should be considered in any elderly patient with chronic heart failure of unknown cause. Cardiac manifestations of amyloidosis consist of heart failure, arrhythmia, syncope and angina or infarct. Of these, heart failure is the most common finding. Amyloid is deposited in the myocardium which then becomes so stiff and noncompliant as to cause dysfunction. Syncope is due to sudden AV block and standstill, marked sinus bradycardia, sud-

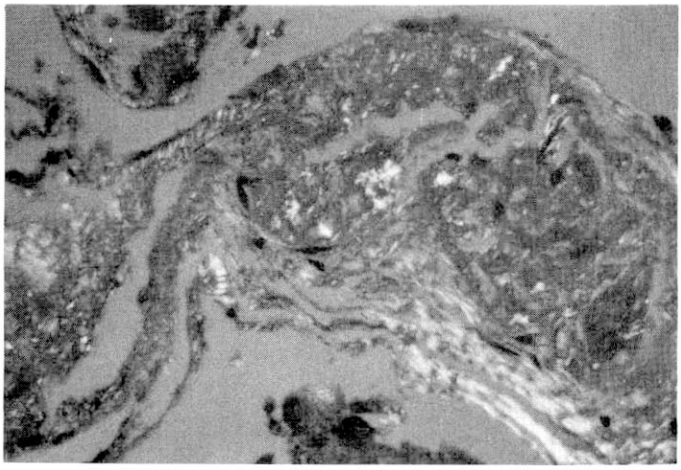

Fig. 4. *The media of intramyocardial vessels are markedly thickned due to amyloid infiltration. Greenwhite birefringence is demonstrated at the amyloid deposit. Bright yellow refractile substances are collageneous fibers. (Brirefringence after Congo red stain, x400).*

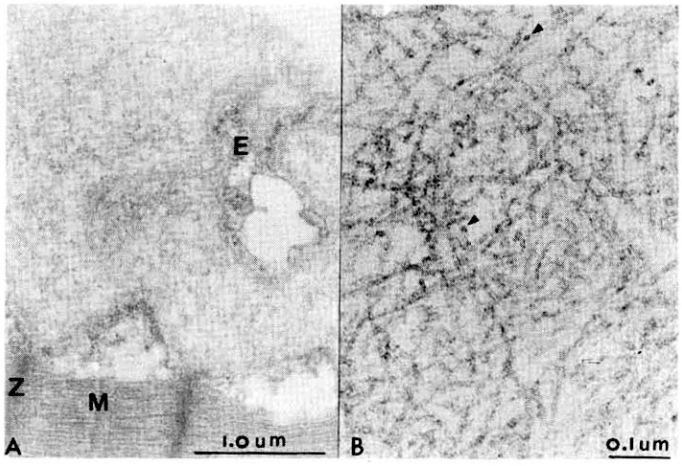

Fig. 5. *A; Subendocardial mass of amyloid fibrils is seen and endocardial cells (E) are entrapped in the amyloid mass. Myocardial fiber is seen in normal contraction. Prominent Z-line (Z) and less prominent M-line (M) are seen and the sarcolemma shows normal undulation with regular attachment to the Z-line (x22,400). B; high magnification of amyloid fibrils. Irregular nonbranching fibrils and fine particles (arrow head) are scattered (x112,000).*

den sinus arrest without efficient escape rhythm and vagal reflex from intracoronary neuroreceptor or sustained VT. The sinus node can be destructed by amyloid deposit,[1] and also its deposition in the cardiac nerve plexus may cause these conduction disturbances.

The mechanism of development of angina or infarct is usually due to intramural coronary narrowing by amyloid deposit without significant coronary atherosclerosis.[2] The involvement of epicardial coronary arteries is only rarely observed.

The myocardium is more commonly involved

than the epicardium or pericardium, and the ventricular septum is more commonly affected than the LV posterior wall.

