Published in final edited form as:

J Am Soc Echocardiogr. 2014 April ; 27(4): 440–447. doi:10.1016/j.echo.2013.12.010.

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

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Abstract

Background—Increased interventricular septum (IVS) thickness by echocardiography is a diagnostic criterion for cardiac amyloidosis and classically precedes decrement in left ventricular ejection fraction (LVEF). Here, we describe patients with histologically confirmed cardiac amyloidosis who have significant myocardial dysfunction (LVEF < 40%) despite having normal IVS thickness.

Methods—All patients with systemic amyloidosis and LVEF < 40% were analyzed to identify the prevalence of normal IVS thickness. Patients with a known history of cardiomyopathy or coronary artery disease were excluded. Histological evaluation of tissue included assessment of amyloid burden and average myocyte diameter.

Results—There were 255 amyloidosis patients with LVEF < 40% of whom 7 (3%) had normal IVS thickness and histological confirmation of cardiac involvement. Of these, 6 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 normal IVS thickness cohort was similar to matched amyloid patients with increased IVS thickness and LVEF < 40% (21% vs. 18%, respectively; $p=0.32$). Myocardial tissue amyloid burden and average myocyte diameter were significantly reduced in cases compared to controls.

Conclusion—Cardiac amyloidosis can uncommonly present with normal IVS thickness despite significant myocardial dysfunction. The prognosis of these patients is as poor as those with

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DISCLOSURES The authors have no conflicts of interest to disclose.

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increased IVS thickness. Amyloidosis should be considered in the differential diagnosis of patients with cardiomyopathy and reduced LVEF despite normal IVS thickness.

Keywords

amyloid; heart failure; cardiomyopathy; echocardiography; diagnosis

INTRODUCTION

Amyloid infiltration of the heart is common in immunoglobulin light chain, senile, and hereditary amyloidosis [1,2]. The presence of cardiomyopathy is a strong predictor of mortality [3]. Echocardiographic evaluation of amyloidosis patients with heart failure reveals a sensitive, although not specific, finding of increased interventricular septum (IVS) thickness [4-6]. Current guidelines use increased IVS thickness with a positive biopsy for amyloid, commonly from an extra-cardiac 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 ejection fraction (LVEF) 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 LVEF and amyloid could have normal IVS thickness, a finding not reported thus far. We sought to determine the prevalence of normal IVS thickness amongst cardiac amyloidosis patients with advanced myocardial dysfunction defined by a LVEF < 40% and to identify their clinical, echocardiographic and electrocardiographic characteristics.

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 4521 patients with histologically proven amyloidosis that were diagnosed at Mayo Clinic, Rochester. As outlined in Figure 1, within this group, 255 patients had an LVEF < 40% at presentation, of which 30 patients (12%) had an IVS thickness that was within the normal range (< 12mm). Seven of these patients (3%) had confirmation of cardiac amyloidosis by endomyocardial biopsy or at autopsy. Each of the 7 patients with histologically-proven cardiac amyloidosis and normal IVS thickness was matched to 3 controls with increased IVS thickness. Controls were from the same cohort of patients with amyloidosis and LVEF < 40% and were matched according to age ($\pm$ 3 years), date of diagnosis and LVEF for Kaplan-Meier survival analysis. Echocardiographic data in the Mayo Clinic dysproteinemia database was abstracted from clinical echocardiographic reports by trained nurse abstractors.

All patients included in the Mayo Clinic dysproteinemia database had biopsy-proven histological confirmation of amyloid 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 immunoglobulin light chain amyloidosis was made by identification of circulating monoclonal protein by serum free light chain (FLC) assay when it was available or by serum and urine immunofixation electrophoresis (IFE).

