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HEART TRANSPLANTATION AND END-STAGE CARDIAC AMYLOIDOSIS: A REVIEW AND APPROACH TO EVALUATION AND MANAGEMENT

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Abstract

Cardiac amyloidosis is one of the most common of the infiltrative cardiomyopathies and is associated with a poor prognosis. The extent of cardiac involvement with amyloid deposition is an important determinant of treatment options and is the major determinant of outcome in patients with amyloidosis. Several small case series with sequential orthotopic heart transplantation and autologous stem cell transplant have demonstrated an improvement in post-transplant outcome and have revived enthusiasm about heart transplantation for patients with end-stage heart failure due to AL amyloidosis. The purpose of this review is to summarize the evaluation and management of cardiac amyloidosis and to provide our single-center experience with end-stage heart failure due to AL amyloidosis treated with heart transplantation followed by an autologous stem cell transplant.

Introduction

Cardiac amyloidosis refers to the disease state where the heart is infiltrated by amyloid protein, whether as part of systemic amyloidosis (as is most commonly the case) or as a localized phenomenon. It is the most common of the infiltrative cardiomyopathies (i.e., sarcoid and hemochromatosis) and is associated with a poor prognosis.[1] There are several types of amyloid, each with its unique features that impact clinical characteristics and treatment (Table 1). The extent of cardiac involvement with amyloid deposition is an important determinant of treatment options and is the major determinant of outcome in amyloidosis.[2,3] Primary systemic or AL amyloidosis is the most commonly diagnosed form of clinical amyloid disease in developed countries.[4] The AL fibrils are derived from monoclonal immunoglobulin light chains, and multi-organ infiltration is typical. While the other forms of amyloid deposits are less commonly associated with clinically significant cardiac disease,[3,5] end-stage heart failure has been reported for patients with senile and familial amyloidosis.[6] The purpose of this review is to summarize the evaluation and management of cardiac amyloidosis with emphasis on AL amyloidosis. In addition, we will provide our experience at The Methodist Hospital with end-stage cardiac amyloidosis and heart transplantation as well as heart and sequential autologous stem cell transplantation (ASCT).

Amyloid Type	Fibril Composition	Symptoms/signs	Patient characteristics	Treatment
AL-Amyloidosis	Monoclonal light chain	Frequently severe cardiac involvement (up to 50%); left and right sided HF (dyspnea, ascites, edema), syncope (ventricular arrhythmia, AV-conduction disease) and autonomic neuropathy; typically multi-organ involvement.	Usually over the age of 50 years old (as early as 3rd decade of life).	Chemotherapy; OHT if severe cardiac involvement; Stem cell transplant if no significant cardiac involvement or after OHT.
Familial (ATTR)	Mutated transthyretin (TTR)	Frequent HF (see above); sinus node or conduction system dysfunction, and neuropathy. HF can be severe.	Usually over the age of 40 years old.	Liver Transplant (removes the major source of variant TTR production and replaces it with normal TTR). Con-commitant OHT has been performed.
Senile (ATTR)	Normal transthyretin	Usually mild cardiac involvement with mild symptoms; HF can be severe.	Elderly patients above 70 years old.	Usually supportive treatment. OHT has been performed.
AA-Amyloidosis	Inflammatory proteins (i.e. Protein A)	Rare cardiac involvement; most commonly proteinuria and renal failure.	Relates to the age of onset of the inflammatory disease.	Control inflammation.

Table 1. Types of amyloidosis with cardiac manifestations and proposed treatments.
HF: heart failure; OHT: orthotopic heart transplantation.

