

An Autopsy Case of Cardiac Amyloidosis with Heterogeneous Deposition of Amyloid Protein: A Possible Mechanism for Relative Apical Sparing of Longitudinal Strain



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INTRODUCTION

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy characterized by amyloid deposition in the myocardium. Although an early diagnosis and timely treatment are important for alleviating CA, detection of CA is still challenging.¹ Echocardiography is a noninvasive, reproducible method of assessing cardiac features and function in patients with CA.² Relative apical sparing of longitudinal strain (LS) on two-dimensional speckle-tracking echocardiography is more useful than traditional echocardiographic parameters for the early diagnosis of CA³ and prognosis in patients with CA.⁴ Despite the clinical usefulness of apical sparing, its pathophysiologic mechanism has been unclear.

Therefore, we performed a quantitative assessment of amyloid deposition at three different cross sections of the entire left ventricle in an autopsy case and compared it with LS at the corresponding level measured on echocardiography before death.

CASE PRESENTATION

A 77-year-old woman presented with congestive heart failure. She was estimated to be in New York Heart Association functional class III. On physical examination, blood pressure was 94/50 mm Hg, heart rate was 55 beats/min with regular rhythm, and oxygen saturation was 96% in ambient air. Laboratory testing revealed increases in the levels of creatinine (3.01 mg/dL) and brain natriuretic peptide (255.2 pg/mL). Transthoracic echocardiography showed left ventricular (LV) wall hypertrophy and impaired LV systolic function (ejection fraction 38%), and transmitral flow showed that the ratio of peak early (E) to late diastolic (A) filling velocity was 2.5, indicating a restrictive pattern (Figure 1, Videos 1 and 2). LS in the apical four-, two-, and

three-chamber views showed severely reduced global LS of -9.15% with a ratio of apical to basal strain (average apical LS/laverage basal LS + mid LS) of 1.1. Visual assessment of a bull's-eye plot of LV peak systolic LS indicated a basal-to-apical strain gradient, known as a relative apical sparing pattern (Figure 2). Cardiac magnetic resonance imaging revealed widespread subendocardial late gadolinium enhancement at the ventricular and atrial walls (Figure 3). Despite intensive medical treatment, the patient's renal function progressively worsened, and she died on the 14th hospital day. Further investigations, including immunohistochemistry and genetic analysis, led to a final diagnosis of wild-type transthyretin CA (ATTR-CA). Cross sections of her left ventricle were obtained at the basal, mid, and apical levels, and the extent of amyloid load was calculated in each of these three sections. Formalin-fixed and paraffin-embedded tissue samples were prepared and stained with Congo red. The percentage of amyloid area was measured and expressed as a percentage of the total surface area of each cross section using image analysis software (WinROOF; Mitani, Fukui, Japan). The amyloid loads at the basal, mid, and apical levels were 28.7%, 17.9%, and 10.3%, respectively (Figure 4).

DISCUSSION

In this case of ATTR-CA, the deposition of amyloid protein appeared to increase from the apex to the base. Relative apical sparing pattern on two-dimensional speckle-tracking echocardiography was first reported by Phelan *et al.*³ Thereafter, various deformation metrics involving ratios of apical to midventricular or basal strain derived from echocardiography were found to differentiate CA from other causes of wall-thickening diseases.⁴⁻⁶ A recent study showed that relative apical sparing pattern, N-terminal pro-brain natriuretic peptide, and New York Heart Association functional class were independent and important risk factors for major adverse cardiac events in CA.⁷ Despite the clinical use of apical sparing, its pathophysiologic mechanism has been unclear. Most recently, Bravo *et al.*⁸ demonstrated significant base-to-apex gradients in LS, maximal LV wall thickness, and LV mass in light-chain CA using positron emission tomography and cardiac magnetic resonance imaging. The total amyloid load showed a marked base-to-apex gradient, whereas the amyloid fraction showed no significant base-to-apex gradient, suggesting that segmental differences in the distribution of total amyloid volume rather than the proportion of amyloid deposited might be correlated with LS in light-chain CA. Although there is a difference in cardiac structure and dysfunction as well as clinical outcome between light-chain CA and ATTR-CA,⁹ the amyloid protein was found to be distributed in a base-to-apex gradient in our patient with ATTR-CA, which was

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VIDEO HIGHLIGHTS

Video 1: Transthoracic echocardiography (long-axis view) showed LV wall hypertrophy and impaired LV systolic function.

Video 2: Transthoracic echocardiography (apical four-chamber view) showed LV wall hypertrophy and impaired LV systolic function.

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compatible with the findings in light-chain CA of Bravo *et al*. Further studies using multimodality diagnostic tools are warranted to replicate the correlation between the distribution of total amyloid volume and LS in CA. However, our study had a limitation: a single histologic microsection at each level does not provide sufficiently detailed information on amyloid involvement.

