INTERNAL MEDICINE

□ CASE REPORT □

The Imaging Diagnosis of Less Advanced Cases of Cardiac Amyloidosis: The Relative Apical Sparing Pattern

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Abstract

An early diagnosis is important for improving the prognosis of cardiac amyloidosis (CA). We herein describe the utility of two-dimensional speckle tracking echocardiography (2-D STE) in diagnosing CA at a less advanced stage. A 63-year-old woman with exertional dyspnea was suspected of having CA based on her echocardiographic and electrocardiographic findings. A myocardial biopsy was negative for amyloid deposits, while the relative apical sparing pattern was detected on 2-D STE, which was highly suggestive of CA. Chemotherapy was initiated as a treatment for CA, and the patient's symptoms were immediately relieved. Thereafter, amyloid deposits were detected in a skin biopsy specimen.

Key words: amyloidosis, speckle tracking echocardiography, relative apical sparing pattern

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Introduction

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that is characterized by amyloid fibril deposition in the myocardium. CA is usually accompanied by refractory heart failure and conduction abnormalities; hence, most patients do not survive for very long after the diagnosis (1). Although an early diagnosis and timely treatment are important for improving the prognosis of CA, they are difficult to achieve due to the absence of specific symptoms in less advanced cases.

Myocardial biopsy, which is considered to be the gold standard method for diagnosing CA, is associated with an increased risk of bleeding and cardiac tamponade. Thus, specific and non-invasive measures are required for definitively diagnosing CA. A number of echocardiographic findings, such as increased left ventricular (LV) wall thickness, atrial dilatation and "granular sparkling" have been reported to be suggestive of CA (2). However, each of these findings is non-specific (3). Two-dimensional speckle tracking echocardiography (2-D STE) is a newly developed imaging technique that enables the evaluation of the global and regional myocardial function (4). It has recently been reported that the detection of a regional longitudinal strain pattern; i.e., base-to-apex-directed myocardial deformation, on 2-D STE can contribute to the diagnosis of CA (5).

Case Report

A 63-year-old woman had visited our hospital complaining of exertional dyspnea and edema of the lower extremities two years previously. The symptoms had appeared one year prior to her visit, and gradually worsened.

At the first visit, the patient's blood pressure was 117/58 mmHg, her pulse rate was 95 bpm with a regular rhythm, and her oxygen saturation was 98% in ambient air. She also displayed slight edema of the lower extremities. A laboratory test revealed a slight increase in the level of troponin-I and a brain natriuretic peptide (BNP) concentration (135.9 pg/mL). Cardiomegaly was detected on a chest radiograph (Fig. 1). The electrocardiogram (ECG) revealed a low QRS voltage in the limb leads, poor R-wave progression in the chest leads and an abnormal Q wave in leads V1-4 (Fig. 2).

On transthoracic echocardiography, LV wall hypertrophy (end-diastolic interventricular septal wall thickness, 14 mm;

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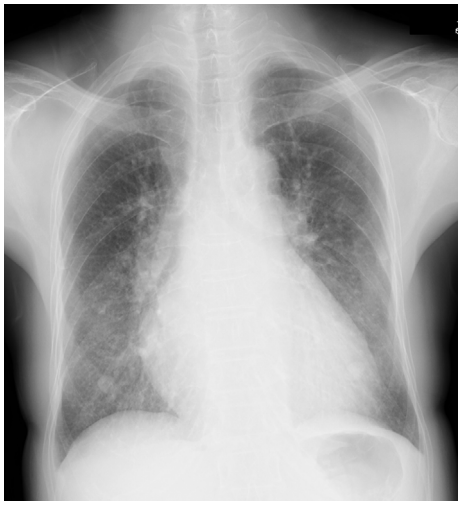

Figure 1. A chest radiograph showing cardiomegaly. The patient's cardiothoracic ratio was 65%.

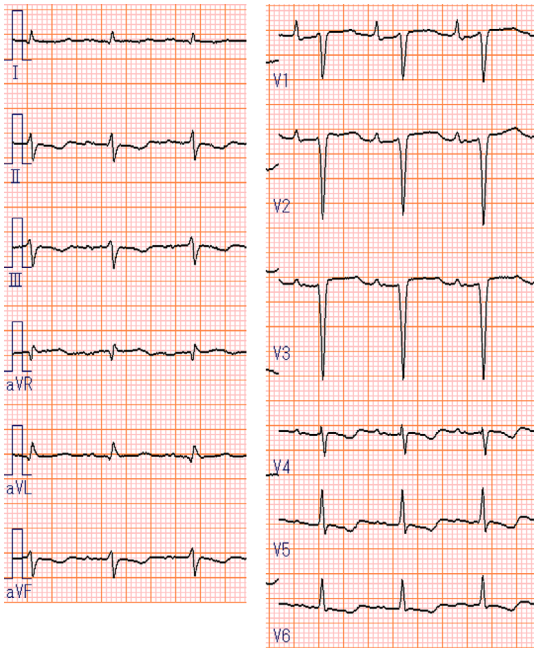

Figure 2. An electrocardiogram showed low QRS voltages in the limb leads and poor R-wave progression in the chest leads (the pseudo-infarction pattern). An abnormal Q wave was also detected in leads V1-4.

