Case Report

Cardiac Involvement in Four Patients with Immunoglobulin Light-Chain Systemic Amyloidosis

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Abstract: In immunoglobulin light-chain (L) amyloidosis the cause of death is most commonly due to cardiac involvement. Cardiac amyloidosis is frequently diagnosed by postmortem examination. There are many reports of diagnoses of cardiac amyloidosis established by autopsy of cardiac tissue. We report four patients whom we could diagnose as having cardiac amyloidosis by echocardiogram and electrocardiogram. They were referred to our hospital because of congestive heart failure. All patients had thickened ventricular walls, increased myocardial echogenicity, and normal ventricular chamber size on echocardiogram. Our 4 cases showed low voltage and pseudoinfarction pattern on electrocardiogram. Biopsies from the myocardium, rectal mucosa and/or abdominal wall revealed extracellular deposition of amyloid in all cases. Two cases were associated with myeloma and the other two cases were primary amyloidosis. Cardiac involvement from amyloid light-chain (AL) amyloidosis is rapidly fatal. Unfortunately, the diagnosis of AL amyloidosis is often delayed. AL amyloidosis should be considered as a cause of congestive heart failure and requires further investigation.

Key words: Cardiac amyloidosis, Wall thickening, Granular sparkling, Low QRS amplitude

Introduction

Primary immunoglobulin light-chain (L) amyloidosis is a disorder of the protein metabolism characterized by extracellular deposition of monoclonal light-chain protein. Amyloid light-chain (AL) amyloidosis is a relatively uncommon disease. It is estimated that there are 1000 to 2500 new cases of AL amyloidosis in the United State each year1,2). Cardiac involvement in AL amyloidosis is a frequent findings. One third to one half of patients with AL amyloidosis have clinically-significant cardiac involvement3). In AL amyloidosis the cause of death is most commonly due to cardiac involvement3,4). The median survival from the onset of cardiac symptoms to death is less than 6 months5,6). Unfortunately, the diagnosis of AL amyloidosis is often delayed. Cardiac amyloidosis is frequently diagnosed by postmortem examination. There are many reports of diagnoses of cardiac amyloidosis established by autopsy of cardiac tissue. However, a significant number of patients with cardiac amyloidosis probably go undiagnosed. We suspected cardiac amyloidosis in 4 patients who developed heart failure, because they demonstrated wall thickening on echocardiogram and low amplitude of QRS complex on electrocardiogram. We report four patients whom we could diagnose as having cardiac amyloidosis by echocardiogram and electrocardiogram.
CASE 1

A 64-year-old Japanese man was referred to our hospital because of general fatigue, dyspnea on effort, and pretibial edema in April 1997. He was a thin man (height 160 cm, weight 55 kg). Blood pressure was 102/64 mmHg; the conjunctivas were anemic, the jugular vein was dilated, the face was edematous, there was a systolic murmur on auscultation of apex, the liver was palpable, and the pretibia was edematous. Standard 12-lead electrocardiogram at admission showed a sinus rhythm, low amplitude of QRS complex in limb leads, poor R wave progression in precordial leads, T wave inversion in inferior leads, and prolongation of the QT interval (Fig. 1). When the sum of the QRS amplitude in leads I, II and III was 15 mm or less, we defined it as a low voltage electrocardiogram. A chest roentgenogram revealed bilateral pleural effusion and interstitial edema (Fig. 2). Aspirated pleural fluid was a transudate. An echocardiogram showed left ventricular wall thickening (interventricular septal thickness was 24 mm and posterior wall thickness was 19 mm), increased echogenicity (granular

Fig. 1. Electrocardiographic findings in case 1. Standard 12-lead electrocardiogram showed sinus rhythm, low amplitude of QRS complex, poor R wave progression in precordial leads.

Fig. 2. Chest roentgenogram in case 1. Chest roentgenogram showed bilateral pleural effusion and interstitial edema.
sparkling), and moderate tricuspid regurgitation (Fig. 3). The left ventricular systolic function was normal. Blood laboratory data showed anemia, an elevated serum transaminase and decreased serum albumin. Serum electrophoresis detected a monoclonal gammopathy, and immunoelectrophoresis revealed a free lambda light chain. Urinary Bence-Jones protein was not detected in the urine. A bone marrow biopsy specimen contained 6.4% of plasma cells. Right cardiac catheterization was compatible with a restrictive cardiomyopathy, and showed dip-and-plateau configuration. Holter electrocardiogram showed sinoatrial block. The diagnosis of amyloidosis was made by a right ventricular endomyocardial biopsy and a rectal biopsy.

![Fig. 3. Echocardiographic findings in case 1.](image)

Echocardiogram showed left ventricular thickening and increased echogenicity.

