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Original article

Clinical correlates and prognostic values of pseudoinfarction in cardiac light-chain amyloidosis

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ABSTRACT

Background: Pseudoinfarction is one of the most common electrocardiographic characteristics in cardiac light-chain (AL) amyloidosis. The aim of the present study was to analyze the prognostic significance of pseudoinfarction and define the relation between pseudoinfarction and clinical parameters in cardiac AL amyloidosis.

Methods: A total 110 consecutive patients who presented with a diagnosis of cardiac AL amyloidosis and without a positive history of coronary disease between 2010 and 2014 were enrolled. Patients were divided into two groups according to the presence ($n = 40$) or absence ($n = 70$) of pseudoinfarction on electrocardiography (ECG). Clinical parameters including laboratory tests, echocardiography, and follow-up were collected and analyzed.

Results: Patients with pseudoinfarction had higher N-terminal pro-brain natriuretic peptide levels (9131 pg/ml vs 4644 pg/ml, $p = 0.02$) and a worse New York Heart Association (NYHA) function ($p < 0.001$). The pseudoinfarction group also had a larger left atrium size (44 mm vs 41 mm, $p = 0.03$), a thicker ventricular wall (septum 14 mm vs 13 mm, $p = 0.005$ and posterior wall 14 mm vs 13 mm, $p = 0.01$), a lower left ventricular ejection fraction (50% vs 58%, $p = 0.013$), and higher early-to-atrial transmitral flow velocity ratio ($p = 0.001$). Also, the pseudoinfarction group was closely associated with a lower voltage (70% vs 38.6%, $p = 0.002$), poor precordial R wave progression (78.4% vs 43.9%, $p = 0.001$), lower Sokolow–Lyon index (13 mm vs 9 mm, $p < 0.001$), and lower voltage to mass ratio (0.521 vs 0.442, $p = 0.028$) on the ECG. After a median follow-up of 39 months, Kaplan–Meier survival analysis showed that lifetime was significantly shorter in the pseudoinfarction group (median 4 months vs 17 months, $p < 0.001$). By adopting the multivariate Cox proportional model, NYHA heart failure III to IV and the presence of pseudoinfarction remained the only two independent prognostic determinants with death hazard ratio of 3.16 and 1.9, respectively.

Conclusions: The presence of pseudoinfarction on the ECG has a negative prognostic effect on AL patients with cardiac involvement.

Introduction

Cardiac amyloidosis is caused by extracellular deposition of insoluble fibrils composed of multiple serum proteins (amyloid) in the heart. In most cases, this condition is part of primary amyloidosis which is caused by deposition of monoclonal immunoglobulin light-chain and is associated with clonal plasma cells or other B cell dyscrasias [1]. Median survival for patients with cardiac light-chain (AL) amyloidosis and congestive heart failure is likely to be less than six months. The identification of patients with cardiac AL amyloidosis at high risk of death is urgently needed, especially by using non-invasive methods [2]. Electrocardiogram (ECG), a convenient examination in clinical experience, presents two most common abnormalities in patients with cardiac AL amyloidosis: low voltage QRS complex and a pseudoinfarction pattern [2]. Studies by Boldrini [3] and Cyrille [4] have demonstrated the prognostic values of conduction disturbances and low QRS voltage in cardiac AL amyloidosis respectively.

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Moreover, Perlini et al. [5] proved that fragmented QRS probably predicted a worse prognosis in cardiac AL amyloidosis. In the literature, there have been no relevant studies focusing on the prognostic significance of pseudoinfarction in cardiac AL amyloidosis. Therefore, the present study aimed to investigate the prognostic role of pseudoinfarction ECG and its clinical correlation with other parameters in patients with cardiac AL amyloidosis.

Methods

We enrolled all consecutive patients diagnosed with cardiac AL amyloidosis who were treated at Peking Union Medical College Hospital from January 2010 to December 2014. AL amyloidosis was confirmed by immunohistochemical staining or mass spectrometry based proteomics along with proof of clonal plasma dyscrasias [6]. The presence of cardiac amyloidosis was defined according to either the demonstration of amyloid deposits on the endomyocardial biopsy or by echocardiographic evidence of cardiac amyloidosis in the setting of a defined systemic disease [7]. Echocardiographic criteria for cardiac amyloidosis included thickness of left ventricular (LV) septum or posterior wall >12 mm without any potential causes of LV hypertrophy. Results of blood tests, ECG, and echocardiography were collected within 2 weeks of the histological diagnosis of cardiac amyloidosis. To avoid the interference on the presence of pseudoinfarction, patients with a positive history of coronary disease, implantable cardioverter defibrillator (ICD), and left bundle branch block were excluded from analysis; therefore, 110 patients with cardiac AL amyloidosis were included in the final analysis.

