

Immunoglobulin Light-chain (AL) Amyloidosis with Myasthenic Symptoms and Echocardiographic Features of Dilated Cardiomyopathy

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Abstract

Myasthenic symptoms and the echocardiographic findings of dilated cardiomyopathy are very rare in primary AL amyloidosis. We report a 59-year-old man with dyspnea on effort and weakness after exercise. His electrocardiogram showed ischemic heart disease and echocardiography indicated dilated cardiomyopathy. Muscle biopsy revealed amyloidosis with deposits of lambda light chain-derived amyloid within the vessel wall. Treatment with PGE1 resulted in improvement of the myasthenic symptoms. This patient indicates that myasthenic symptoms and dilated cardiomyopathy would be a unique syndrome associated with systemic AL amyloidosis involving mainly the small vessels, i.e., AL amyloid angiopathy, in the skeletal muscles and myocardium vessels.

Key words: amyloidosis, dilated cardiomyopathy, myasthenia

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Introduction

Myasthenia like symptoms, such as orbital, jaw, bulbar, and limb claudication without pain, are very rare in primary systemic AL amyloidosis. Cardiac involvement in AL amyloidosis is a frequent finding, and has characteristic appearances on two-dimensional echocardiography; it is the archetypal example of a restrictive cardiomyopathy (1, 2). It is usually manifested grossly by nondilated ventricles with increased ventricular wall thickness (3).

Here, we describe a patient with AL amyloidosis, primarily of the vascular type, characterized by myasthenic weakness and dilated cardiomyopathy.

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Case Report

A 59-year-old Japanese man was admitted to our hospital

complaining of dyspnea on effort and weakness after exercise in November 1998. Exercise induced chest discomfort and shortness of breath, and easy fatigability of both the upper and lower extremities had appeared 6 months before admission. Later, bilateral carpal tunnel syndrome developed. One month before admission, bilateral ptosis, jaw fatigue on chewing, and swallowing disturbance in later phase of meals appeared.

He was 170 cm tall and weighted 69 kg. Blood pressure was 120/68 mmHg, pulse rate was 56 bpm with a regular rhythm, the palpebral conjunctivas were slightly anemic, the jugular vein was not dilated, there was systolic ejection murmur at cardiac apex on auscultation. The carotid and femoral pulses were normal without bruit. There was no palpable cervical, axillary, or femoral lymphadenopathy. The abdomen was soft and no tender, with normal bowel sounds. The liver edge was palpable one finger breadth under the right costal edge without tenderness. Rectal examination was unremarkable. There were no other cutaneous lesions, glosomegaly or pseudohypertrophy of muscles. In neurological examination, ptosis, a symmetric moderate reduction of

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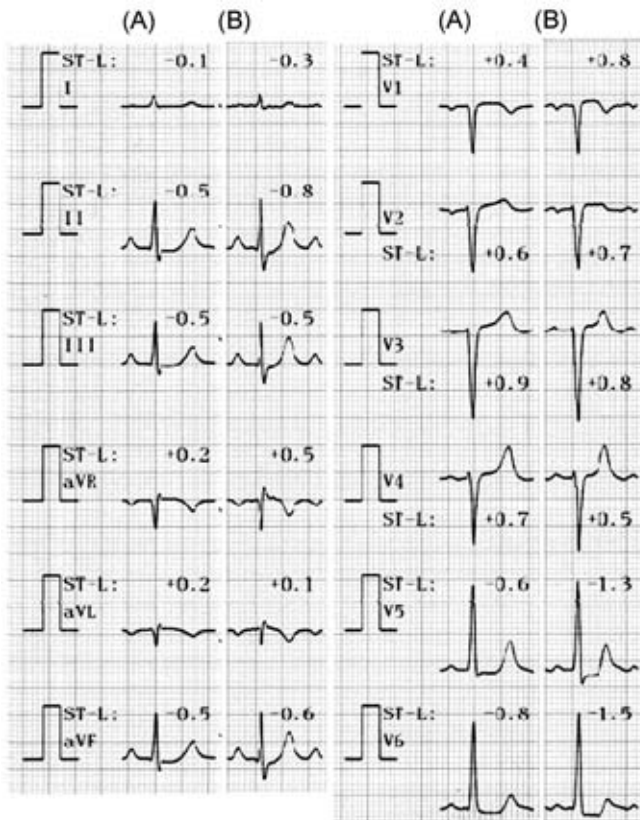


Figure 1. Treadmill exercise ECG. (A) is ECG at rest and (B) is after exercise. The voltage was decreased. R waves were absent in leads V1 and small in V2, V3 and V4. ST-segment depressions were shown in both limb and precordial leads after exercise.

strength (grade 4/5 on Medical Research Council [MRC] scale) without pain was found in the muscle of orbicularis oculi, masseter, neck, and limbs on the end of repeated manual muscle strength test. Deep tendon reflexes were normal. Flexor planter reflexes were present bilaterally. Bilateral carpal tunnel syndrome with positive Tinel sign was found. In the other regions, touch, temperature, pin prick, joint position, and vibration sensation were normal.