Both atria and ventricles may be affected diffusey or focally.[3] The valves may be involved as well, and become thick and incompetent.[1-4]

The most common ECG finding is low voltage. There is an inverse relation between voltage and cardiac mass. In 1982, Carroll described SV1 + RV6 or RV5 as a low voltage index in amyloid patients and reported that it was 14.6 + 4.8mm (normal range 15-35mm) in his patients.[5] But in 1984, Cueto-Garcia reported that the sum of QRS deflection in 12 leads was more sensitive than $SV_1 + RV_6$ or RV_5.

In our case, SV1 + RV6 was 7.5mm and the sum of QRS deflection in 12 leads was 79mm. Another frequent ECG finding in cardiac amyloidosis is poor-R progression or the patterns of old myocardial infarction.[7] The ECG finding in our patient also suggested old infarctions of inferior and anteroseptal areas.

Conduction disturbances of amyloidosis include LBBB, RBBB, LAH, 1st-, 2nd- or 3rd degree AV block, atrial flutter, atrial fibrillation, or junctional rhythm.

Its possible mechanisms are 1) direct infiltration of amyloid in the conduction system, 2) ischemia, fibrosis and atrophy of the conduction system caused by the involvement of feeding vessels, 3) idiopathic atrophy of the AV conduction network and 4) neurologic influence because of the deposition in the intracardiac nerve plexus.[8]

M-mode echocardiographic features include 1) normal or slightly decreased LV dimension, 2) increased thickness of IVS, LV posterior wall and RV anterior wall, 3) left atrial enlargement, and 4) occassionally pericardial diffusion.

Two-dimensional echocardiography can provide additional information, sich as thickened papillary muscle or valves, and "granular sparkling" of the thickened ventricular wall which is characteristic finding of amyloidosis.[3-6] In our case, we could observe the thickened LV wall and IVS with granular sparkling. There have been many reports on the evaluation of LV mass or function by echocardiography,[3-5] but we omit the discussion here.

Cardiac catheterization findings include the elevation and equalization of RA and RV pressure in diastole, and the early diastolic dip and plateau pattern that simulate the pattern in constrictive pericarditis. End diastolic pressure of LV can be also elevated.[3,5,9,10]

LV angiogram in cardiac amyloidosis shows hypokinetic wall motion with a normal or slightly decreased LV cavity.

In a myocardial scan with 99m-Tc pyprophosphate, we can observe diffuse myocardial uptake that is of equal or greater intensity than that of the rib.[11] Its mechanism is unknown, but may be due to the increased calcium concentration in amyloid infiltrated tissue.

Amyloidosis can simulate noncalcific constrictive pericarditis and hypertrophic cardiomyopathy, and differential diagnosis with these conditions is important.

Besides these, differential diagnosis is also needed with pericardial effusion, coronary artery disease, and valvular heart disease.[5,9,10,12] Frankly, we could not initially suspect amyloidosis in our case, our first impression was hypertrophic cardiomyopathy, and to confirm the diagnosis, endomyocardial biopsy was done. For diagnosis of amyloidosis limited to the heart, endomyocardial biopsy can be done relatively easily and safely. There have been several reports of cardiac ayloidosis diagnosed by endomyocardial biopsy.[13,14]

Pathologic diagnosis of cardiac amyloidosis can be made by routine histological examination of the endomyocardial biopsy. Green birefringence on polarization after Congo red stain and fluorescence after phorwhite BBU stain are reported to be sensitive and specific.[15] Transmission electron microscopic examination and X-ray crystallographic analysis have been used to explain the physicochemical properties of amyloids. Major immunochemical types of amyloid substance, based on the peroxidase-antiperoxidase (PAP) method, are amyloid A(AA), A-kappa, A-lambda, and amyloid of familial polyneuropathy (AF). Most of the causes of cardiac amyloidosis are reported to be primary amyloidosis of A-lambda type.[14-17]

Amyloid patients are especially sensitive to digitalis, so the main treatment of these patients is rest, salt restriction, and diuretics. Digitalis may be used with extreme caution while monitoring the drug concentration in intractable cases with the above management. We have been treating our patient as above, and did not use digitalis. The response of this management is relatively good.

However, the prognosis of cardiac amyloidosis is very poor. The disease progresses to death despite meticuous treatment.

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