Medical histories, baseline symptoms, and laboratory test results were collected for analysis. Standard 12-lead ECG closest to time of diagnosis was reviewed by an independent physician blinded to the clinical diagnosis. QRS, QT, and QT corrected (QTc) intervals were measured in all patients. A pseudoinfarction pattern was defined as pathologic Q waves (1/4 R amplitude) or QS waves on 2 consecutive leads in the absence of previous ischemic heart disease, left bundle branch block, and/or evidence of akinetic/dyskinetic wall segments. Low voltage pattern was taken into consideration if a QRS voltage amplitude $\leq$0.5 mV in all limb leads or $\leq$1 mV in all precordial leads. Poor R-wave progression was defined as R wave $\leq$0.3 mV by V_3. To compare voltage to mass ratio, we calculated Sokolow–Lyon index, which was defined as the sum of the S wave amplitude in the lead V_1 and of the R wave in V_5 or V_6, and divided it by the cross-sectional area of the LV wall. Atrioventricular conduction delays were considered in the presence of atrioventricular block at any degree. Intraventricular conduction delays were defined as complete and incomplete right bundle branch block (RBBB, iRBBB).

Transthoracic echocardiography was performed with commercially available GE Vivid 7 Ultrasound (GE Healthcare, Little Chalfont, UK) machines and analyzed for wall thickness and chamber dimensions. Left atrial (LA) dimension, interventricular septum (IVS) thickness, LV posterior wall (LVPW) thickness, LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and inferior vena cava were measured in the standard fashion following the criteria of American Society of Echocardiography recommendations [8]. LV fractional shortening was evaluated as the difference between the end-diastolic and the end-systolic diameters. LV ejection fraction (EF) was evaluated using the biplane Simpson's equation from 4-chamber views and considered impaired when less than 50%. Early-to-atrial transmitral flow velocity ratio (E/A ratio) was assessed by conventional pulsed Doppler in the apical 4-chamber view. The E to e′ ratio was assessed as the ratio between early diastolic transmitral flow velocity (E) and tissue Doppler derived early diastolic peak velocity at lateral mitral annulus. The deceleration time (EDT) was measured as the time required for the peak E velocity to decline to baseline. LV mass was calculated using the method of Devereux et al. [9] and classified as increased when >110 g/m^2 in women and >130 g/m^2 in men.

We carried out the follow-up through telephone and all-cause mortality was the primary endpoint.

Continuous variables are presented as median and interquartile ranges, and categorical variables in the form of frequencies and percentages. Continuous variables were assessed on the basis of ANOVA followed by the 2-tail Mann–Whitney test and all categorical variables were compared by chi-square analysis using the Pearson correlation test. A p-value <0.05 was considered statistically significant. Survival curves were plotted according to Kaplan–Meier and differences were assessed by the log-rank test. Univariate Cox proportional hazard analysis was conducted to explore the association and possible interactions between baseline variables and predictors of death. Moreover, multivariate Cox proportional models with stepwise regression were fitted to examine the hazard ratio of death for pseudoinfarction. Variables were excluded from the model if not significant ($p > 0.05$). All statistical analyses were performed using SPSS Statistics version 20.0 (IBM, Chicago, IL, USA).

Results

A total of 110 patients with cardiac AL amyloidosis were evaluated in the final analysis. The mean age was 55 (46–63) years and 63.6% were male. Pseudoinfarction pattern was observed in 40 patients (36.4%). This cohort was divided into two groups (pseudoinfarction and non-pseudoinfarction) depending on the presence (n = 40) or absence (n = 70) of pseudoinfarction on the ECG. The types of infarct pattern were anterior septal, inferior, and lateral in 20.9%, 12.7%, and 10.9% of patients, respectively, with 7 patients having two involved sites of pseudoinfarction. Baseline demographic and clinical characteristics of patients at the time of histological diagnosis are summarized in Table 1. Two groups did not differ in age, gender, body mass index, heart rate, and diastolic blood pressure and the level of creatine kinase (CK), CK-MB-mass, and cardiac troponin I. Patients with pseudoinfarction had lower systolic blood pressure, higher N-terminal pro-brain natriuretic peptide (NT-proBNP) level, more involved organs and advanced New York Heart Association (NYHA) heart failure classification.

Table 2 presents the echocardiographic parameters. The pseudoinfarction group had a thicker IVS and LVPW, larger left atrium, smaller LV end-diastolic diameter and lower LV ejection fraction than the non-pseudoinfarction one. Patients with a pseudoinfarction pattern had a higher E/A ratio, which may be due to impaired diastolic function. The ECG indexes of the two groups are shown in Table 3. Patients with pseudoinfarction were associated with higher prevalence of peripheral low voltage and poor R wave progression and lower Sokolow–Lyon index and voltage to mass ratio, whereas no differences were observed in the presence of conduction delays and the duration of QRS, QT, and QTc intervals between the two groups.

The mean follow-up was 39 (26–52) months, over which there were 82 deaths. Survival was significantly shorter in the pseudoinfarction group (median 4 months vs 17 months, $p < 0.001$) (Fig. 1). Table 4 shows the analyses of univariate and multivariate Cox proportional hazards models. In the univariate analysis, predictors of death included NYHA III to IV, E/A ratio, the presence of pseudoinfarction, impaired EF, NT-proBNP, and left atrial enlargement. After fitting a multivariate Cox proportional hazards model including all the parameters analyzed in the univariate model, NYHA heart failure III to IV and the presence of pseudoinfarction remained the only two independent prognostic determinants with death hazard ratio of 3.16 and 1.9, respectively.

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