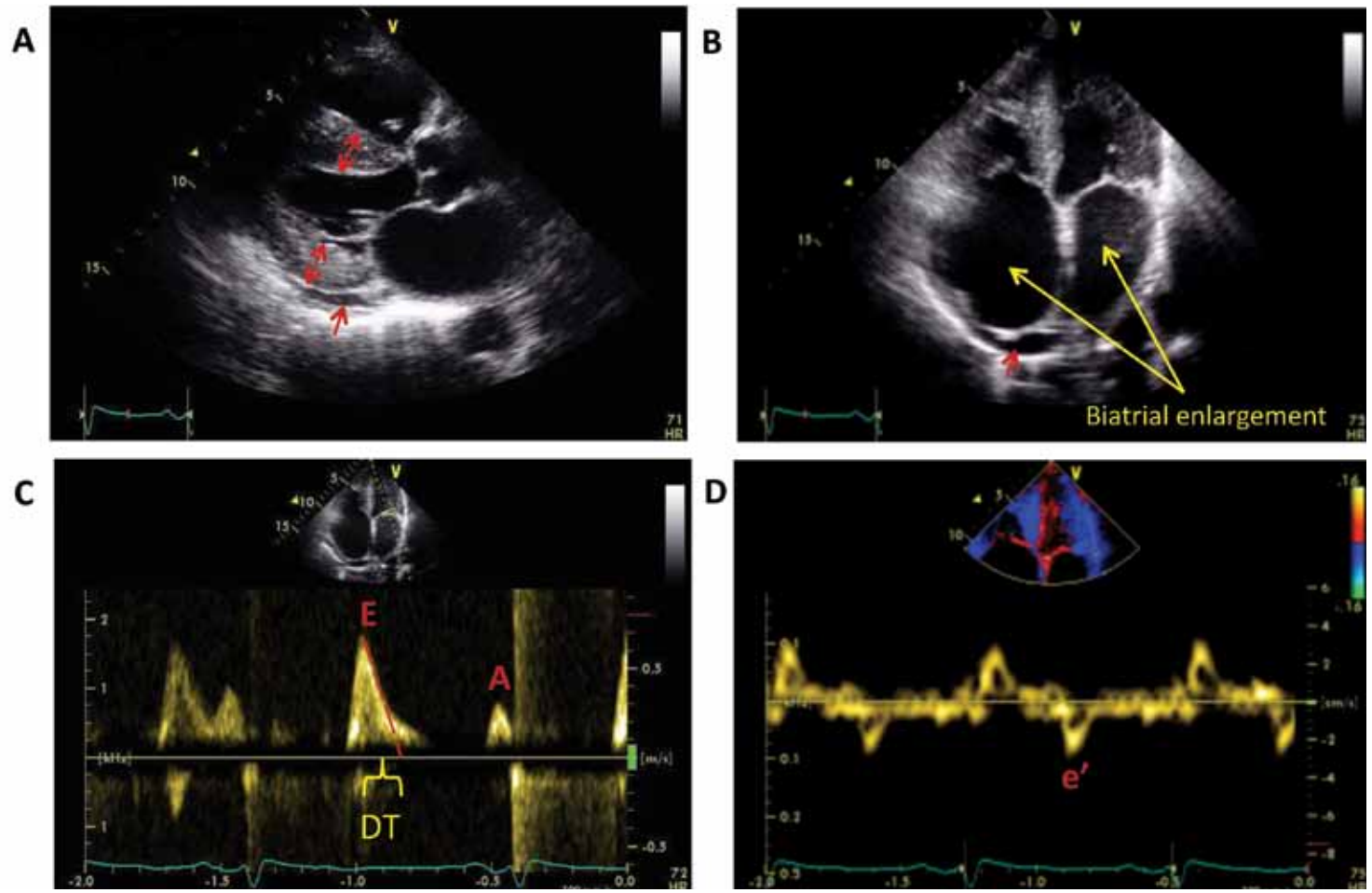

Figure 1. Echocardiographic features of advanced cardiac amyloidosis.
(A) Two-dimensional (2D) echo illustration (parasternal long-axis view) of moderate concentric left ventricular hypertrophy present (septal and posterior wall thickness~1.6 cm marked by double-headed red arrows), small pericardial illustrated by the single-headed red arrow along with "sparkling" ventricular wall appearance. (B) 2D echo illustration (4-chamber view) of biatrial enlargement. (C) Spectral Doppler illustration of restrictive mitral valve inflow pattern (early diastolic inflow velocity, E wave~68 cm/sec and late diastolic inflow velocity, A wave~30 cm/sec equates to an E/A ratio~2.3; short mitral valve deacceleration time, DT~138 msec noted by the red broken line). (D) Tissue Doppler illustration of severely impaired left ventricular relaxation (peak early diastolic lateral mitral valve annulus velocity, e'~3 cm/sec) consistent with marked elevation of underlying LV filling pressure (E/e' ratio~22).

Evaluation to Detect Cardiac Involvement

Noninvasive Testing

The evaluation of cardiac amyloidosis involves a noninvasive and invasive assessment in selected patients. A standard 12-lead electrocardiogram (ECG) and a two-dimensional (2D) echocardiogram including spectral and Tissue Doppler examination (Figure 1) are considered first-line cardiac tests to screen for cardiac amyloidosis. A study from the Mayo Clinic demonstrated that low-voltage ECG was present in ~51% with cardiac amyloidosis with biopsy proven cardiac involvement.[7] A more specific and sensitive finding is the combination of increased left ventricular wall thickness (i.e., >1.1 cm) by echo in the presence of low ECG (seen in 70–74% of patients with cardiac amyloidosis).[8]

Echo features suggestive of cardiac amyloidosis include normal biventricular dimensions with concentric left ventricular wall thickening (especially in the absence of systemic hypertension), valvular thickening, biatrial enlargement, and a pericardial effusion.[5] The echocardiograph granular or "sparkling" ventricular wall appearance, a reported classic feature, is primarily associated with low sensitivity to detect cardiac amyloidosis, can occur in other causes of LV hypertrophy, and is less specific with the application of tissue harmonics (increases myocardial echogenicity in general) in contrast to standard 2D echocardiography imaging alone.[5] "Left ventricular hypertrophy" is a misnomer given that the histologic pathological hallmark of cardiac amyloid disease is extracellular infiltration and not myocyte hypertrophy (Figure 2). While there are many echocardiographic features common in amyloid disease, none are highly specific and a combination of several is often needed to make a diagnosis.

Recently, gadolinium-enhanced cardiac magnetic resonance (CMR) has been clinically utilized to demonstrate late gadolinium enhancement (LGE) in cardiac disease states characterized by cardiac interstitial or extracellular expansion.[9] This extracellular cardiac expansion represents fibrosis replacement or scar in the context of coronary artery disease, lymphocytic infiltration in the context of myocarditis, and amyloid deposition in the context of cardiac amyloidosis. In the largest series to date (120 patients with amyloidosis), of the 35 patients with histologically verified cardiac amyloidosis, abnormal LGE was present in 34 (97%). A smaller case series of patients with histologically proven AL amyloidosis showed LGE by CMR in 76% of patients.[10] Interestingly, in these cohorts of patients, increased echocardiographic left ventricular wall thickness