Initial laboratory studies revealed a hyperchromic, hypercyclic anemia (hemoglobin, 10.5 g/dl). Serum haptoglobin was not detected. Serum levels of vitamin B12 and folic acid, immunocomplexes, cryoglobulins, and HbA1c were within normal limits. Guaiac stool testing was negative. The analysis of thyroid function, glucose tolerance curve, and CSF examination were normal. Urinalysis showed proteinuria. M-protein peak was detected in electrophoresis of the serum. Serum immunoglobulin levels were 961 mg/dl for IgG, 127 mg/dl for IgA, and 67 mg/dl for IgM. Immunoelectrophoresis revealed monoclonal gammopathy for IgG-lambda in the serum and Bence Jones protein of lambda-type in the urine. Cytological analysis of a bone marrow aspirate showed hypocellularity, with normal numbers and maturation of plasma cells. Anti-AChR antibody was negative and there was no waning and waxing at evoked EMG

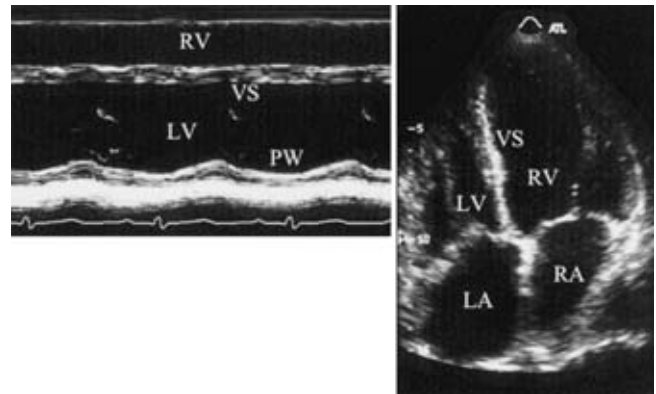


Figure 2. Echocardiograms in M-mode (left) and 2 dimensional (apical view) (right) show a dilated left ventricular cavity and normal thickness of walls and septum. LA : left atrium, LV : left ventricle, PW : posterior wall, R : right, RA : right atrium, RV : right ventricle, VS : ventricular septum.

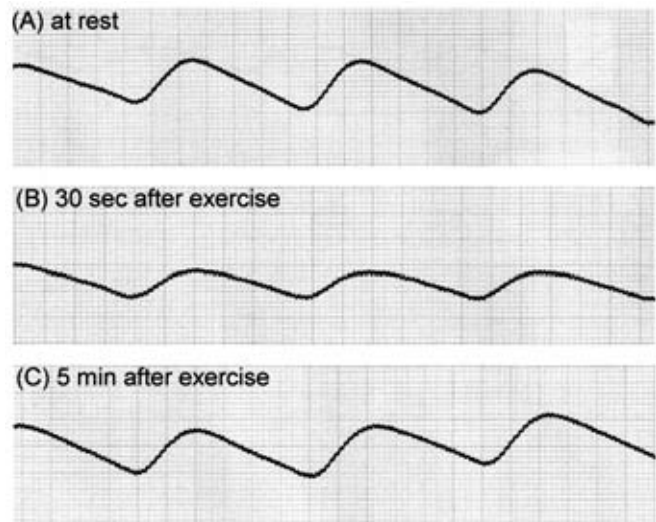


Figure 3. Toe pulse wave of the first toe of the left foot. Sensitivity was amplified 3 times. Plateau wave was shown at rest (A). The amplitude was reduced after the extension-flexion exercise of a left ankle (B).

by repetitive nerve stimulation of hand, orbicularis oris and orbicularis oculi muscle, and no response to the edrophonium test.