![Fig. 4. 1) Light micrograph of the biopsy specimen (amyloid stain, × 400). Right ventricle endomyocardial biopsy specimens stained positive for amyloid.](image)

![Fig. 4. 2) Macroscopic findings of the heart. The heart was thickened, and weighed 510 g.](image)
Right ventricular endomyocardial biopsy specimens stained positive for amyloid (Amyloid stain, × 400) (Fig. 4-1). Amyloid was present between the myocardial fibers. Although therapy was initiated with a 6-day course of melphalan (8 mg) and prednisolone (60 mg) every 4 weeks, the patient died of heart failure in November 1997. At autopsy, the heart was thickened, and weighed 510 g (Fig. 4-2). Amyloid was present in the 12 mm internal layer of the heart.

**CASE 2**

A 55-year-old Japanese man was admitted to our hospital because of severe anterior chest pain in May 1989. An electrocardiogram at admission showed a QS pattern from leads V1 to V3. However, an echocardiogram showed no regional wall motion abnormality, but showed thickening of the left ventricular wall. Immunoelectrophoresis revealed serum monoclonal M protein (IgG) with urinary Bence-Jones protein. The bone marrow contained 21% atypical plasma cells, and a rectal biopsy demonstrated an amyloid deposit. Electrocardiogram findings revealed various arrhythmia, including first degree atrioventricular (AV) block, supraventricular and ventricular premature complexes, two types of supraventricular tachycardia with AV block, and sinus arrest. Since he complained of fainting due to sinus arrest, a VVI pacemaker was implanted. However, he died of refractory congestive heart failure. The postmortem examination confirmed cardiac amyloidosis. The heart weighed 650 g and presented a thickened ventricular wall. Amyloid deposition was found in the myocardial interstitium, including that in the periventricular region.

**CASE 3**

A 72-year-old Japanese woman was referred to our hospital because of dyspnea on effort and pretibial edema in January 1998. An electrocardiogram at admission showed sinus rhythm, low voltage QRS complex in limb leads, and poor R wave progression from V1 to V3 leads. An echocardiogram showed left ventricular wall thickening (interventricular septal thickness was 16 mm and posterior wall thickness was 16 mm), and increased echogenicity. The left ventricular systolic function was normal, and left ventricular hypertrophy was not severe compared with the other 3 patients. The diagnosis of amyloidosis was made by a rectal biopsy. Examination of bone marrow aspirate showed an increased number of plasma cells (51%) and malignant forms were noted. Immunoelectrophoresis revealed serum monoclonal M protein (IgA) with urinary Bence-Jones protein. This case was multiple myeloma associated AL amyloidosis. The cardiac amyloidosis was detected in the early stage, and her cardiac involvement was mild. She was treated with melphalan and prednisolone. The chemotherapy was effective. Nine months after initiation of therapy there seemed to be no progression in cardiac manifestations, reflected by constant echocardiographic findings as well as clinical symptoms. She is still alive, because her cardiac involvement was mild.

**CASE 4**

An 83-year-old Japanese man was referred to our hospital because of dyspnea on effort and pretibial edema in March 1997. An electrocardiogram at admission showed a sinus rhythm, low voltage QRS complex in the limb leads, and poor R wave progression in the precordial leads. An echocardiogram showed left ventricu-
lar thickening (septum was 18 mm and posterior was 20 mm), pericardial effusion, and increased echogenicity. The diagnosis of amyloidosis was made by a gastric biopsy. He showed diastolic and systolic dysfunction, and had severe congestive heart failure (NYHA Class IV). His renal function was impaired. He could not be treated with chemotherapy because of his poor general condition. Only treatment for congestive heart failure was given, and he died of heart failure 3 months later.

The clinical findings of the present cases are shown in Table 1. All patients showed symptoms of congestive heart failure. They showed low voltage electrocardiogram, but the myocardial wall was thickened. We suspected cardiac amyloidosis, and AL amyloidosis was diagnosed by biopsy in all cases. Bone marrow biopsies revealed that 2 cases were multiple myeloma and the others were primary amyloidosis. Three patients were treated with melphalan and prednisolone, while the fourth could not be treated with chemotherapy because of his poor general condition. Three patients died of heart failure and patient 3 is still alive.

