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Impact of clinical and echocardiographic characteristics on occurrence of cardiac events in cardiac amyloidosis as proven by endomyocardial biopsy

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ABSTRACT

Background: Although patients with immunoglobulin light chain (AL) cardiac amyloidosis exhibit worse outcomes than those with transthyretin (TTR) cardiac amyloidosis, few data exist regarding the occurrence of cardiac events and the echocardiographic indices in endomyocardial biopsy (EMBx) proven amyloidosis.
Methods: From November 2007 to October 2012, we identified 33 patients with EMBx-proven amyloidosis. There were 12 patients (8 men; mean age: 66 years) with AL and 21 patients (20 men; mean age: 78 years) with TTR. We performed serial echocardiography and observed the patients during follow-up; defining all-cause mortality as the primary endpoint and hospitalization for heart failure as the secondary endpoint.
Results: The survival rates at 12 months were 20.8% and 85.7% in AL and TTR, respectively ($p < 0.001$). The cumulative incidences of the composite of death or readmission for heart failure at 12 months were 91.7% and 51.3% in AL and TTR, respectively ($p < 0.001$). A multivariate analysis showed that the AL type amyloid was the powerful predictor of mortality (hazard ratio: 8.50, 95% confidence interval: 1.79 to 40.57, $p < 0.05$). Under these conditions, the E/e′ in AL tended to increase from 23 ± 13 to 28 ± 11 ($p = 0.06$) with marked increases in B-type natriuretic peptide (779 ± 456 pg/ml to 1576 ± 895 pg/ml, $p < 0.05$), although these remained unchanged in TTR, which exhibited significantly increased left ventricular end-diastolic dimensions from 40 ± 4 mm to 42 ± 4 mm ($p < 0.05$).
Conclusions: The survival rate was generally worse in AL cardiac amyloidosis, although the readmission for heart failure remains high in TTR cardiac amyloidosis with the occurrence of left ventricular dilatation.

1. Introduction

Among the type of systemic amyloidosis, immunoglobulin light chain (AL) and transthyretin (TTR) amyloidosis are frequently associated with cardiac involvement [1]. In particular, AL amyloidosis patients presenting with heart failure (HF) have poor outcomes with a median survival of <6 months [2]. Indeed, despite the use of chemotherapy, patients with AL cardiac amyloidosis exhibit higher mortality than those without cardiac involvement [3]. In contrast, the clinical time course of senile systemic amyloidosis, which mainly consists of wild-type TTR cardiac amyloidosis, is considered to be less aggressive than that of AL amyloidosis, with a median survival of 5 years [4,5]. This suggests that the prognosis of cardiac amyloidosis depends on the type of amyloidosis, although the original disease can also affect prognosis. It remains controversial, however, whether the immunohistochemical diagnosis accurately represents the type of amyloidosis [6], because of the difficulty of immunohistochemical staining for amyloid deposits, particularly in AL amyloidosis [7]. A recent study reported a highly-specific detection method for AL amyloidosis, overcoming this difficulty [8]. Therefore, based on this strict method for immunohistochemical determination, the present study aimed to elucidate differences in the clinical characteristics of two types of cardiac amyloidosis, and to investigate the long-term outcomes of patients who had been diagnosed by endomyocardial

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biopsy (EMBx). We also determined related factors based on serial echocardiography.

2. Methods

2.1. Patient population

From November 2007 to October 2012, we performed endomyocardial biopsy (EMBx) on 82 consecutive patients for further workup of myocardial hypertrophy, suggestive of hypertrophic cardiomyopathy, at Kokura Memorial Hospital. All patients underwent a comprehensive assessment, including clinical evaluation and echocardiography. The indication for EMBx included left ventricular dysfunction with unexplained myocardial hypertrophy. EMBx was not performed for any patients who exhibited severe hypertension or valvular heart disease, which could alone be sufficient to explain the occurrence of ventricular hypertrophy. The diagnosis of HF was made on the basis of the criteria recommended in the Framingham Heart Study [9]. All tests and evaluations were performed just prior to EMBx. Informed consent was obtained from all patients prior to undergoing EMBx.

2.2. ECG and echocardiography

Standard 12-lead ECG was obtained, including heart rate, rhythm, axis, and voltage. Low voltage was defined as a QRS voltage amplitude < 0.5 mV in all limb leads or <1 mV in all precordial leads. A pseudo-infarct pattern was defined as QS waves in any 2 consecutive leads. Left ventricular hypertrophy was assessed according to the Sokolow-Lyon criteria. Echocardiography was performed using commercially available ultrasound equipment (Artida, Toshiba Medical System Corp, Tochigi, Japan, or Vivid 7, GE Vingmed, Horten, Norway). Standard 2-dimensional measurements were obtained as recommended by the guidelines of the American Society of Echocardiography [10]. Early (E) and late (A) mitral inflow velocities were measured using the pulsed wave Doppler method by placing the sample volume at the level of the tips of the mitral leaflets. Deceleration time, measured as the distance from the peak of the E wave in the mitral inflow view to the baseline and peak velocities of the E and A waves, was measured if patients exhibited a normal sinus rhythm. The E/A-wave ratio was calculated in a standard fashion. Left ventricular restrictive filling pattern was defined in terms of an E/A wave ratio > 2 or an E/A wave ratio 1–2 and E-wave deceleration time < 140 ms on pulsed Doppler echocardiography [11,12]. Patients with atrial fibrillation were regarded as a non-restrictive group. The trans-tricuspid pressure gradient was calculated using a tricuspid regurgitant flow velocity, as determined in the continuous-wave Doppler mode. Additional apical and parasternal views were also recorded for the assessment of tissue velocity. The echocardiographic data were gathered at the time of enrollment, at an intermediate period and 12 months after enrollment, and were analyzed by 2 experienced echocardiographers (T.A. and A.I.) who were blinded to the clinical data.