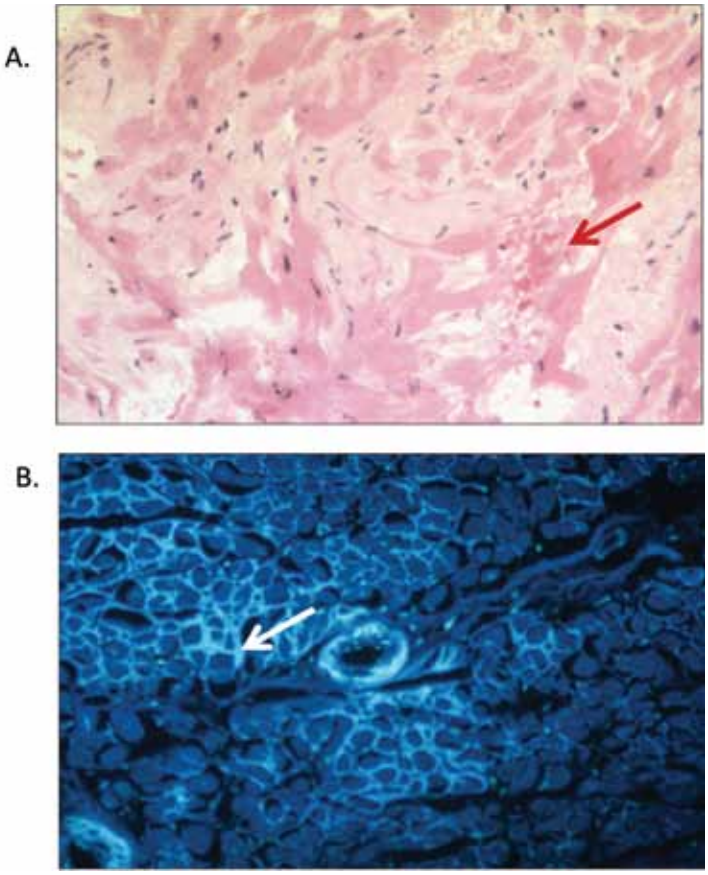

Figure 2. Endomyocardial biopsy findings of cardiac amyloid deposition. (A) Light microscopy of cardiac tissue with intervening stroma (extracellular) with hyalinized appearance (appears pink to red with Congo red staining, see red arrow) secondary to amyloid deposits. (B) Polarized light reveals negative apple green birefringence (white arrow) within the extracellular space.

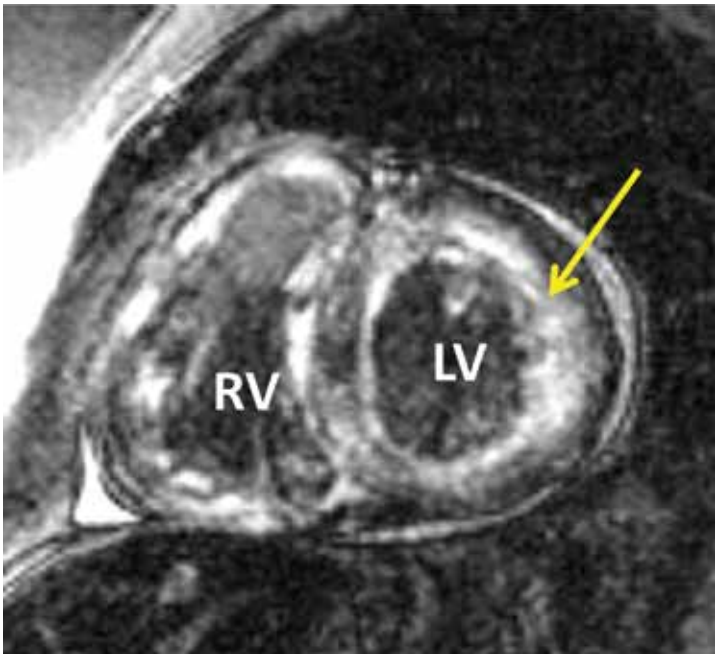

Figure 3. Delayed enhancement cardiovascular magnetic resonance imaging detection of cardiac amyloidosis.
Short axis mid-ventricular view of the left (LV) and right ventricles (RV). Yellow arrows indicates global late gadolinium enhancement (transmural bright white pattern) that reflects extracellular expansion secondary to amyloid deposition in a patient with biopsy proven cardiac amyloidosis.

was less frequently present as an imaging surrogate of cardiac amyloid deposition (32, or 91% of patients).[7] The most common pattern of LGE seen by CMR is transmural or subendocardial global enhancement (Figure 3). While global LGE is most common in patients with cardiac amyloidosis, focal patchy LGE has also been observed.[7]

Cardiac biomarkers including troponin T and I and brain natriuretic peptide (BNP) and N-terminal (NT)-proBNP can be elevated in cardiac amyloidosis.[2] The presumed mechanism to account for myocardial necrosis in cardiac amyloidosis is small-vessel ischemia due to amyloid deposition. BNP and NT-proBNP expression are increased secondary to increase ventricular wall stress due to amyloid infiltration. Proposed cut-off values to detect cardiac amyloidosis for serum troponin T and NT-proBNP are 0.035 mcg/L and 332 pg/ml, respectively.[2] However, these biomarkers are not 100% specific and can be elevated with other disease states including renal failure and liver failure, which may be the case in AL amyloidosis with multi-organ involvement.