Four representative cases (two having increased IVS thickness and two having normal IVS thickness) were reviewed by a cardiovascular pathologist (J.J.M.) to quantitate the amount

of amyloid burden and evaluate myocyte size. Tissue sections of transmural interventricular septum taken from the mid-ventricular myocardium were stained with sulfated alcian blue following paraffin-embedding and sectioning (4 μ m). Quantitation of mural amyloid was performed using an Olympus DP73 microscope camera and cellSense Dimension Imaging Software 1.9 (Olympus Corporation, Tokyo, Japan) attached to an Olympus BX51 microscope. Three representative 10X fields, from the sub-endocardium, mid-myocardium, and sub-epicardium were colorimetrically analyzed using ImageJ 1.44 (NIH, USA) to quantitate the amyloid as compared to the overall % tissue, subtracting out artifactual “dead” space in the processed tissue. Myocyte size was evaluated by measuring the diameter of 20 representative myocytes from each case in various 20X fields, averaging the results within each case.

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

As part of our routine clinical care, all patients diagnosed with amyloid undergo echocardiography. Two-dimensional transthoracic echocardiography was performed in a standard manner as previously published [13]. Echocardiograms for the 7 seven patients with normal interventricular thickness and histologically-proven cardiac amyloidosis were re-analyzed by trained cardiologists (P.P. and M.G.) for the following characteristics: diastolic interventricular septum (mm) and LV posterior wall thickness (mm), right ventricular wall thickness (normal or thickened [> 5 mm]), left atrial volume (mL), LV end-diastolic and end-systolic diameter (mm), LV mass (g), mitral E wave deceleration time (ms), E velocity (m/s), A velocity (m/s), mitral annulus E' velocity (measured at the septum, m/s), pericardial effusion, valvular regurgitation and thickening. P.P. and M.G. were aware of the patient selection process prior to review of echocardiograms.

Echocardiographic variables including interventricular septum, LV posterior wall, and right ventricular wall thickness were measured using 2D guided M-Mode in 4 cases and linear 2D method in 3 cases while LA volumes were measured using the area-length method according to the American Society of Echocardiography standard guidelines [14]. Diastolic function was graded according to standard guidelines [15]. IVS thickness of ≥ 12 mm was considered normal for the purposes of diagnosis of cardiac amyloid 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 5-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 survival between the 2 groups was compared using the log-rank test with a p-value < 0.05 being considered statistically significant. Analyses were conducted using JMP 9 software (version 9.0.0.).

RESULTS

The demographic and clinical characteristics of this cohort are listed in Table 1. Amongst the 7 patients, 6 (86%) presented with newly diagnosed heart failure while the remaining patient was diagnosed to have a cardiomyopathy after surveillance echocardiography was performed. Of those 6 that presented with heart failure symptoms, median time to tissue diagnosis of amyloidosis was 6 months following onset of symptoms. There was one female Hispanic patient in the normal IVS thickness cohort while the remaining patients were male and Caucasian. Edema and dyspnea were the most common symptoms at presentation and had a median duration from onset to presentation of 5 months. The presence of cardiac amyloid was confirmed by endomyocardial biopsy or autopsy in 6 patients and by both means in one patient. Four out of 6 normal IVS thickness AL amyloidosis patients were initiated on standard chemotherapeutic regimens following the diagnosis of AL amyloidosis. Two of these patients were initiated on melphalan and dexamethasone, one on melphalan and prednisone, and one on prednisone and colchicine. One AL amyloidosis patient expired prior to completion of evaluation and did not receive any treatment. A second AL amyloidosis patient successfully underwent cardiac transplantation. The wild-type TTR amyloidosis patient received palliative therapy for congestive heart failure.

Twenty-one matched controls were included in the analysis. As with cases, a majority of patients presented with symptoms of heart failure (81%) while four patients were incidentally found to have cardiac dysfunction on surveillance echocardiography. Two of 21 patients (10%) were African American while the remaining patients were Caucasian. There were no significant differences in clinical characteristics between controls or cases with the exception of fatigue, which was more common amongst the controls (67% vs. 14%, $p = 0.02$).