end-diastolic LV posterior wall thickness, 15 mm) was detected (Fig. 3A). On the other hand, her LV systolic function was preserved with a normal ejection fraction of 66%. The mitral inflow profile showed that the patient's peak early filling (E) and late diastolic filling (A) velocity ratio was 1.08. Her lateral mitral annular diastolic velocity (e') had decreased to 2.2 cm/s, indicating that she had a pseudonormal mitral inflow filling pattern (Fig. 3B). A coronary angiogram did not show any evidence of coronary stenosis. She was diagnosed with heart failure with a preserved ejection fraction.

Her symptoms were initially categorized as New York Heart Association (NYHA) functional class II, but gradually progressed despite medical treatment. Her serum BNP concentration simultaneously increased. Paroxysmal atrial fibrillation also occurred, and catheter ablation was performed - after which sinus rhythm was maintained.

Although LV hypertrophy was observed on echocardiography, high voltage signals were not detected on ECG. This discrepancy was suggestive of infiltrative cardiomyopathy, which usually occurs in CA. A myocardial biopsy was performed, but no amyloid deposits were seen.

Ten months previously, a C3 compression fracture had been found. Laboratory studies revealed an elevated serum protein level and a reduced serum albumin concentration, and an M-protein peak was detected in the gamma zone in serum protein electrophoresis. A cytological analysis of the patient's bone marrow aspirate showed normocellular bone marrow and the proliferation of atypical plasma cells. As a result, she was diagnosed with multiple myeloma. On the other hand, 2-D STE showed a marked reduction in the longitudinal strain of the basal wall segments and normal strain levels in the apical segments (Fig. 4). These findings, the so-called relative apical sparing pattern, are considered to exhibit high sensitivity and specificity in the diagnosis of CA (5).

Although there was still no pathological proof of amyloid deposits, CA complicated with multiple myeloma was strongly suspected and bortezomib-based chemotherapy was initiated. The patient's exertional dyspnea and lower-extremity edema were immediately relieved, and her serum BNP level decreased. These improvements were accompanied by improvements in the serological markers of multiple myeloma (e.g., her serum IgG level fell) (Fig. 5).

A series of biopsy examinations was performed after the initiation of chemotherapy. Although biopsies of the duodenum, rectum and bone marrow produced negative results, amyloid deposits were finally detected by skin biopsy. This led to the diagnosis of CA (6) due to amyloid light-chain (AL) amyloidosis concomitant with multiple myeloma.

Four months after the initiation of the chemotherapy, M-protein disappeared from the patient's serum. In addition, her clinical symptoms improved from NYHA functional class III to class II. Sequential echocardiographic examinations were performed during the follow-up period. In spite of the above-mentioned improvements in the patient's clinical symptoms and laboratory findings, the relative apical sparing pattern did not change from 2-D STE, and there was only a slight improvement in her global longitudinal strain (Fig. 6). In addition, she continued to exhibit a pseudonormalized mitral inflow filling pattern at the 6-month follow up examination. The patient's LV hypertrophy also remained unchanged during the follow-up period.

Discussion

We obtained two important findings regarding the utility of 2-D STE for CA. First, the relative apical sparing longi-

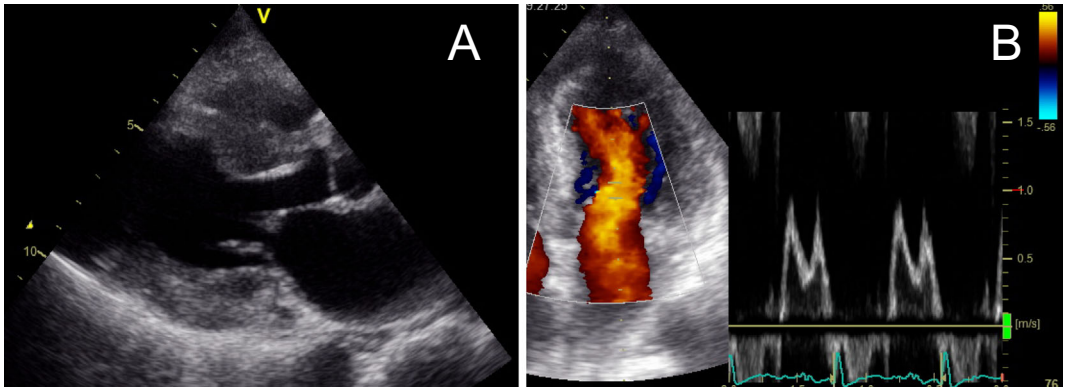

Figure 3. **A transthoracic echocardiogram (long axis view) showed LV wall hypertrophy (A) and the patient's mitral inflow profile showed a pseudo-normal mitral inflow filling pattern (B).**

