Advanced Cardiac Amyloidosis Associated with Normal Interventricular Septal Thickness: An Uncommon Presentation of Infiltrative Cardiomyopathy

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Background: Increased interventricular septal (IVS) thickness on echocardiography is a diagnostic criterion for cardiac amyloidosis and classically precedes decrement in left ventricular ejection fraction (LVEF). The investigators describe patients with histologically confirmed cardiac amyloidosis who had significant myocardial dysfunction (LVEF $\leq$ 40%) despite having normal IVS thickness.

Methods: All patients with systemic amyloidosis and LVEFs $\leq$ 40% were analyzed to identify the prevalence of normal IVS thickness. Patients with known histories of cardiomyopathy or coronary artery disease were excluded. Histologic evaluation of tissue included assessment of amyloid burden and average myocyte diameter.

Results: There were 255 patients with amyloidosis with LVEFs $\leq$ 40%, of whom seven (3%) had normal IVS thickness and histologic confirmation of cardiac involvement. Of these, six had immunoglobulin light chain amyloidosis, and one had senile amyloidosis. A majority of patients (86%) presented with new-onset cardiac dysfunction associated with edema and/or dyspnea. Electrocardiographic findings included low voltage (43%) and a pseudoinfarct pattern (29%). The 1-year survival from initial tissue diagnosis in the cohort with normal IVS thickness was similar to matched patients with amyloidosis with increased IVS thickness and LVEF $\leq$ 40% (21% vs 18%, respectively, P = .32). Myocardial tissue amyloid burden and average myocyte diameter were significantly reduced in cases compared with controls.

Conclusions: Cardiac amyloidosis can uncommonly present with normal IVS thickness despite significant myocardial dysfunction. The prognosis of these patients is as poor as those with increased IVS thickness. Amyloidosis should be considered in the differential diagnosis of patients with cardiomyopathy and reduced LVEFs despite normal IVS thickness. (J Am Soc Echocardiogr 2014;27:440-7.)

Keywords: Amyloid, Heart failure, Cardiomyopathy, Echocardiography, Diagnosis

Amyloid infiltration of the heart is common in immunoglobulin light chain (AL), senile, and hereditary amyloidosis.[1,2] The presence of cardiomyopathy is a strong predictor of mortality.[3] Echocardiographic evaluation of patients with amyloidosis with heart failure reveals a sensitive, although not specific, finding of increased interventricular septal (IVS) thickness.[4-6] Current guidelines use increased IVS thickness with positive biopsy results for amyloid, commonly from an extracardiac site, to make a diagnosis of cardiac involvement.[7] We have previously demonstrated that 5% of patients with histologically confirmed cardiac amyloidosis and preserved left ventricular (LV) ejection fractions (LVEFs) have normal IVS thickness, suggestive of early cardiac involvement.[8] It is thought that with increasing infiltration, there is increasing thickening and, eventually, progressively worsening systolic function. Therefore, patients with advanced myocardial dysfunction and amyloidosis are typically thought to have increased IVS thickness. However, the mechanism of myocardial dysfunction in amyloidosis may be due to a direct oxidative stress effect of circulating light chains.[9-11] Therefore, patients with decreased LVEFs and amyloidosis could have normal IVS thickness, a finding not reported thus far. We sought to determine the prevalence of normal IVS thickness in patients with cardiac amyloidosis with advanced myocardial dysfunction, defined by an LVEF $\leq$ 40%, and to identify their clinical, echocardiographic, and electrocardiographic characteristics.

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Abbreviations

AL = Immunoglobulin light chain

BNP = Brain natriuretic peptide

IFE = Immunofixation electrophoresis

IVS = Interventricular septum

LVEF = Left ventricular ejection fraction

SPEP = Serum protein electrophoresis

METHODS

Approval for this study was obtained from the Mayo Clinic Institutional Review Board. We conducted a retrospective search of the Mayo Clinic dysproteinemia database and identified 4,521 patients with histologically proven amyloidosis who were diagnosed at Mayo Clinic (Rochester, MN). As outlined in Figure 1, within this group, 255 patients had LVEFs ≤ 40% at presentation, of whom 30 (12%) had IVS thicknesses within the normal range (≤12 mm). Seven of these patients (3%) had confirmation of cardiac amyloidosis by endomyocardial biopsy or at autopsy. Each of the seven patients with histologically proven cardiac amyloidosis and normal IVS thickness was matched to three controls with increased IVS thickness. Controls were from the same cohort of patients with amyloidosis and LVEFs ≤ 40% and were matched according to age (±3 years), date of diagnosis, and LVEF for Kaplan-Meier survival analysis. Echocardiographic data in the Mayo Clinic dysproteinemia database were abstracted from clinical echocardiographic reports by trained nurse abstractors.

All patients included in the Mayo Clinic dysproteinemia database had biopsy-proven histologic confirmation of amyloidosis made by visualization of green birefringence when Congo red–stained tissue was viewed in cross-polarized light. Typing of amyloid was performed by laser capture tandem mass spectrometry when it was available. Otherwise, diagnosis of AL amyloidosis was made by identification of circulating monoclonal protein by serum free light chain assay when it was available or by serum and urine immunofixation electrophoresis (IFE).