Endomyocardial biopsy

Endomyocardial biopsy is the most direct evidence of amyloid deposition to diagnose cardiac amyloidosis. However, Congo red staining of a screening biopsy (i.e., abdominal subcutaneous fat aspirate or rectal biopsy) with associated clinical cardiac features — along with positive noninvasive test results (ECG, echo, or CMR findings suggestive of cardiac amyloidosis) and evidence of an amyloidogenic disorder based on serum and urine monoclonal immunoglobulin testing — is highly suggestive of cardiac amyloidosis. Investigators have shown that amyloid deposition can be uneven,[11] as suggested by patchy focal LGE obtained through CMR.[7] Hence, multiple endomyocardial biopsies may be needed to confirm the diagnosis in such cases. Direct evidence of amyloid deposition in organs other than through screening biopsy can be provided by serum amyloid P (SAP) component scintigraphy, however planar SAP scintigraphy is unable to image amyloids in the moving heart.[5]

Evaluation to Prognosticate

An acquired cardiomyopathy secondary to amyloid deposition displaying clinical features consistent with congestive failure is associated with a poor prognosis. The 1- to 2-year survival with cardiac amyloidosis is less than 50%.[1] Dispenzieri et al. demonstrated that patients with AL amyloidosis stratified by biomarker (troponin T and NT-proBNP) elevation were associated with median survivals of 27, 11, and 4 months, respectively, for stages I, II, and III, with stage 1 showing normal to low levels of both biomarkers, stage II showing one elevated biomarker, and stage III showing elevation of both biomarkers.[2, 12] Detectable cardiac troponin I or T confers on average a median survival of approximately 6 to 8 months.[12]

Echocardiographic imaging surrogates to further prognosticate are based on underlying elevated ventricular filling pressures, which accounts for the clinical congestive heart failure. Those patients with cardiac amyloidosis and a restrictive mitral valve inflow pattern (i.e., deceleration time <150 msec with an E/A ratio >2.0, Figure 2) in the presence of impaired relaxation had a 1-year survival less than 50% compared to patients with normal LV filling pressures having a 1-year survival greater than 90%.[13] Similarly, those patients with AL amyloidosis showing echo features of left ventricular hypertrophy and symptoms of clinical heart failure have a 6-month survival of only 50%.[14] Based on

newer imaging techniques, the presence of LGE by CMR in patients with amyloidosis is strongly associated with New York Heart Association functional class as well as morphologic (LV mass index and RV wall thickness) and cardiac biomarkers of prognosis.[7]

Cardiovascular-Based Treatment Options

Heart Failure Treatment

Diuretics are the first line of treatment in patients with shortness of breath and evidence of volume overload on exam. Concomitant nephritic syndrome may contribute to the need for high-dose diuretics or a combination of loop and thiazide diuretics. Ultrafiltration has been used at our center and others[15] to treat advanced, refractory, decompensated heart failure due to restrictive cardiac physiology.

In contrast to other causes of stage C heart failure, there is no data on the beneficial use of beta blockers, angiotensin-converting enzyme inhibitors, or angiotension II inhibitors in patients with cardiac amyloidosis. In fact, these medications should be used with caution because not uncommonly there is associated autonomic neuropathy that may lead to profound bradycardia and systemic hypotension.[5, 16]

Atrial and ventricular dysrhythmias and sudden cardiac death have been described in patients with cardiac amyloidosis. Both digoxin and calcium channel blockers have a relative contraindication in patients with amyloidosis because both agents bind to amyloid fibrils and may account for increased susceptibility to digoxin toxicity and to impaired cardiac contractility and/or systemic vasodilation.[5] Standard indications for pacing apply to patients with cardiac amyloidosis. While implantable cardiac defibrillators have not been widely used in patients with amyloidosis, these patients are predisposed to ventricular dysrhythmias (even in the absence of traditional signs of cardiac involvement by echo) that can respond to defibrillation (Figure 4). Reported additional mechanisms of death relate to pulseless electromechanical dissociation or progressive biventricular pump failure.