CONCLUSION

The present case suggests that amyloid fibrils were distributed unevenly and that a relative apical sparing pattern of LS could

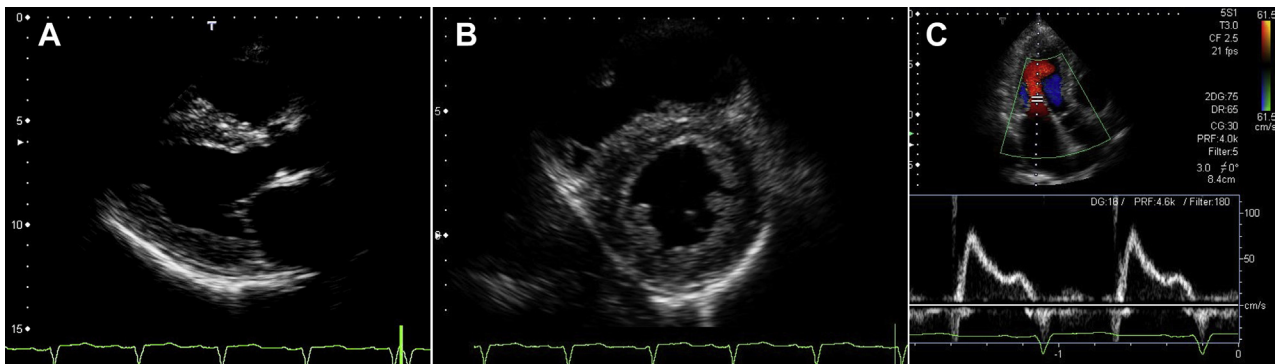


Figure 1 Transthoracic echocardiography (A, parasternal long-axis view; B, parasternal short-axis view) showed LV hypertrophy and a restrictive mitral inflow pattern (C).

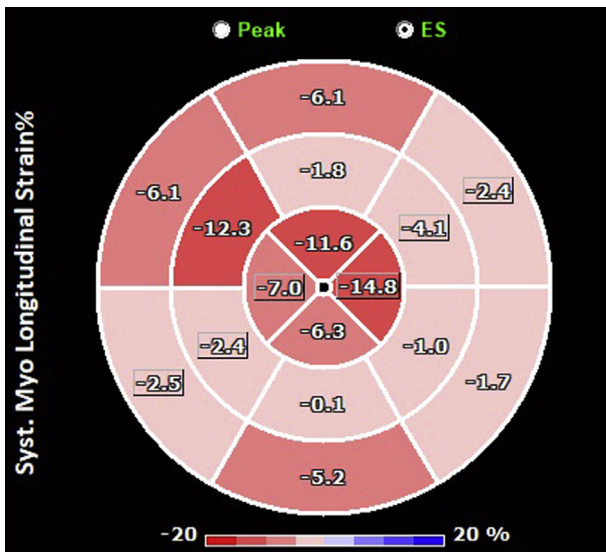


Figure 2 Two-dimensional speckle-tracking echocardiography. A bull's-eye plot (a color-coded map of LV peak systolic LS) showed a basal-to-apical strain gradient: LS was markedly reduced in the basal and midventricular wall segments, while it was preserved in the apical segments. This finding is known as the relative apical sparing pattern.

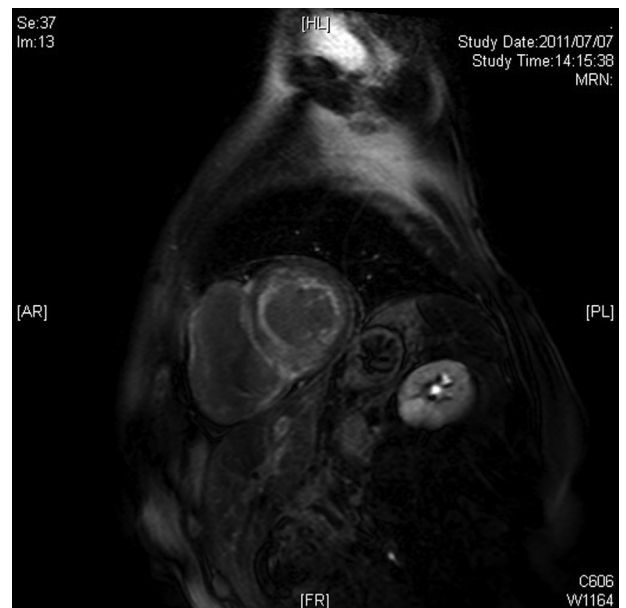


Figure 3 Cardiac magnetic resonance imaging showed symmetric hypertrophy and diffuse subendocardial delayed gadolinium enhancement at the ventricular and atrial walls.