Four representative cases (two with increased IVS thickness and two with normal IVS thickness) were reviewed by a cardiovascular pathologist (J.J.M.) to quantify the amount of amyloid burden and evaluate myocyte size. Tissue sections of transmural interventricular septum taken from the midventricular myocardium were stained with sulfated Alcian blue after paraffin-embedding and sectioning (4 μm). Quantification of mural amyloid was performed using an Olympus DP73 microscope camera and cellSense Dimension Imaging Software version 1.9 (Olympus Corporation, Tokyo, Japan) attached to an Olympus BX51 microscope. Three representative 10× fields, from the subendocardium, midmyocardium, and subepicardium were colorimetrically analyzed using ImageJ version 1.44 (National Institutes of Health, Bethesda, MD) to quantify the amyloid compared with the overall percentage tissue, subtracting out artifactual "dead" space in the processed tissue. Myocyte size was evaluated by measuring the diameters of 20 representative myocytes from each case in various 20× fields, averaging the results within each case.

Pertinent clinical data for each patient from the time of initial diagnosis, before the start of treatment, were obtained by review of the medical record and from the dysproteinemia, echocardiography, and electrocardiography databases as applicable to cases and controls. Electrocardiograms were analyzed for rhythm, conduction abnormalities, LV hypertrophy, low-voltage pattern (presence of QRS voltage ≤ 0.5 mV in all limb leads or ≤ 1 mV in all precordial leads)[12] and pseudoinfarct pattern (pathologic Q waves on electrocardiography with no evidence of infarction on echocardiography).

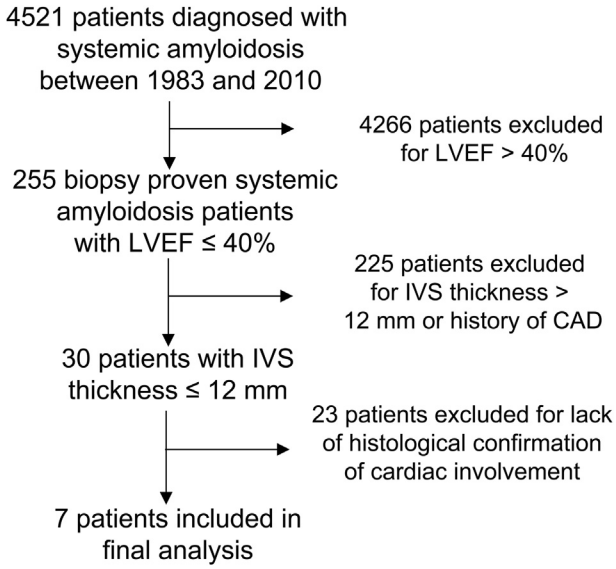

Figure 1 Flowchart describing the selection of the study cohort from the Mayo Clinic dysproteinemia database. *CAD*, Coronary artery disease.

As part of our routine clinical care, all patients diagnosed with amyloidosis undergo echocardiography. Two-dimensional transthoracic echocardiography was performed in a standard manner as previously published.[13] Echocardiograms for the seven patients with normal IVS thickness and histologically proven cardiac amyloidosis were reanalyzed by trained cardiologists (P.A.P. and M.G.) for the following characteristics: diastolic interventricular septum (millimeters) and LV posterior wall thickness (millimeters), right ventricular wall thickness (normal or thickened [>5 mm]), left atrial volume (milliliters), LV end-diastolic and end-systolic diameters (millimeters), LV mass (grams), mitral E-wave deceleration time (milliseconds), E velocity (meters per second), A velocity (meters per second), mitral annular E′ velocity (measured at the septum; meters per second), pericardial effusion, and valvular regurgitation and thickening. P.A.P. and M.G. were aware of the patient selection process before review of echocardiograms.

Echocardiographic variables including IVS, LV posterior wall, and right ventricular wall thickness were measured using two-dimensionally guided M-mode imaging in four cases and the linear 2D method in three cases, while left atrial volumes were measured using the area-length method according to the American Society of Echocardiography's standard guidelines.[14] Diastolic function was graded according to standard guidelines.[15] IVS thickness ≤ 12 mm was considered normal for the purposes of diagnosis of cardiac amyloidosis, as established in the most recent consensus statement of the International Symposium on Amyloid and Amyloidosis.[7] Valve thickening was assessed as normal or thickened while valvular regurgitation was qualitatively graded on a five-point scale (normal, trivial, mild, moderate, or severe) using all views. Mitral regurgitation was quantitatively assessed using the proximal isovelocity surface area method whenever it was considered to be more than mild. The severity of tricuspid regurgitation was assessed using color flow imaging and vena contracta width.

All continuous variables are reported as median (range) and categorical variables as number (percentage of total). Median and 1-year survival from initial tissue diagnosis was determined for patients and matched controls using Kaplan-Meier survival analysis. Difference in