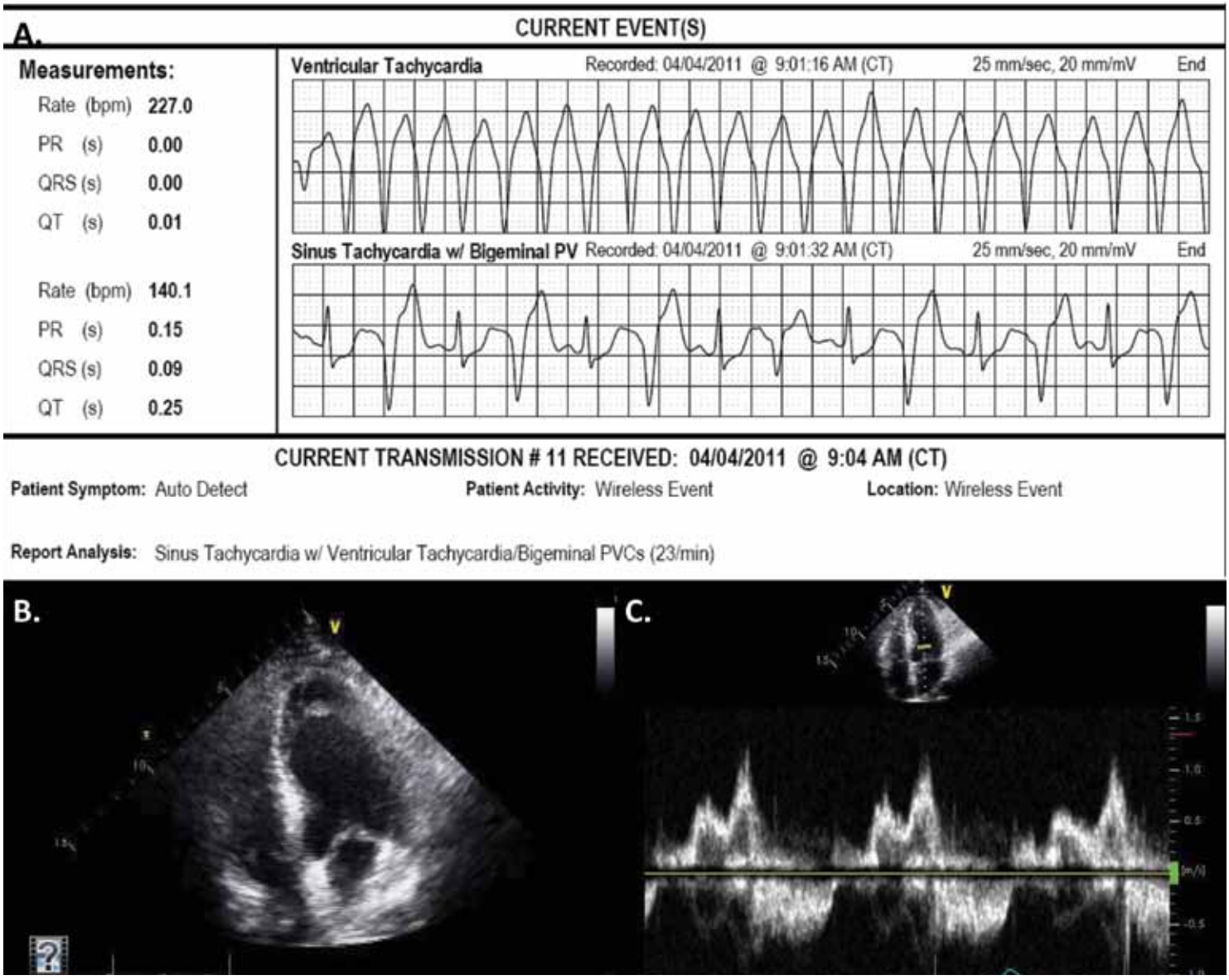

Figure 4. Ventricular tachycardia in a patient with AL cardiac amyloidosis. Example of a 70-year-old patient with palpitations from ventricular tachycardia due to AL amyloidosis, which was detected by endomyocardial biopsy. An AICD was implanted for primary prevention of sudden cardiac death with appropriate AICD shock 2 months later (aborted cardiac arrest) and restoration of sinus rhythm. Of note, the patient had no evidence of significant left ventricular hypertrophy or biatrial enlargement (panel B) and he had normal estimated LV filling pressure by echocardiography (panel C).
AICD: implantable cardioverter defibrillator; LV: left ventricular.

Mechanical Circulatory Support Options

First-line treatment for patients with impending or overt cardiogenic shock, regardless of the underlying etiology of heart failure, is the intra-aortic balloon pump (IABP). We and others have used the IABP to bridge patients with complicated heart failure to permanent left ventricular assist device (LVAD) support and/or to heart transplantation. Advances in the field of device support have led to increased utilization of continuous-flow LVADs to improved outcomes in patients with end-stage heart disease. The feasibility of placing a permanent, continuous-flow LVAD has been reported in six patients with end-stage cardiac amyloidosis [three patients with the Heartmate II, (Thoratec, Pleasanton, CA),[6] one patient with the Jarvik 2000,[17] and two patients with unspecified LVAD type.[18] Patients with severe cardiac amyloidosis and other forms of restrictive cardiomyopathies are largely not represented in the multicenter trials that have established LVAD as a therapeutic option for patients with end-stage disease. In addition, these patients are not significantly represented in the INTERMACS registry to provide definitive recommendations on the safety and efficacy of LVAD, biventricular assist device (BiVAD), or total artificial heart therapy as a bridge to transplantation or destination therapy.[19]

An established risk factor for post-LVAD morbidity and mortality relates to pre-existing right-sided heart failure reflected by a high right-atrial pressure.[20, 21] Right-sided heart failure is a not uncommon cardiac manifestation in patients with end-stage cardiac amyloidosis that potentially equates to higher early postoperative risk compared to patients with nonamyloid dilated advanced cardiomyopathies. Ideal mechanical circulatory support options for patients with end-stage cardiac amyloidosis who have biventricular failure include BiVADs and the total artificial heart.[22] Overall, there is a paucity of data regarding the benefits versus risks of biventricular circulatory support as a bridge to heart transplantation in patients with end-stage systemic amyloidosis. Moreover, the use of biventricular mechanical support as destination therapy not linked to heart transplantation is associated overall with a poor 1-year survival (less than 50%).[20]

Heart Transplantation

The major risk associated with heart transplantation for patients with end-stage cardiac amyloidosis is progression in other major organ systems, including recurrence in the cardiac allograft leading to decreased l- and 5-year post-transplant survival.[23,24] Early transplant experience from the United Kingdom in 24 cases (the majority due to AL amyloidosis) without adjunctive chemotherapy showed a dismal 1- and 5-year survival of 50% and 20%, respectively.[23] Compared to the current U.S. national post-heart-transplant benchmarks provided by the SRTR (1-year survival around 89%, 5-year survival around 75%), heart transplantation for cardiac amyloidosis historically has been associated with the poorer post-transplant survival.[25] However, the implementation of light-chain reductive chemotherapy and post-heart-transplant autologous hematopoietic stem cell transplant (ASCT) has improved post-heart-transplant outcome for patients with cardiac amyloidosis. Based on the United Kingdom experience, post-heart-transplant reductive chemotherapy has improved survival to 71% at 1 year.[23]