2.3. Endomyocardial biopsy

EMBx was performed at more than two points on the interventricular septum, on either the right or the left ventricular side. All biopsy specimens were fixed in 10% neutral buffered formalin and embedded in paraffin using routine methodologies. Tissue blocks were sectioned and stained with hematoxylin and eosin. All biopsied specimens were also stained with Congo red or direct-first-scarlet to identify the presence of amyloidosis. Finally, we performed immunohistochemical staining to confirm the amyloid subtypes.

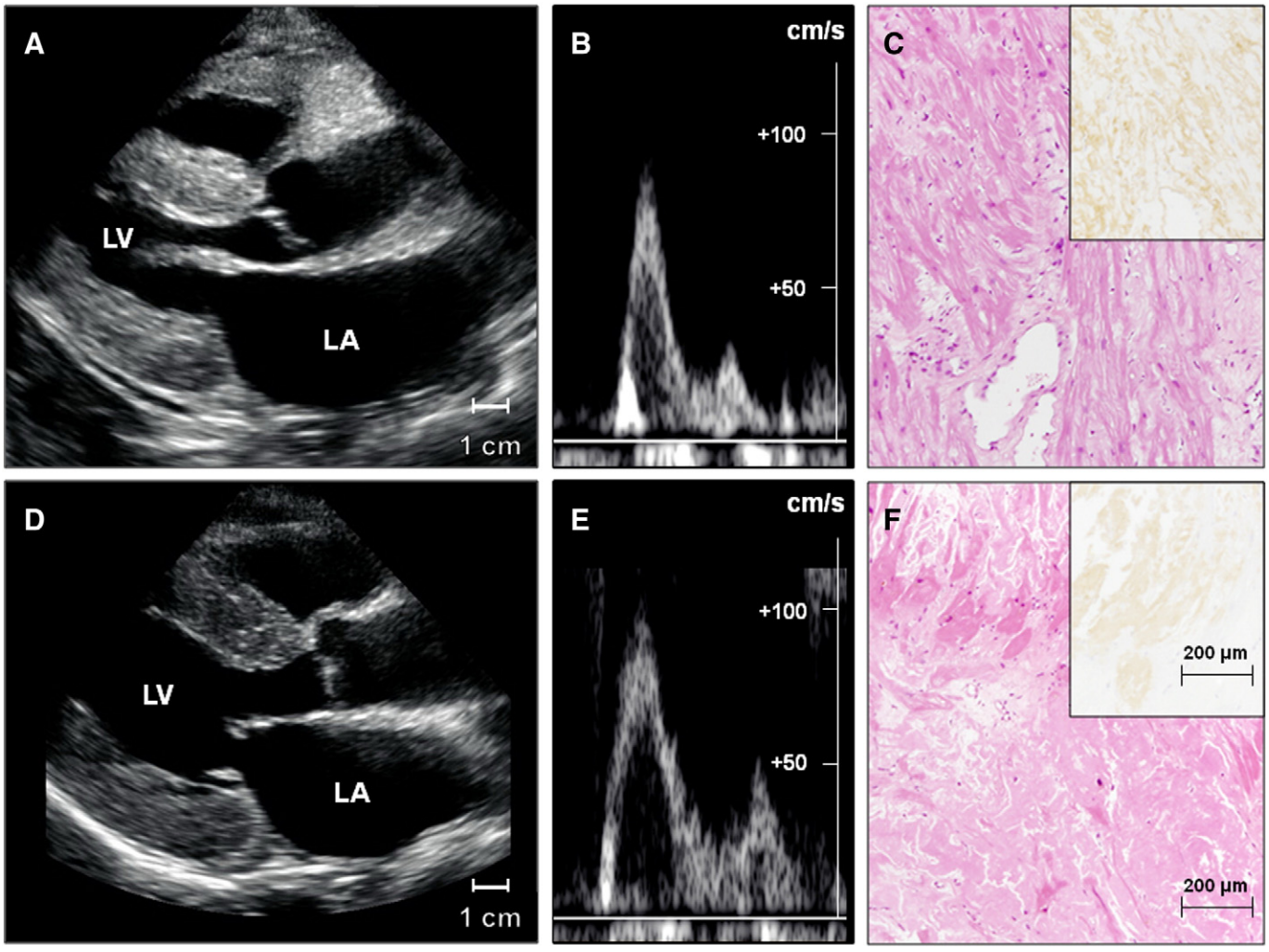

Fig. 1. Representative cases of immunoglobulin (upper) and transthyretin (lower) cardiac amyloidosis. (A) Parasternal long-axis view shows a thickened left ventricular wall of 15 mm with a granular sparkling sign. (B) The transmitral flow pattern is restrictive with an E/A ratio of 2.8. (C) Histological findings show amyloid deposition with immunoglobulin-positive tissues (inset). (D) Parasternal long-axis view also shows a thickened left ventricular wall of 16 mm with granular sparkling sign. (E) Transmitral flow pattern is restrictive with an E/A of 2.2. (F) Histological findings show amyloid deposition with transthyretin positive tissues (inset). E/A = ratio of the early to late ventricular filling velocities, LA = left atrium, LV = left ventricle.