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Cardiac Amyloidosis Without Increased Left Ventricular Wall Thickness

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Abstract

Objectives: To determine how often left ventricular wall thickness (LVWT) is normal and to assess the effect of LVWT on clinical outcomes of patients with immunoglobulin light chain (AL) cardiac amyloidosis.

Patients and Methods: A total of 117 patients with systemic AL amyloidosis were retrospectively categorized from April 1, 1995, to September 15, 2012; group A included cardiac amyloidosis patients with an LVWT greater than 12 mm (45 patients); group B, cardiac amyloidosis patients with an LVWT of 12 mm or less (25 patients); and group C, no evidence of cardiac amyloidosis (47 patients). We compared echocardiographic parameters and survival rates among the 3 groups.

Results: No differences were found between groups A and B in the following parameters: left ventricular ejection fraction (median, 56% [interquartile range (IQR), 46%-63%] vs 56% [IQR, 49%-63%], P=.76), left arterial volume index (median, 44.5 [IQR, 38.5-59.7] vs 43.9 [IQR, 33.8-57.1] mL/m^2, P=.79), e' (median, 0.04 [IQR, 0.03-0.05] vs 0.05 [IQR, 0.04-0.06] m/s, P=.10), and E/e' (early diastolic mitral inflow velocity (E)/e') (median, 18.4 [IQR, 12.0-23.3] vs 18.0 [IQR, 13.6-25.0], P=.98). Patients in group C exhibited significantly different values for these parameters (median, 65% [IQR, 61%-69%], 23.4 [IQR, 18.0-29.0] mL/m^2, 0.08 [IQR, 0.06-0.09] m/s, and 8.8 [IQR, 7.2-10.5], respectively; all P<.001). The survival rates were statistically different, with median survival times of 422, 729, and 2080 days in groups A, B, and C, respectively (P=.002). Using multivariate Cox proportional hazards regression analysis, we found that age, an N-terminal pro–B-type natriuretic peptide level of 1800 pg/mL or greater, E/e', and complete hematologic remission were significant predictors of survival.

Conclusions: A third of patients with AL cardiac amyloidosis were diagnosed as having an LVWT of 12 mm or less. Because appropriate therapy can improve the survival of patients with AL cardiac amyloidosis, early detection by sensitive diagnostic methods should be pursued even when LVWT is not increased.

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Amyloidosis is a disease in which abnormal fibrillar material accumulates in the extracellular matrix, resulting in dysfunction of the affected organs. In immunoglobulin light chain (AL) amyloidosis, which is caused by monoclonal plasma cell dyscrasia,[1] the heart is one of the most frequently affected organs, and cardiac involvement contributes to approximately 75% of deaths.[2] In the absence of treatment, AL amyloidosis patients with heart failure symptoms have a median survival time of 6 months.[3] Therefore, early diagnosis is crucial to proper treatment of these patients.

The 10th International Symposium on Amyloid and Amyloidosis defined cardiac involvement in AL amyloidosis as having a positive heart biopsy result or increased left ventricular wall thickness (LVWT >12 mm) in the absence of another cardiac cause.[4] The definition that uses the LVWT has been widely adopted in clinical practice and many research studies.[5-7] Recently, however, typical patterns of delayed gadolinium enhancement (DGE) on cardiac magnetic resonance imaging (MRI) have revealed high sensitivity and specificity for the diagnosis of cardiac involvement in AL amyloidosis, even in patients without significantly increased LVWT.[8-11] However, data on the prognosis for patients with cardiac AL amyloidosis with normal LVWT are limited. Hence, this study was conducted to assess the effect of LVWT on clinical outcomes of patients with AL cardiac amyloidosis. In

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addition, prognostic factors for AL amyloidosis were analyzed.

METHODS

Patients and Study Design

We conducted a single-center, retrospective study to assess clinical characteristics and survival rates of AL amyloidosis patients on the basis of their LVWT. A total of 127 patients were diagnosed as having AL amyloidosis between April 1, 1995, and September 15, 2012, at our tertiary medical center. Amyloidosis was confirmed by the presence of histologically proven amyloid deposits in at least one organ, and AL amyloidosis was determined by immunohistochemical stain (in 48 patients) or by monoclonal gammopathy in serum with an abnormal free light chain ratio (in 79 patients). Echocardiographic assessment was not available in 10 patients, who were subsequently excluded from the study.