The resting ECG showed a normal sinus rhythm, low voltage, nonspecific ST-segment and T-wave changes. In precordial leads, the healed anteroseptal myocardial infarction pattern was found. The exercise ECG was highly abnormal, showing ST-segment depression in leads II, III, aVf, IV and V on a treadmill exercise (Fig. 1). A chest radiograph was unremarkable except for slight pleural effusion. Cardiothoracic ratio was 56% on chest X-P. An ultrasound of the abdomen revealed mild hepatomegaly. Two-dimensional echocardiography showed a moderately enlarged left atrium (36 mm, normal range: 25–40 mm) and

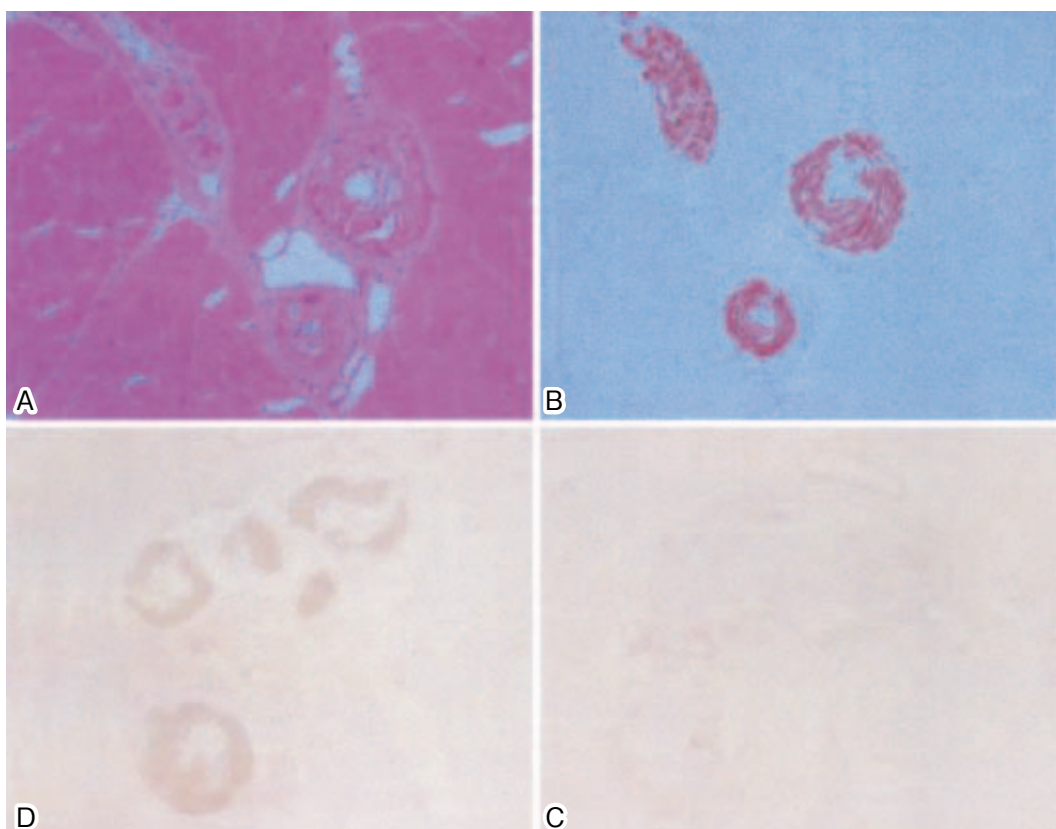


Figure 4. Biopsy of the right deltoid muscle. In HE stain (A), eosinophilic amorphous deposits are found in the blood vessels. The muscle fibers appear normal; however, Congo red stain shows massive amyloid deposition in the vessel walls, but not in the interstitial tissue (B). In immunohistochemical studies, the amyloid deposits are positive for immunoglobulin lambda light chain (C), but negative for kappa light chain (D). (A, HE stain, $\times 75$; B, Congo red stain, $\times 75$; C, immunostain with an antibody to immunoglobulin lambda light chain, $\times 75$; D, immunostain with an antibody to immunoglobulin kappa light chain, $\times 75$).

left ventricle (end diastolic diameter, 54 mm, normal range: 39–55 mm), while left ventricular wall thickness was within normal limits. Left ventricular contraction appeared to be diffusely decreased to a moderate degree (Fig. 2). Color Doppler analysis showed mitral valve regurgitation of II degree. Coronary angiography revealed a normal coronary artery. The left ventriculography showed a dilated left ventricle with a diffusely reduced ejection fraction (EF, 40%, normal range: 55–86%). A myocardial single photon emission MIBI scintigram confirmed exercise-induced myocardial ischemia and diffuse hypokinetic wall motion. On ^{123}I -MIBG myocardial scintigraphy, early and delayed heart to mediastinum uptake ratios were 1.70 and 1.52 (normal range: early >2.07 , delayed >2.18) respectively. Serdinger arteriography of the femoral artery demonstrated a remarkable delay, though the arterial tree and venous flow of bilateral legs were patent.