ASCT, the ultimate intervention aimed to create remission of the underlying bone marrow plasma dyscrasia, has been used by a few centers,[26-28] including ours, to potentially improve long-term post-heart-transplant survival. The Mayo Clinic group reported their experience with ASCT 6 months post-OHT in 11 patients with AL amyloidosis, with a survival rate of 82% and 65% at 1 and 5 years, respectively.[27] Similarly, the Stanford group reported on three patients with AL amyloidosis who received ASCT for approximately 8 months (6.9–9.9 months) post-OHT, with 100% survival at 1 year and no evidence of amyloid deposition in the cardiac allograft.[28] The group from the Massachusetts General Hospital in Boston reported their experience with 8 patients with cardiac amyloidosis who received sequential OHT and ASCT, with a median time of 7 months before ASCT initiation.[18] At a median follow-up of 4.6 years from cardiac transplant, 62.5% (5 of the 8 patients) were alive and well with no signs of recurrent amyloidosis.[18] The overall reported experience with sequential OHT and ASCT for patient with AL amyloidosis, with the noted improvement in long-term survival comparable to patients who receive heart transplants for nonamyloid heart disease, has created enthusiasm at transplant centers like ours.

The Methodist Hospital Experience with End-Stage Cardiac Amyloidosis

Screening Process for Heart Transplantation

In addition to our routine cardiac transplantation evaluation studies, patients at The Methodist Hospital undergo testing by physician-amyloid experts to assess the extent and severity of amyloidosis. Our Amyloid Working Group includes members from the departments of cardiology, hematology, nephrology, gastroenterology, and thoracic surgery. All patients have the diagnosis of AL amyloidosis established based on serum and urine electrophoresis with immunofixation studies, measurement of serum-free light-chain concentrations, and bone marrow biopsies. Cardiac amyloidosis is confirmed as mentioned above with focus on the severity of heart failure established by right-heart catheterization. All patients undergo coronary angiography to exclude epicardial occlusive disease. In addition, upper and lower gastrointestinal (GI) endoscopies with biopsies are obtained to screen for GI extent of disease. Also, a liver biopsy is performed on those patients with suspected liver involvement based on abnormal liver function tests (transaminases >2x upper limits of normal) or with ascites out of proportion to right-sided hemodynamics. Patients with concomitant renal dysfunction (defined as a glomerular filtration rate <40 cc/kg/min) and/or significant proteinuria (>1 g/day) receive a kidney biopsy. Exclusion criteria for heart or heart-multi-organ transplant consideration include the following: significant GI involvement (based on mucosal amyloid deposition by histology and clinical signs of diarrhea or malabsorption), patients with multiple myeloma (10% or more clonal bone marrow plasma cells and evidence of symptomatic multiple myeloma that is stage I or greater), severe lifestyle limiting peripheral neuropathy on exam, severe coagulopathy, medication noncompliance, or lack of a social support care plan.

Immediate Pre- and Post-Cardiac Transplantation Care

All patients considered eligible for cardiac heart transplantation were listed as recipients with the Organ Procurement and Transplantation Network (OPTN). Mechanical circulatory support (IABP with and without inotropic support in seven patients and a BiVAD in one patient) was used based on the presentation with refractory heart failure due to end-stage amyloidosis. High-dose chemotherapy was avoided while listed 1A to avoid early post-OHT complications related to bleeding or infection.

OHT was performed using the biatrial anastomosis technique, and immunosuppression was given according to our standard institutional protocol (no induction therapy, intraoperative methylprednisolone administered). All patients were discharged from the hospital receiving tacrolimus (target whole blood trough level 8–15 ng/ml), mycophenolate mofetil (1–1.5 g/day), and a prednisone taper to reach a goal of 5 mg/day. Post-cardiac-

	n=9
Age	55 ± 9
Gender (male)	5 (56%)
NYHA class (IIIb/IV)	9 (100%)
Type of Amyloid (AL)	9 (100%)
Type of light chain (Lambda)	8 (89%)
Echocardiographic parameters	
LVEF (%)	41 ± 18
RWT (cm)	0.8 ± 0.1
LVEDd (cm)	3.8 ± 0.6
Right heart cath parameters	
Mean RAP (mmHg)	17 ± 5
Mean PAP (mmHg)	35 ± 10
Mean PCWP (mmHg)	24 ± 4
Mean CI (L/min/m^2)	2 ± 0.3
Mechanical support at time of OHT	
Intraaortic Balloon Pump	7 (78%)
BiVAD	1 (11%)
Renal involvement pre-OHT	
Creatinine Clearance (ml/min)	61 ± 20
Kidney Biopsy*	6 (67%)
Gastrointestinal biopsy*	5 (56%)
Liver biopsy*	4 (45%)
Peripheral Neuropathy	4 (45%)
Days from list 1A to OHT (median, range)	20 (10-145)
Months of Follow-up (median, range)	18 (1-90)