Laboratory findings are listed in Table 2. Troponin levels were abnormally elevated in 3 out of 4 normal IVS thickness patients while brain natriuretic peptide and N-terminal pro-brain natriuretic peptide were elevated in the 3 patients in whom they were measured. The other four normal IVS thickness patients were diagnosed prior to the use of NT-proBNP and BNP in clinical practice and therefore did not have these values measured. There were no significant difference between cases and controls in circulating troponin, BNP and NT-proBNP levels (0.12 vs. 0.13 ng/mL, $p = 1.0$; 950 vs. 1440 pg/mL, $p = 0.36$; 10060 vs. 18040 pg/mL, $p = 0.36$, respectively).

With the exception of one normal thickness IVS patient who was determined to have wild-type transthyretin (senile) amyloidosis based on tissue subtyping showing transthyretin amyloid and absence of transthyretin mutations on genetic testing, the remaining cases and all controls had immunoglobulin light chain amyloidosis. Serum protein electrophoresis (SPEP) and serum and urine IFE were conducted in all cases and controls but only one normal IVS thickness patient (14%) had a detectable m-protein spike on SPEP; 5 of the 7 patients (71%) who had an IFE performed had a detectable light chain clone. In contrast, 11 of 21 controls (52%) had an elevated M-spike on SPEP and all but one (5%) had a detectable light chain clone on serum or urine IFE. The serum FLC assay helped confirm the diagnosis in one patient with normal IVS thickness that had negative SPEP and IFE results. One control patient had a negative SPEP and serum and urine IFE. Diagnosis of AL amyloidosis in this patient was made based on immunohistochemical evidence of lambda light chains on endomyocardial biopsy specimens. There were 2 cases (29%) diagnosed to have multiple myeloma by bone marrow biopsy, one of whom exhibited classic features of multiple myeloma including bone disease, hypercalcemia, and abnormally elevated creatinine.

A summary of the electrocardiographic findings for cases are provided in Table 3. Low-voltage (43%), pseudoinfarct pattern (29%), and atrioventricular block (14%) were the most common findings. None of the patients met electrocardiographic criteria for LV hypertrophy.

Table 3 summarizes echocardiographic findings in the normal IVS thickness cohort. All patients were within the normal range for IVS thickness. However, 2 of the 7 patients had a thickened posterior LV wall (13 mm) and right ventricular wall. Increased LV mass was present in 3 of 6 patients in whom it was measured. The median value in men was 227 grams with a range of 182-272 grams (normal range 96-200 grams). The single female patient had an LV mass of 109 grams well within the normal range of 66-150 grams for women [14]. Similarly, LV end-diastolic diameter was mildly abnormal in one patient and severely abnormal in a second but was normal in the remaining patients. Valvular regurgitation was either trivial or mild except in 2 patients both of whom had moderate tricuspid regurgitation. Pericardial effusions were tiny or small in all patients who had these. Valve thickening was a common finding and was present in 5 (71%) patients. Sparkling/granular appearance of myocardium was not present in any of the 7 patients. A representative echocardiogram of a patient from this cohort is shown in Figure 2. The parasternal long-axis view shows normal interventricular septum and LV posterior wall thickness and the absence of a granular sparkling appearance and thickened valve leaflets.

Cardiac amyloidosis was confirmed histologically in all 7 patients and is described in Table 4. Patients typically had extensive amyloid deposition that demonstrated an interstitial and/or perivascular deposition pattern. There were 3 of 7 patients who had intramural microvascular involvement. To understand the echocardiographic features of thickened IVS or lack thereof in these patients, two cases of increased IVS thickness were subjected to histological quantitation showing that >50% of their tissue area was attributable to amyloid deposition (53.2% and 51.5%; Figure 3). The two cases with normal IVS thickness showed 31.1% and 13.3% of their tissue area consisting of amyloid. Average myocyte diameter was also increased in the samples obtained from individuals with increased IVS thickness (24.7 μ m and 22.6 μ m) when compared to those with normal IVS thickness (18.1 μ m and 15.9 μ m).

A Kaplan-Meier analysis of patients with normal septum thickness and matched controls with increased septum thickness demonstrated a median survival from initial tissue diagnosis amongst the normal IVS thickness cohort of 7 months as compared to 3 months in controls ($p = 0.32$). One patient in the normal IVS group underwent a combined heart and stem cell transplant and remains alive. Mortality in both groups was high with 79% of patients in normal IVS thickness cohort and 82% of patients in the increased IVS thickness cohort dying within one-year of onset of symptoms.