### Table 1. Clinical characteristic of four patients.

| Case | Age (years) | Gender | Height (cm) | Body weight (Kg) | Chief complaint | Blood pressure (mmHg) | Pulse rate (bpm) | Orthostatic hypotension | Serum creatinine (mg/dl) | Hemoglobin (g/dl) | Alkaline phosphatase (U/l) | Serum protein (mg/dl) | M-protein IgG (mg) | Bence-Jones protein in urine | Biopsy | Cardiac amyloidosis % | Cardio thoracic ratio (%) | Electrocardiogram | Echocardiogram (mm) | Ejection fraction (%) | Pulmonary hypertension | Doppler E/A | Deceleration time (msec) | Holter ECG | Chemotherapy | Clinical course | E/A = early / late diastolic mitral inflow peak velocity |
|------|-------------|--------|-------------|-----------------|-----------------|---------------------|------------------|------------------------|-------------------------|-----------------|------------------------|------------------|------------------|------------------------|--------|------------------|------------------|-------------------|-------------------|-------------------|-----------------|-----------------|------------------|-------------------|
| 1    | 64          | man    | 160         | 55              | fatigue, dyspnea, edema | 102/64             | 64               | +                      | 0.88                    | 9.3             | 536                    | 5.9              | IgG (λ)         | negative              | Myocardium, rectum | 6.4             | 50                 | low voltage | IVSth 24, PWth 19 | 68               | +                | 2.2               | 155              | SA block          | melphalan, prednisolone | died of CHF in 3 months | E/A = early / late diastolic mitral inflow peak velocity |
| 2    | 55          | man    | 157         | 51              | chest pain, dyspnea   | 116/76             | 68               | -                      | 0.6                     | 13.3            | 133                    | 7.1              | IgG (λ)         | positive              | rectum               | 56              | 56                 | low voltage | IVSth 22, PWth 21 | 79               | -                | 1.3               | 129              | S.S.S., first degree AV block | melphalan, prednisolone | died of CHF in 2 months |
| 3    | 72          | woman  | 144         | 40              | dyspnea, edema        | 114/68             | 90               | -                      | 0.47                    | 7.3             | 257                    | 5.7              | IgA (λ)         | positive              | rectum               | 70              | 70                 | low voltage | IVSth 16, PWth 16 | 68               | -                | 2.0               | 144              | melphalan, prednisolone | alive             | died of CHF in 3 months |
| 4    | 83          | man    | 154         | 41              | dyspnea, edema        | 88/60              | 84               | -                      | 1.47                    | 10.8            | 188                    | 7.1              | IgG (λ)         | positive              | stomach, duodenum    | 62              | 62                 | low voltage | IVSth 18, PWth 20 | 38               | +                | 1.8               | 115              | melphalan, prednisolone | died of CHF in 3 months |
DISCUSSION

It is now clear that there are multiple clinically and biochemically different forms of amyloid. The following classification is clinically the most useful: (1) primary [amyloid light-chain (AL) type] amyloidosis (no evidence for preexisting or coexisting disease), (2) amyloid associated with multiple myeloma (AL type), (3) secondary or reactive [amyloid A protein (AA) type] amyloidosis associated with chronic infectious disease or chronic inflammatory diseases, (4) heredofamilial amyloidosis, (5) local amyloidosis, (6) amyloidosis associated with aging, and (7) amyloid associated with long-term hemodialysis. The proportion of the total number of cases that represents multiple myeloma or primary amyloid is difficult to judge, since marrow plasmacytosis may be significant in both and the diagnostic distinctions between the primary disease and myeloma are blurred. In our four cases of AL amyloidosis, two cases were primary amyloidosis, and two were amyloid associated with multiple myeloma.

In AL amyloid heart disease, the echocardiogram is frequently diagnostic. Echocardiographic features of cardiac amyloidosis are thickened ventricular walls, atrial septum and valve leaflets, increased myocardial echogenicity, normal ventricular chamber size, atrial dilatation, and initially normal systolic function. Our four cases were compatible with these findings, and showed diastolic dysfunction. However, patient 4 showed systolic dysfunction, and had severe congestive heart failure. Heart failure and survival in AL amyloidosis is correlated with the degree of myocardial thickening seen on echocardiogram. The Doppler-derived index of combined systolic and diastolic myocardial performance correlates with global cardiac dysfunction and is useful predictor of clinical outcome in patients with cardiac amyloidosis. However these findings are not sufficient for diagnosis of cardiac amyloidosis.

Electrocardiographic features of cardiac amyloidosis are a low voltage, pseudoinfarction pattern. Our four cases showed low voltage and pseudoinfarction pattern. Some patients showed conduction system disease and arrhythmia. In our cases, patient 1 showed sinoatrial block, and patient 2 showed first degree atrioventricular block and sick sinus syndrome with supraventricular tachyarhythmias.

AL amyloidosis is progressive systemic disease with a far worse prognosis than the AA type. Cardiac involvement from AL amyloidosis is rapidly fatal. Unfortunately, the diagnosis of AL amyloidosis is often delayed. If diagnosis of cardiac amyloidosis is delayed, the patient may not be treatable with chemotherapy because of poor general condition. Treatment of AL amyloidosis has met with limited success, essentially because of the relative resistance of the amyloidogenic clone to conventional chemotherapy, and because diagnosis is frequently so late that patients already show advanced disease with resultant irreversible compromise of vital organ function. Thus an early diagnosis is necessary. The clinical features of amyloidosis have been reported by many investigators, but diagnosis of amyloidosis was suggested by the occurrence of classical signs of amyloidosis in their reports. We suspected four cases as having cardiac amyloidosis using electrocardiogram and echocardiogram. Despite the increased left ventricular wall thickness, electrocardiogram showed low voltage, and this should arouse suspicion of amyloidosis. AL amyloidosis should be considered as a cause of congestive heart failure and requires further investigation, including rectal biopsy, colonic biopsy, and myocardial biopsy with bone marrow aspiration. Early diagnosis
and treatment before apparent congestive heart failure might improve the prognosis of patients with AL amyloidosis. Electrocardiogram and echocardiogram could be useful tools to estimate the cardiac involvement in AL amyloidosis. Early diagnosis is of great importance in AL amyloidosis.

REFERENCES