All 117 patients underwent transthoracic echocardiography and were classified into 3 groups according to the presence of cardiac involvement and end-diastolic LVWT measured by echocardiography. Mean LVWT was calculated from ventricular septal and posterior wall thicknesses measured at end diastole. Group A included 45 patients with a mean LVWT greater than 12 mm in the absence of hypertension or other potential causes of increased LVWT, thus fitting the definition of organ involvement put forth in the 10th International Symposium on Amyloid and Amyloidosis.[1,4] Twenty-two patients with an LVWT of 12 mm or less with evidence of cardiac amyloidosis on endomyocardial biopsy or cardiac MRI were classified into group B. (The images of a representative case from group B are shown in Figure 1). In addition, 3 patients who underwent low-voltage electrocardiography (defined as voltage <5 mm in the limb leads and <10 mm in the precordial leads)[5] and who had borderline LVWT apparent on echocardiography (LVWT=12 mm) were also included in group B. In the patients without increased LVWT, the need for further evaluation was determined by the clinician during the study period. Unexplainable exertional dyspnea or a restrictive pattern apparent on echocardiography was a general indication for endomyocardial biopsy or cardiac MRI. Finally, patients who had no evidence of cardiac amyloidosis on cardiac MRI or endomyocardial biopsy were classified as group C. In addition, the patients who presented with normal electrocardiographic and echocardiographic findings without exertional dyspnea were categorized as group C without further investigation. Hence, group C included a total of 47 amyloidosis patients (Figure 2).

Endomyocardial specimens were considered as positive for cardiac amyloidosis when they showed apple-green birefringence under polarized light after Congo red stain. On cardiac MRI, a diffuse subendocardial pattern of DGE and suboptimal nulling of the myocardium were considered typical findings of cardiac

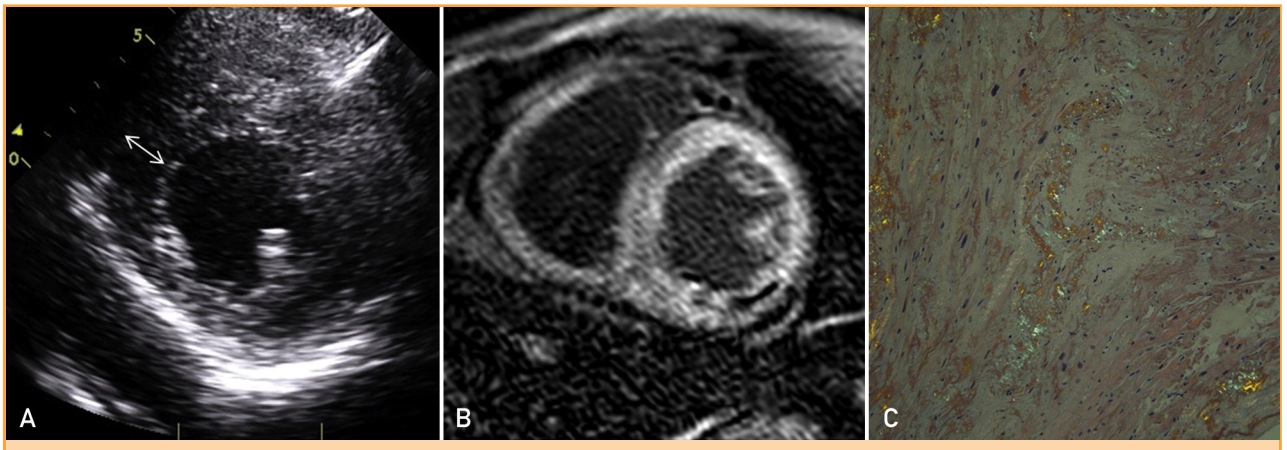

FIGURE 1. A representative case of cardiac amyloidosis with normal left ventricular wall thickness. A, Normal left ventricular wall thickness apparent on echocardiography. B, Diffuse subendocardial delayed gadolinium enhancement on cardiac magnetic resonance imaging. C, Endomyocardial biopsy specimen showing apple-green birefringence under polarized light (Congo red stain, original magnification ×400).