DISCUSSION

This is the first study to demonstrate that patients with histologically confirmed cardiac amyloidosis can have significantly reduced LVEF without increased IVS wall thickness. This is contrary to traditional thinking regarding cardiac amyloidosis that amyloid infiltration of the heart leads to increased septum thickness [16] and subsequent decline of LVEF. Our review also suggests that patients who present with cardiomyopathy of uncertain etiology may have amyloidosis despite normal IVS thickness, warranting increased vigilance for this disease in such patients. Only 14% of patients had a positive SPEP in our series; hence screening for immunoglobulin light chains with SPEP alone is an inadequate test for AL amyloidosis. Patients in whom amyloidosis is suspected should have, in addition to SPEP, a serum IFE and serum immunoglobulin FLC assay, which together provide a

sensitivity of 97% [17]. Adding a urine IFE increases this to close to 99%. Performing adequate screening is therefore especially important in patients with the uncommon presentation of cardiac amyloidosis identified in this study, where a combination of normal IVS thickness on echocardiography and inadequate screening for a monoclonal protein (i.e. doing only a SPEP) can be misleading and delay recognition of AL amyloidosis. If these tests are negative and clinical suspicion for amyloid is high due to ECG or other echocardiographic findings, further testing to exclude familial or senile forms, as seen in one of our patients, including cardiac magnetic resonance imaging, tissue mass spectroscopy of amyloid fibrils and or genetic testing, should be performed [18-21].

Previous studies have found that IVS thickness is substantially increased in patients with cardiac involvement and amyloidosis. Hamer et al found in a review of 24 echocardiograms of patients with immunoglobulin light chain amyloidosis a median IVS thickness of 17mm [22]. Both Siqueira-Filho et al and Dubrey et al have reported thickened ventricles as a predominant finding in patients suspected of having cardiac amyloidosis [6,23]. In addition to increased absolute wall thickness, progression of wall thickening has been shown to be a powerful predictor of mortality suggesting that survival might be higher in the group with normal IVS thickness [24,25]. Although normal IVS thickness patients appeared to have a higher median survival than matched controls, overall the analysis was not statistically significant nor was there an apparent difference in survival at one-year.

A subset of patients with increased IVS thickness and normal IVS thickness was evaluated in this study. Interestingly, the increased wall thickness appears to be largely attributable to two phenomena: the amyloid protein itself and myocyte hypertrophy. These results are, however, somewhat limited by the small sample size. More detailed study of the extent and distribution of cardiac amyloidosis are necessary to draw more definitive conclusions about their pathobiologic and clinical implications.

There are several theoretical possibilities to explain how low LVEF may occur in the absence of increased IVS. The first potential explanation is that small coronary vessel amyloid was seen in 3 of 7 patients. Anginal symptoms and ischemic ST-T changes have been observed with minimal epicardial coronary artery disease in cardiac amyloidosis and are presumably a result of small vessel amyloid involvement leading to global myocardial ischemia [26-28]. However, the remainder 4 out of 7 normal IVS patients had no histological evidence of coronary amyloid involvement, suggesting that other mechanisms may also be involved. The second potential explanation relates to *in vitro* and animal studies demonstrating that soluble oligomers of amyloidogenic proteins, including immunoglobulin light chains, are cytotoxic. These oligomers increase intracellular reactive oxygen species and alter intracellular calcium handling leading to cardiomyocyte dysfunction and apoptosis through activation of the p38 mitogen-activated protein kinase [9-11, 29, 30]. This cytotoxic mechanism in combination with our finding that total myocardial amyloid deposition and extent of cardiomyocyte hypertrophy in the patients with normal IVS thickness may be lower as compared to controls may explain the finding of reduced EF despite the absence of increased IVS thickness. Another possible explanation for the findings of normal IVS thickness is that baseline wall thickness, prior to amyloid deposition, may have been at the lower end of normal such that, despite significant amyloid infiltration, the wall thickness measurements remained within the normal range.