$^{99\text{m}}\text{Tc}$ -methylene diphosphate bone scintigram showed high spots in the bilateral shoulder and left femoral bone head. MRI of the bilateral shoulder and coxal joints showed cystic changes of bone heads of arm and femoral, though brain MRI was normal. These findings were thought to be

amyloid arthropathy (4–6). Toe pulse waves showed a plateau wave, and its amplitude was reduced after the extension-flexion exercise of the ankle (Fig. 3).

Biopsies were obtained from the right deltoid muscle (Fig. 4). Although the muscle fibers and small nerve twigs showed no abnormality, massive amyloid deposits were found in the vessel walls. There was no interstitial amyloid deposition. In an immunohistochemical study, the amyloid was positive for lambda light-chain and P-component, but not for AA, kappa light-chain or transthyretin.

The diagnosis of primary A-lambda amyloidosis was made. Therapy was initiated with prostaglandin E1 (PGE1) derivatives, resulting in improvement of claudication of the lower limbs. However, cardiac dysfunction gradually got worse and he had to be bed ridden. His general condition was too poor to start chemotherapy against AL amyloidosis, and he died suddenly in March 2001.

Discussion

The present patient with systemic AL amyloidosis demonstrated two rare manifestations, i.e., myasthenia and

ischemic dilated cardiomyopathy without LV hypertrophy. First, intermittent claudication of limbs or jaws is sometimes reported in primary amyloidosis (7), but that of other regions including orbital, neck and swallowing muscles without pain is very rare (6, 8, 9). In the present patient, the symptoms closely resembled myasthenic syndrome. Massive amyloid deposition confined to the vascular walls in the muscle, plateau wave, and slow-flow phenomenon in the angiogram indicate that amyloid angiopathy in small arteries would cause the reduction of microcirculation in the skeletal muscles, leading to intermittent claudication without muscle pain and hypertrophy resembling myasthenic symptoms. This type of skeletal muscle involvement in AL amyloidosis is quite different from amyloid myopathy characterized by massive interstitial amyloid deposition with pseudo-hypertrophy of the muscles (10, 11).

Second, echocardiographic pattern in the present patient showed diffuse hypokinesis of wall motion with normal wall thickness and LV dilatation. The features of echocardiography and coronary angiography indicated ischemic dilated cardiomyopathy. In most cases of cardiac amyloidosis, echocardiographic features include thickened ventricular walls and normal ventricular size resembling hypertrophic cardiomyopathy (2). In a necropsy study of 54 patients with cardiac amyloidosis, it is reported that features of cardiac amyloidosis were heart weight gain and enlarged heart wall thickness (3). These differences in cardiac involvement would depend upon the type and extent of amyloid deposition in the heart. Although amyloid deposition is found with both the interstitial and vascular, when the interstitial depo-

sition dominantly contributes to pathophysiology, patients present with restrictive cardiomyopathy with thickened vascular walls resembling full hypertrophic cardiomyopathy (HCM) which is common in cardiac amyloidosis. While as shown in our patient, when severe amyloid deposition is almost confined to interstitial blood vessels, patients show ischemic dilated cardiomyopathy, which is a rare form of cardiac amyloidosis (12). Cueto-Garcia et al suggested that the echocardiographic pattern of patients with ischemic heart disease resulting from amyloid might be characterized by left ventricular dilatation and normal wall thickness (13). This echocardiographic feature was rare even in intramural cardiac amyloidosis (14).

Although we did not have the chance to treat our patient with high-dose melphalan and autologous stem cell transplantation (15) due to fetal cardiac amyloidosis, PGE1 derivatives used for micro vascular circulation was effective for myasthenic symptoms. PGE1 would be useful for ischemia associated with amyloid angiopathy, which results in some improvement of QOL.

In conclusion, we emphasize that myasthenic symptoms and dilated cardiomyopathy is a unique syndrome associated with systemic AL amyloidosis involving mainly the small vessels, i.e., AL amyloid angiopathy, in the skeletal muscles and myocardium, and that PGE1 may be useful for myasthenic symptoms.

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