**Biopsy was performed and was positive for Amyloid*

Table 2. Patient Characteristics at time of Evaluation for OHT.
OHT: orthotopic heart transplant; LVEF: left ventricular ejection fraction; RWT: relative wall thickness; LVEDd: left ventricular end diastolic dimension; RAP: right atrial pressure; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; BiVAD: biventricular assist device.

transplant surveillance to assess cardiac allograft function and to screen for rejection included serial right-heart catheterization and endomyocardial biopsy (once weekly for 4 weeks, then once every 2 weeks for 8 weeks, then once monthly for 3 months) for total 6-month surveillance. Preparation for ASCT began at 1-year post-OHT for all patients per protocol. Patients were evaluated for ASCT based on our institutional ASCT eligibility criteria. Retrospective data were reviewed for demographics, clinical outcomes, treatments, echocardiography, and hemodynamics, and post-transplant biopsy sections were analyzed for Congo red staining 6 months after heart transplant.

Cardiac Amyloidosis and Cardiac Transplantation Results

Between December 2004 and July 2012, a total of 891 patients have been referred to our advanced heart failure service for mechanic circulatory support or heart transplant consideration. Twenty patients (2%) with systemic amyloidosis and severe heart failure were evaluated. Three patients died during the evaluation process, 11 patients were listed with the OPTN as potential heart recipients (two patients died on the waiting list for heart transplant), one patient received LVAD support as a bridge to decision regarding transplant candidacy, and five patients were excluded due to significant contraindications to OHT followed by ASCT (see patient flow diagram, Figure 5).

Of the 9 patients transplanted (Table 2), mean age was 55 ± 9 years and 5 were male. Wait list status was 1A for all transplanted patients, with a median wait time of 20 days (range 10–145 days). Eight out of nine patients (88.8%) who have received heart or heart multi-organ transplant are alive (Table 3), with a median post-heart-transplant follow-up of 18 months (range 1–90 months). Seven patients received heart alone, and two patients received heart multi-organ transplants (one heart-kidney transplant and one heart-double lung transplant). The hemodynamic profile at 6 months post-OHT (available for five patients) was normal (mean right-atrial pressure of 5 ± 3 mm Hg, mean pulmonary artery pressure 18 ± 5 mm Hg, and pulmonary capillary wedge pressure 10 ± 4 mm Hg). Echocardiography results at 6 months demonstrated stable cardiac allograft function (mean left ventricular ejection fraction of 65 ± 3.7%) and normal LV size and LV mass (LV end-diastolic diameter 4.2 ± 0.32 cm and LV mass 147.7 ± 24.9 g). Congo Red Staining at 6 months showed only minimal amyloid recurrence in 1 patient.

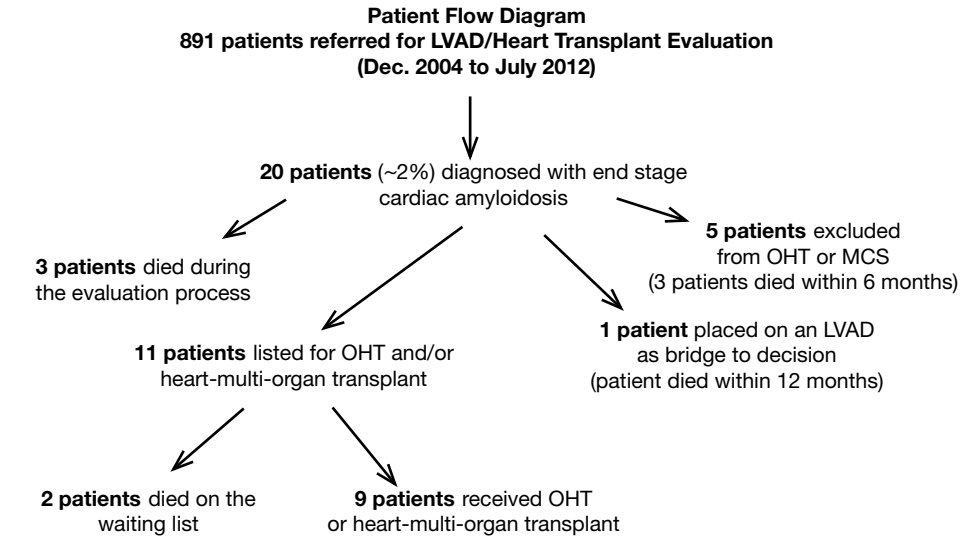

Figure 5. Patient flow diagram.
LVAD: left ventricular assist device; OHT: orthotopic heart transplant; MCS: mechanical circulatory support; IABP: intra-aortic balloon pump.

Pt	Age^	Sex	Amyloid sub-type	Organ Involvement	Time to OHT or multi-organ transplant after listing status 1A (days)	Time to ASCT s/p OHT (months)	Survival post OHT (months)
1	63	F	AL-lambda	Heart, gastrointestinal, kidney, peripheral nerves	22 days-IABP# (OHT-1A)	13	Alive, 39+
2	62	F	AL-lambda	Heart, kidney, liver, peripheral nerves	16 days-IABP# (OHT-1A)	16	Alive, 35+
3	44	M	AL-lambda	Heart, kidney	20 days-IABP# (OHT-1A)	13	Alive, 23+
4	45	M	AL-lambda	Heart, kidney, liver	145 days-IABP# (OHT-cadeveric kidney transplant)	NA*	Alive, 16+
5	62	M	AL-lambda	Heart, kidney, liver, tongue	11 days-IABP# (OHT-1A)	NA**	Dead, multi-organ failure
6	54	M	AL-lambda	Heart, lung	165 days-IABP# (heart-double lung transplant-1A)	Awaits ASCT	Alive, 5+
7	65	M	AL-lambda	Heart, gastrointestinal	11 days-Swan Ganz monitoring plus 2 inotropes (OHT-1A)	6	Alive, 90+
8	42	F	AL-kappa	Heart, gastrointestinal, kidney, liver, peripheral nerves	20 days-BiVAD (OHT-1A)	Awaits ASCT	Alive, 2+
9	54	F	AL-lambda	Heart, gastrointestinal, peripheral nerves	10 days-IABP# (OHT-1	Awaits ASCT	Alive, 1+