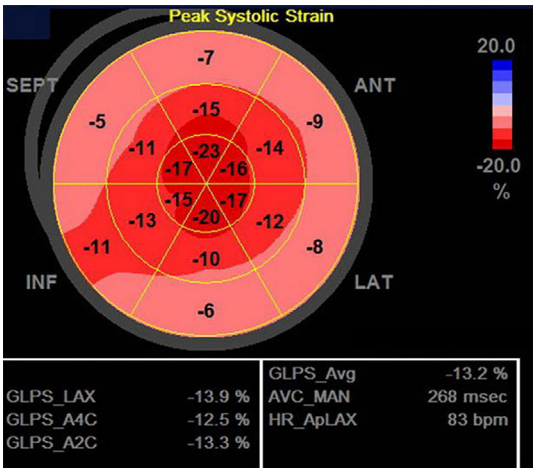

Figure 4. **A "bull's-eye" plot (a color-coded map of LV peak systolic longitudinal strain) showed a base-to-apex strain gradient: the longitudinal strain was markedly reduced in the basal and mid-ventricular wall segments while it was preserved in the apical segments. This finding is known as the relative apical sparing pattern.**

tudinal strain pattern is useful for diagnosing CA. This pattern is easy to recognize and exhibits high sensitivity and specificity for CA.

Imaging techniques based on 2-D STE could contribute to the differential diagnosis of conditions involving the thickening of the LV wall (7). For example, in patients with hypertensive heart disease, wall thickening and a significant reduction in the degree of longitudinal strain in the basal part of the septum are sometimes noted as initial signs of the disease, and such findings can even precede the reduction in the LV ejection fraction (8). On the other hand, in patients with hypertrophic cardiomyopathy (HCM), the longitudinal strain in the hypertrophic myocardial regions decreases in accordance with the severity of the hypertrophy (9). Contrarily, in patients with late-stage Fabry cardiomyopathy, longitudinal strain is often significantly reduced in the lateral and posterior wall segments, whereas it is preserved in the hypertrophic septal regions (10).

The relative apical sparing longitudinal strain pattern was originally described in advanced CA patients whose median LV wall thickness was over 14 mm (5). Recently, it was reported that the finding is also clinically useful for detecting CA in less advanced patients with a borderline or mildly thickened LV wall (those with LV wall thickness values of <14 mm) (11). Our patient exhibited an LV wall thickness of 14 mm, which was suggestive of a less advanced stage of CA. An early diagnosis is vital to the successful treatment of CA. Thus, 2-D STE, which is non-invasive, should be performed prior to a biopsy in cases of suspected CA.

Second, an improvement in our patient's heart condition did not alter the relative apical sparing pattern on 2-D STE. To date, the utility of serial 2-D STE examinations to follow-up CA patients in order to assess their clinical status and response to treatment has not been examined. In the present case, although the patient's heart condition improved and a serological response was achieved, the relative apical sparing pattern did not change. Similar discrepancies have previously been described using conventional echocardiography (12-14), which suggests that the cardiac dysfunction seen in AL amyloidosis is mediated via direct toxic effects on amyloidogenic proteins rather than the physical effect of the amyloid deposits (15-17). Thus, our patient's heart failure might have improved independently of the amyloid fibril infiltration in her heart. The fact that few changes were observed on cardiac magnetic resonance (CMR) imaging after the chemotherapy supports this assertion.

In a previous case of CA, a significant reduction in the LV wall thickness was noted after chemotherapy (18). In another case report, the CMR imaging findings changed 2.5 years after autologous stem cell transplantation, which suggested cardiac amyloid regression (19). These cases may indicate the solubility of myocardial amyloid proteins. However, such echocardiographic or radiographic changes are considered to be rare. The precise pathophysiological response that occurs in CA patients remains unclear.

