Having a Heavy Heart
Approaches to Infiltrative Cardiomyopathy

Patrick R. Lawler, MD*; Brian A. Bergmark, MD*; Jacob P. Laubach, MD; Neal K. Lakdawala, MD

Forward
Information about a real patient is presented in stages (boldface type) to expert clinicians (Drs. Neal K. Lakdawala and Jacob P. Laubach) who respond to the information, sharing his or her reasoning with the reader (regular type). A discussion by the authors follows.

A 63-year-old man with previous combat-related Agent Orange exposure and no healthcare contact for 40 years presented to his primary care physician with dyspnea on exertion, orthopnea, and bilateral lower extremity edema. Electrocardiography reportedly showed sinus rhythm, and transthoracic echocardiography demonstrated moderate left ventricular hypertrophy with normal systolic function. New onset heart failure with preserved ejection fraction, attributed to hypertensive heart disease, was diagnosed, and he was begun on diuretics with an initial modest improvement in his symptoms. He presented to our hospital 1 month later with worsening heart failure symptoms and inadequate outpatient response to escalating doses of oral furosemide.

The patient reported dyspnea with minimal activity, severe orthopnea, nightly paroxysmal nocturnal dyspnea, and worsening lower extremity edema. There was a history of abdominal distension, although he found that his arms were thinner and his eyes appeared more sunken-in. On examination he was cachectic with a pulse of 85 beats per minute, blood pressure of 82/70 mm Hg, and respiratory rate of 28 breaths per minute with labored breathing. His skin was cool to touch. A diminished single first heart sound, persistently split second sound with a prominent pulmonary component, and S3 gallop were present. Jugular venous pressure was estimated at 18 cm H2O. The remainder of the examination was notable for dullness to percussion at the lung bases, ascites, tender hepatomegaly, and marked lower extremity edema. ECG revealed sinus rhythm with low voltages in the limb leads and no criteria for left ventricular hypertrophy (Figure 1). Laboratory studies revealed a creatinine of 0.8 mg/dL and normal electrolytes. The hematocrit was 33.3%, platelet count 100 000, ALT 586 u/L (normal range, 7–52 u/L), AST 226 u/L (normal range, 5–34 u/L), alkaline phosphatase 153 u/L (normal range, 40–150 u/L), total bilirubin 1.08 mg/dL (normal range, 0.2–1.2 u/L), serum lactate 2.6 (normal range, 0.5–1.8 mmol/L), albumin 2.6 g/dL, and total protein 8.4 g/dL.

Dr Neal K. Lakdawala: The clinical presentation is of profound and rapidly progressive biventricular heart failure. Evidence of right heart failure is apparent, with marked elevation in the jugular venous pressure with associated ascites and edema. Signs and symptoms (orthopnea and paroxysmal nocturnal dyspnea) of left heart failure are also present. Meta-analyses have shown the presence of a S3 gallop, increased jugular venous pressure, and positive abdominal reflux to be predictive of increased left ventricular filling pressure. However, the absence of pulmonary rales is not helpful in ruling out left-sided heart failure, as chronic pulmonary venous congestion leads to pulmonary lymphatic adaptation, which limits the development of alveolar edema and associated rales. The persistently split second sound with a prominent pulmonary component suggests elevated pulmonary arterial pressures with delayed right ventricular emptying.

The physical examination in decompensated heart failure is critical to triaging the severity of the patient’s condition and selecting appropriate medical therapy. Several findings in this patient are concerning. First is the degree of respiratory impairment with increased work of breathing, and urgent management of the patient’s respiratory status should be a top priority. Additionally, the patient’s skin temperature was described as cool, suggesting a low cardiac output state. This is supported by the finding of a low pulse pressure proportion (by convention <25%), which suggests impairment in cardiac output (≤ 2.1 L/min/m²). Given the constellation of biventricular congestion and diminished cardiac output, positive inotropic therapies are typically needed to augment diuresis.