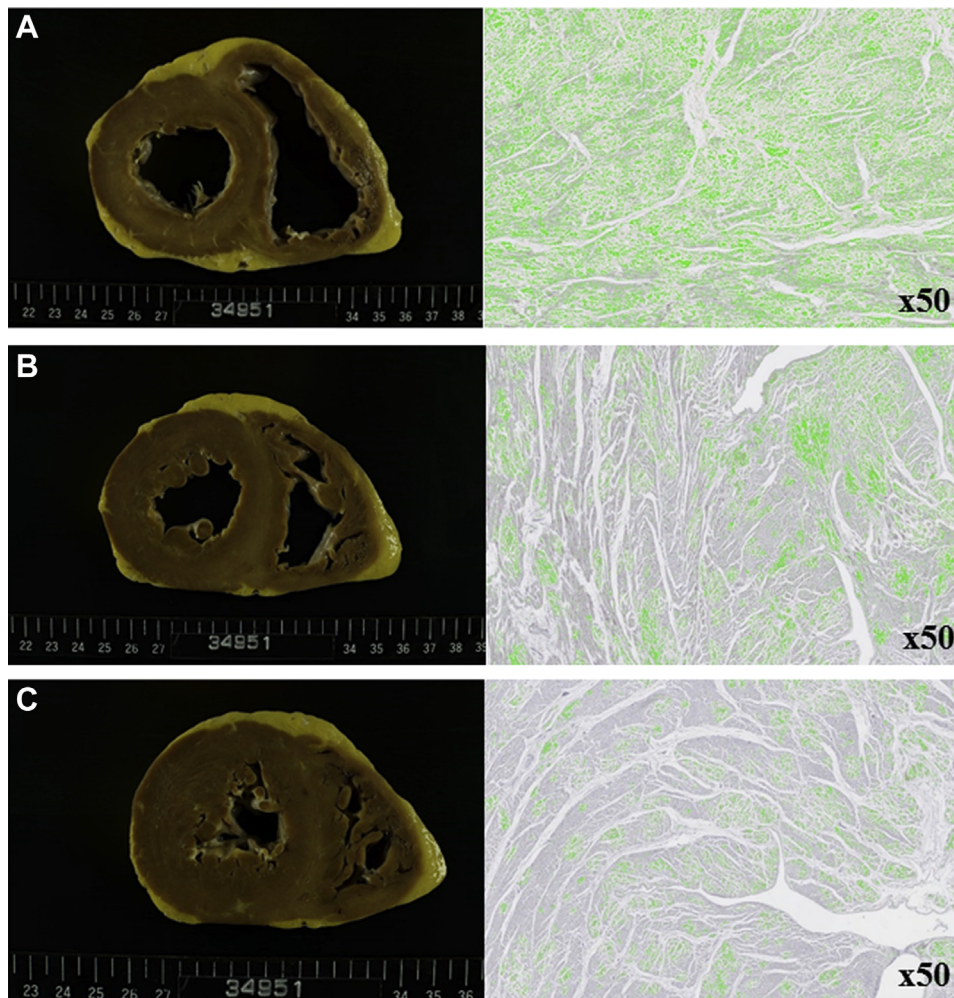


Figure 4 The macroscopic heart section and amyloid load at three different levels of the left ventricle: **(A)** 28.7% at the basal level, **(B)** 17.9% at the midcavity level, and **(C)** 10.3% at the apical level.

be due to less amyloid deposition in the apex compared with the base.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2019.09.009>.

REFERENCES

- Falk RH. Diagnosis and management of the cardiac amyloidosis. *Circulation* 2005;112:2047-60.
- Falk RH, Plehe JF, Deering T, Schick EC Jr, Boinay P, Rubinow A, et al. Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. *Am J Cardiol* 1987;59:418-22.
- Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;98:1442-8.
- Senapati A, Sperry BW, Grodin JL, Kusunose K, Thavendiranathan P, Jaber W, et al. Prognostic implication of relative regional strain ratio in cardiac amyloidosis. *Heart* 2016;102:748-54.
- Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Störk S, et al. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. *Circ Cardiovasc Imaging* 2013;6:1066-72.
- Salinaro F, Meier-Ewert HK, Miller EJ, Pandey S, Sancharawala V, Berk JL, et al. Longitudinal systolic strain, cardiac function improvement, and survival following treatment of light-chain (AL) cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging* 2017;18:1057-64.
- Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, et al. Causes and consequence of longitudinal LV dysfunction assessed by 2D strain echocardiography in cardiac amyloidosis. *JACC Cardiovasc Imaging* 2016;9:126-38.
- Bravo PE, Fujikura K, Kijewski MF, Jerosch-Herold M, Jacob S, El-Sady MS, et al. Relative apical sparing of myocardial longitudinal strain is explained by regional differences in total amyloid mass rather than the proportion of amyloid deposits. *JACC Cardiovasc Imaging* 2019;12:1165-73.
- Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, et al. Left ventricular structure and function in transthyretin related versus light-chain cardiac amyloidosis. *Circulation* 2014;129:1840-9.