One limitation of this study is that our analysis was based on an ultrasound system and software program from a single vendor; thus, different findings might be obtained by re-

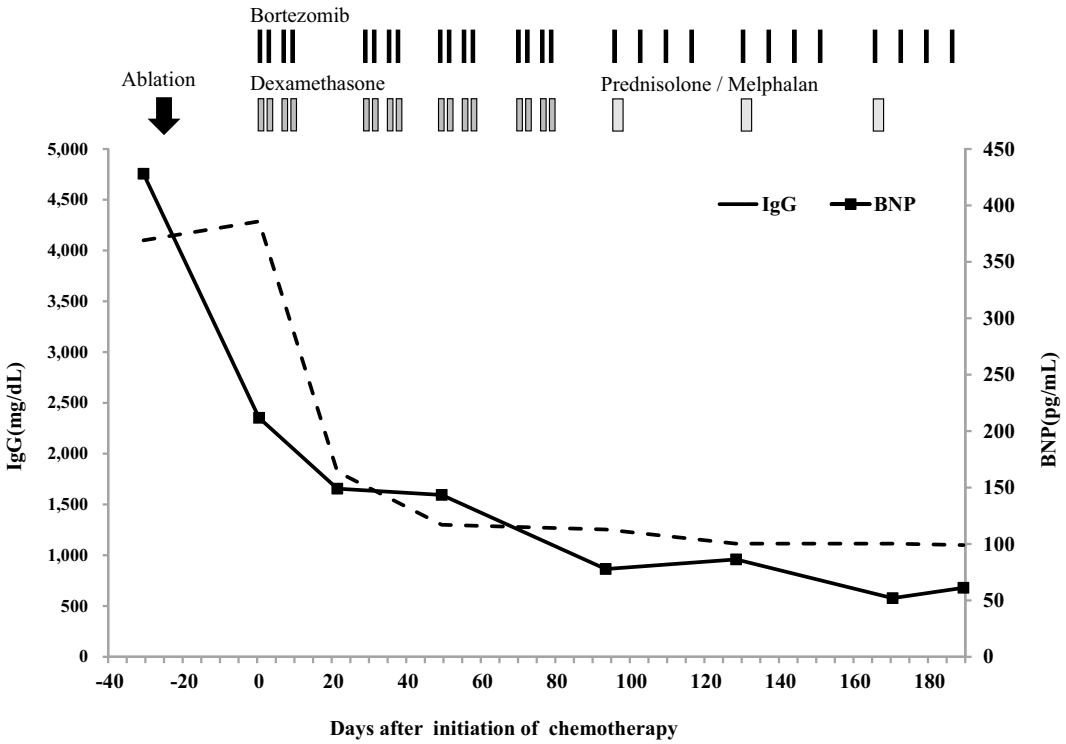

Figure 5. **The patient's clinical course. Catheter ablation (as a treatment for paroxysmal atrial fibrillation) led to a reduction in the patient's serum BNP levels. After the procedure, bortezomib-based chemotherapy was initiated. The patient's clinical symptoms were immediately relieved, and her BNP levels continued to decrease. These improvements were accompanied by a reduction in her IgG levels. Four months after the initiation of chemotherapy, M-protein disappeared from the patient's serum.**

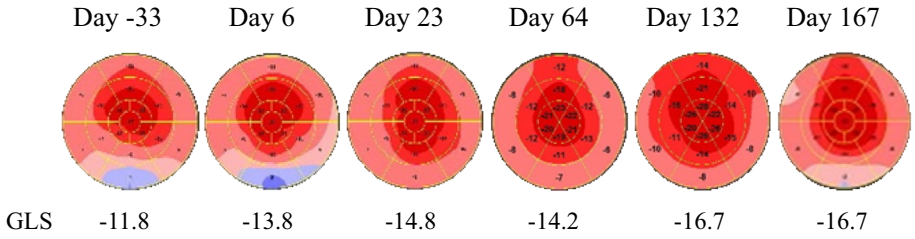

Figure 6. **Sequential two-dimensional speckle tracking echocardiographic examinations. In spite of the improvements in the patient's clinical symptoms and laboratory findings, the relative apical sparing pattern remained, and her global longitudinal strain only showed a slight improvement. GLS: global longitudinal strain**

searchers using ultrasound systems/software programs from other vendors. In addition, the changes in the appearance of the heart on 2-D STE in CA patients following more intensive therapy, such as high-dose chemotherapy followed by autologous stem cell transplantation, remain unclear. A further analysis is needed to determine whether our findings can be generalized to other cases.

In conclusion, the present case suggests that 2-D STE is useful for the non-invasive diagnosis of CA at a less advanced stage; however, the induction of disease remission with chemotherapy did not result in changes in the relative apical sparing pattern on 2-D STE.

The authors state that they have no Conflict of Interest (COI).

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