Table 3. Heart transplantation results in 9 patients with cardiac amyloidosis. Age^ at time of heart transplantation; NA* (received ASCT 1 year prior to heart-kidney transplant); IABP # (left axillary artery IABP support); NA**(died within 30 days post-OHT).
OHT: orthotopic heart transplantation; ASCT: autologous stem cell transplant.

Four of the nine patients who received OHT have received ASCT (one underwent ASCT at a different institution and three underwent ASCT 1 year after heart transplant at our institution), with a median time between OHT and ASCT of 14 months. For these three patients, plasma-cell targeted therapy between OHT and ASCT was with lenalidomide and dexamethasone in two patients and bortezomib (Velcade) and dexamethasone in the third patient. Bortezomib was approved by the Food and Drug Administration in May 2003 for patients with multiple myeloma who had recurrence of disease after other treatments and has been used in patients with amyloidosis.[29]

All three patients post-OHT followed by ASCT at our institution have done well — with 100% survival and resolution of clinical heart failure based on 23 to 39 months of available post-OHT follow-up. ASCT resulted in complete hematologic remission of the underlying amyloid process in 1 of the 3 patients (patient 2, Table 3) and partial remission in the remaining two patients. There has been no evidence of amyloid recurrence in the cardiac allograft in these three patients based on endomyocardial biopsy surveillance. One patient with partial remission post-ASCT received a donor-related kidney transplant 20 months after ASCT and is currently doing well.

Discussion

Cardiac amyloidosis is a potentially life-threatening condition that describes clinically significant involvement of the heart by amyloid deposition, which in the setting of AL amyloidosis is often associated with involvement of other organs. A combination of noninvasive screening tests (i.e., low-voltage ECG) and typical echocardiographic findings (i.e., left ventricular hypertrophy with biatrial enlargement in the absence of systemic hypertension) is highly suggestive of cardiac amyloidosis. CMR with LGE is a relatively new technique that detects extracellular myocyte expansion from cardiac amyloid deposition and can potentially facilitate early detection of this disease. Moreover, the presence of CMR-related LGE and pattern of LGE is strongly associated with clinical and functional markers of prognosis. The combination of elevated biomarkers (troponin T and BNP) and most importantly clinical heart failure (especially low cardiac output heart failure) with elevated left ventricular filling pressure (detected by echocardiography or by right-heart catheterization) is associated with a dismal prognosis of typically several weeks to months.

Several small case series with sequential OHT and ASCT have revived enthusiasm about heart transplantation for patients with end-stage amyloidosis. Cardiac transplantation in patients with AL amyloidosis without sequential ASCT is associated with a poor 3- to 5-year survival. In contrast, based on our ongoing experience as well as that reported by others,[18, 27, 28] sequential OHT-ASCT improves survival measured after 1 year. Our planned waiting time after 2004 of at least 1-year post-OHT prior to ASCT is different from other reported small case series (waiting times between 6 and 9 months between OHT and ASCT) and importantly

has not translated into amyloid disease recurrence in the cardiac allograft or clinically significant cardiac allograft dysfunction. However, our patient with partial remission post-ASCT did require a kidney transplant due to amyloid-related kidney progression. It is unclear if ASCT sooner after OHT would have halted amyloid-related disease progression.

Conclusion

Unfortunately, patients with end-stage amyloidosis listed for heart transplantation continue to have an extraordinarily poor prognosis, with 50% death on the waiting list reported by others[18] and similarly high at our institution (death during the evaluation process plus wait-list mortality ~ 35%). Death on the waiting list is often due to progressive biventricular failure and/or complications of systemic amyloidosis coupled with long waiting times for a donor heart. Earlier use of biventricular mechanical circulatory support may be beneficial in this high-risk patient population. More importantly, perhaps earlier referral to an established amyloid center like ours may allow for earlier listing and initiation of less-invasive mechanical support (i.e., IABP support) to successfully bridge patients to OHT followed by ASCT. At our program, we place the IABP percutaneously in the left axillary artery position to permit upright sitting and ambulation while waiting for OHT.[30]

At our center, a multidisciplinary approach including hematology and cardiovascular specialists is dedicated to promptly obtaining an exact diagnosis, initiating appropriate screening to determine the extent of end-organ involvement and, most importantly, carefully selecting patients for OHT or heart-multi-organ transplantation. In addition, after heart transplantation we use standard and newer treatments (i.e., bortezomib) in conjunction with anti-rejection therapy, all guided by our Amyloid Working Group, to minimize AL amyloid-related disease progression and to best prepare our patients to undergo ASCT for the most optimal chance at remission and improvement in long-term survival.

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Keywords: Cardiac amyloidosis, amyloid protein, AL amyloidosis, autologous hematopoietic stem cell transplant, end-stage cardiac amyloidosis

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