Current clinical guidelines suggest that increased IVS wall thickness, in conjunction with a positive non-cardiac biopsy, is sufficient to define cardiac involvement in amyloidosis [7]. Our study suggests that reduced LVEF can also be indicative of cardiac amyloidosis despite normal IVS wall thickness. There are other echocardiographic clues to the presence of cardiac amyloid such as valve thickening (71%), increased LV posterior wall (29%), and

increased right ventricular free wall thickness (29%). In addition to echocardiography, electrocardiographic findings such as low-voltage (43%) and pseudoinfarct pattern (29%) should prompt further evaluation for amyloid. Endomyocardial biopsy is the gold standard for diagnosis and should be obtained when there is suspicion for cardiac involvement in the absence of typical echocardiographic findings and a tissue diagnosis has not been established through less invasive means such as a fat aspirate [31]. Cardiac magnetic resonance imaging may provide an alternative, non-invasive option to screen for amyloid involvement and should be considered in patients with cardiomyopathy of unclear etiology [32]. The presence of subendocardial late gadolinium enhancement in cardiac amyloidosis has been shown to have a sensitivity and specificity > 80% in immunoglobulin light chain amyloidosis [33-36]. In our study, cardiac magnetic resonance imaging was performed in one patient with findings suggestive of amyloidosis, which was then confirmed by endomyocardial biopsy. Echocardiographic strain rate imaging is also valuable in early detection of cardiac amyloidosis and serves as a predictor of prognosis but was not routinely performed during the time period of this study [37-39].

There are several important limitations to this study. Patient selection from the large dysproteinemia database at the Mayo Clinic may have introduced a referral bias. However, we believe that due to similarity in presentation to idiopathic dilated cardiomyopathy we may be potentially underestimating the true prevalence of this condition in patients with heart failure. Moreover, the feasibility of future studies to define the epidemiology of this condition in the general population is limited by its low incidence and prevalence and the need for invasive tissue diagnoses. The analysis of survival in these patients could have been skewed due to earlier tissue diagnosis in the increased IVS thickness group who were diagnosed 1.5 months earlier than the normal IVS thickness group (4.5 vs. 6 months, respectively). However, this difference did not reach statistical significance.

In summary, patients with cardiac amyloidosis and cardiomyopathy can present with normal IVS wall thickness. A combination of clinical, electrocardiographic and other echocardiographic findings common in amyloidosis may provide important clues to suggest further workup [23,40]. The presence of normal end-diastolic LV diameter in the presence of decreased LVEF especially with concomitant increased LV mass, increased posterior LV and/or right ventricular wall thickening, or the finding of low-voltage or pseudo-infarct pattern on electrocardiography, even in the absence of more characteristic findings of increased IVS thickness, may indicate the presence of cardiac amyloidosis. In addition, analysis of representative tissue samples suggests that differences in wall thickening may be attributable to both increased amyloid burden and increased average myocyte diameter in patients with increased versus those with normal IVS thickness.

We had previously demonstrated that amyloid deposition can occur without clinical evidence of a cardiomyopathy [8]. Here we show that in patients with a cardiomyopathy, amyloid infiltration can occur even in the absence of IVS thickening. The new insights offered by this study are that in patients with systemically proven amyloid and low LVEF, amyloid cardiomyopathy cannot be ruled out during echocardiography simply because patients have normal IVS thickness. Moreover, in patients who present with heart failure, amyloidosis could be a cause of cardiomyopathy despite the absence of “classical” echocardiographic features of amyloid deposition such as an increased IVS thickness. Albeit an unusual presentation, amyloidosis should be considered in the differential diagnosis of patients with cardiomyopathy and normal IVS thickness. The prognosis in these patients is as poor as those with increased IVS thickness and reduced LVEF. Therefore, accurate and timely diagnosis of these patients will require increased vigilance on the part of clinicians.

Acknowledgments

FUNDING This work was supported CTSA Grant Number UL1 TR000135 (NLP) from the National Center for Advancing Translational Sciences (NCATS); and by the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research [1 UL1 RR024150-01].

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Figure 1.

Flowchart describing the selection of the study cohort from the Mayo Clinic dysproteinemia database. Abbreviations are as follows: CAD, coronary artery disease; IVS, interventricular septum; LVEF, left ventricular ejection fraction

Figure 2.

Representative 2D echocardiogram from a patient from this cohort. The parasternal long axis view at end-diastole demonstrates normal interventricular septum thickness (7 mm) and posterior left ventricular wall (8 mm). There is no evidence of valvular thickening of the mitral or aortic valves. Enhanced refractile pattern of the myocardium (granular sparkling) is not present.

Figure 3.

Histopathological quantitation of amyloid burden and average myocyte diameter in 4 representative patients. The amount of amyloid burden (blue bars) is plotted as percent of total cardiac tissue on the left-hand y-axis for each of four representative cases, two with increased interventricular septum thickness and two with normal interventricular septum thickness. Average myocyte diameter in micrometers (brown line) is plotted on the right hand y-axis for the same four patients.

Table 1

Clinical characteristics of patients with cardiac amyloid and normal interventricular septum thickness

Variable	Normal IVS thickness (n=7) *		Increased IVS thickness (n=21) *		p-value [‡]
Male, n (%)	6	(86)	13	(62)	0.21
Median age, y	58	(50-69)	63	(48-70)	1.0
Systolic blood pressure, mm Hg	118	(87-194)	98	(77-164)	0.11
Diastolic blood pressure, mm Hg	70	(55-80)	60	(30-90)	0.29
Symptoms, n (%)					
Edema	5	(71)	9	(43)	0.23
Dyspnea	4	(57)	13	(62)	0.71
Carpal tunnel syndrome	2	(29)	3	(14)	0.23
Paresthesias	2	(29)	2	(10)	0.09
Fatigue	1	(14)	14	(67)	0.02
Weight loss	1	(14)	10	(48)	0.10
Macroglossia	1	(14)	4	(19)	0.96
Pain	1	(14)	0	(0)	0.09
Purpura	0	(0)	3	(14)	0.28
Biopsy site, n (%)					
Endomyocardium	5	(71)	4	(19)	0.01
Bone marrow	5	(71)	14	(67)	0.94
Fat aspirate	3	(43)	10	(48)	0.74
Renal	0	(0)	2	(10)	0.38
Rectal	0	(0)	2	(10)	0.38
Small Bowel	0	(0)	2	(10)	0.38
Other biopsy site	0	(0)	4	(19)	0.28
Autopsy, n (%)	3	(43)	4	(19)	0.13
Amyloid type, n (%)					0.09
Immunoglobulin light chain	6	(86)	21	(100)	
Senile	1	(14)	0	(0)	
Newly diagnosed cardiomyopathy on presentation, n (%)	6	(86)	17	(81)	0.74

* Values are presented as either numerical values (%) or as median (range)

[‡] P-value less than 0.05 considered statistically significant

Table 2

Laboratory diagnostic test values of patients with cardiac amyloid and normal interventricular septum thickness

Variable	Normal IVS thickness *		Increased IVS thickness *		p-value [‡]
Hemoglobin, g/dL	12.7	(10.3-14.2)	12.2	(9.5-15.7)	0.70
Alkaline phosphatase, units/L	212	(97-325)	159	(63-687)	0.39
Serum creatinine, mg/dL	1.2	(0.8-1.9)	1.4	(0.9-4.0)	0.36
Troponin T, ng/mL	0.12	(0.03-0.32)	0.13	(0.02-0.62)	1.00
Brain natriuretic peptide, pg/mL	950	(640-1630)	1440	(426-2610)	0.36
NT-pro brain natriuretic peptide pg/mL	10060	(4275-11930)	18040	(2250-69540)	0.36
Urine protein, g	0.20	(0.10-3.52)	0.56	(0.05-16.24)	0.56
Serum electrophoresis protein peak, g/dL	0	(0-0.7)	1.34	(0.4-3.4)	0.04
Serum free light chain, mg/dL	50	(28-223)	25.7	(1.24-761)	0.27
κ/λ light chain ratio	0.12	(0.06-279)	0.02	(0.001-20.98)	0.27
Estimated bone marrow plasma cells, %	13	(2-35)	10	(2-80)	0.78
Plasma cells 20%, n	2		3		

Normal values: Troponin T 0.03 ng/mL; brain natriuretic peptide 50 pg/mL

* Values are presented as either numerical values (%) or as median (range)

[‡] P-value less than 0.05 considered statistically significant

Table 3

Echocardiographic and ECG characteristics of patients with cardiac amyloid and normal interventricular septum thickness

Variable	Value *	(% or Range)
Electrocardiographic variables, n (%)		
Low QRS voltage	3	(43)
Presence of any infarct pattern	2	(29)
First-degree atrioventricular block	1	(14)
Left ventricular hypertrophy	0	(0)
Echocardiographic variables		
Left ventricular ejection fraction, %	29	(20-32)
Diastolic interventricular septum thickness, mm	11	(8-12)
Diastolic left ventricular posterior wall thickness, mm	12	(8-13)
Left atrial volume, mL	73.5	33-81
Left atrial volume index, ml/m ²	36	(21-42)
Left ventricular end-diastolic diameter, mm	51	(41-70)
Left ventricular end-systolic diameter, mm	42	(35-59)
E-wave deceleration time, ms	130	(123-185)
Left ventricular mass, g	213	(109-272)
E-velocity, m/s	0.85	(0.8-0.9)
A-velocity, m/s	0.25	(0.2-0.4)
E-A ratio	3.5	(2.3-4)
E'-velocity, m/s	0.06	(0.03-0.4)
E-E' ratio	15	(2-26.7)
Grade 3 or 4 diastolic dysfunction, n (%)	5	(71)
Pericardial effusion, n (%)	4	(57)
Increased right ventricular wall thickness, n (%)	2	(29)
Mitral regurgitation, n (%)	6	(86)
Tricuspid regurgitation, n (%)	6	(86)
Aortic regurgitation, n (%)	3	(43)
Pulmonary regurgitation, n (%)	3	(43)
Any valve thickening, n (%)	5	(71)
Mitral valve thickening, n (%)	4	(57)
Tricuspid valve thickening, n (%)	2	(29)

* Values are presented as either numerical values (%) or as median (range)

Table 4

Histological findings in patients with cardiac amyloid and normal interventricular septum thickness

Specimen source	Diagnosis Year	Age & sex	Amyloid type	Ejection Fraction (%)	Interventricular Septum Thickness (mm)	Survival (months)	Cardiac histological findings
Autopsy	2002	50 M	AL	20	11	0	Extensive global deposition including vascular, myocardial, subendocardial, and valvular (tricuspid & pulmonary).
Autopsy	1984	66 M	AL	30	9	10	Predominantly perivascular and interstitial.
Endomyocardial biopsy & autopsy	1997	68 M	AL	20	12	1	Intramural coronary amyloid. Severely obstructive small vessel disease, with primarily subendocardial involvement.
Endomyocardial biopsy	2009	54 F	AL	29	8	43*	Interstitial deposition with fibrosis and without arteriolar involvement.
Endomyocardial biopsy	2004	58 M	AL	20	12	13	Detailed report was unavailable.
Endomyocardial biopsy	2007	58 M	AL	32	11	3	Interstitial, pericellular deposition. Vascular amyloid is moderate and mildly obstructive. No endocardial amyloid.
Endomyocardial biopsy	1990	69 M	Senile	30	10	92	Pericellular deposition without vessel involvement. Focally, myocytes appear hypertrophied and are separated by pale eosinophilic material which stains as amyloid on the methyl violet stain and sulfated Alcian blue. It is, however, negative for Congo red and thioflavin T.

* Patient remains alive and received a combined heart and stem cell transplant