Although the patient had been provisionally diagnosed with hypertensive heart disease, it is notable that there are no criteria for left ventricular hypertrophy present on ECG. The finding of low QRS voltages in the limb leads with normal...
voltages in the precordial leads is suggestive of an infiltrative process, including cardiac amyloid.

The case to this point presents an important diagnostic dilemma. A previously healthy man was initially found to have mild clinical heart failure and increased left ventricular (LV) thickness with preserved systolic function on echocardiography. When presented with such a patient, infiltrative heart disease should be considered alongside common hypertensive heart disease. In this assessment, findings incongruent with hypertensive heart disease in the patient’s evaluation should be reviewed. Infiltrative disease is suggested by the severity of heart failure out of proportion to the reported TTE results and increased LV thickness on TTE with diminished QRS amplitude on ECG. Other clinical features and ECG/TTE findings that should instigate further evaluation are detailed in the Table.

The physical examination findings in this patient are supported by the laboratory findings. Whereas passive hepatic congestion typically manifests as cholestatic transaminitis, the finding of hepatocellular transaminitis suggests ischemic hepatitis from diminished cardiac output. Elevation in serum lactate, as is seen here, is a late finding providing evidence of systemic hypoperfusion. The elevated total protein and low albumin suggest an increased level of a circulating monoclonal protein (paraproteinaemia). The bicytopenia and suspected paraproteinaemia provide evidence for an underlying hematologic disorder, although anemia from abnormal iron handling and thrombocytopenia from splenomegaly and sequestration could be alternative explanations in a patient with heart failure.

After initial stabilization of the patient, echocardiography is the next important step toward identifying an etiology.

Patient presentation (continued): Transthoracic echocardiography demonstrated severe concentric biventricular hypertrophy with end diastolic interventricular septal thickness of 1.9 cm and left ventricular posterior wall thickness of 1.7 cm (Figure 2A and 2B; Movie I in the online-only Data Supplement). The left ventricular cavity size was small, and the systolic function was moderately reduced with a left ventricular ejection fraction of 40%. Measures of diastolic filling were consistent with restrictive diastolic filling (at least grade 3 diastolic dysfunction), with E dominant mitral inflow, short E velocity deceleration time (110 ms), peak mitral E velocity 101.0 cm/sec, and E/E' (averaged from tissue Doppler at the lateral mitral annulus and inferoseptum) >13 (Figure 2C). Right ventricular hypertrophy was seen, and the right ventricular function was reduced. Both right and left atria were severely enlarged. There was diffuse thickening of all 4 valves (Figure 2A). The estimated pulmonary artery systolic pressure was 37 mmHg plus right atrial pressure (estimated at 15–20 mmHg based on IVC appearance). There were moderate pleural effusions.

Dr Neal K. Lakdawala: The echocardiogram demonstrates moderate systolic dysfunction in the setting of severe biventricular hypertrophy and restrictive diastolic filling. Biatral enlargement is also seen, which is a common feature of restrictive processes and results from reduced ventricular compliance. The findings are suggestive of an infiltrative cardiomyopathy, including cardiac amyloid. The differential diagnosis based on this echocardiogram includes hypertrophic cardiomyopathy, hypertensive heart disease, infiltrative cardiomyopathy including amyloidosis, storage diseases such as Danon and Fabry diseases, and others.

Including biventricular hypertrophy, valvular thickening, and abnormalities of diastolic filling, the classic appearance of the myocardium...
Table. Differential Diagnosis and Differentiating Features of Diseases With Increased Left Ventricular Wall Thickness*†

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Extracardiac Features</th>
<th>Common ECG Features</th>
<th>Echocardiographic Features</th>
<th>Diagnostic Tests</th>
<th>Disease Gene</th>
<th>Inheritance Pattern</th>
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<tr>
<td>Hypertensive heart disease</td>
<td>Adult</td>
<td>Hypertensive retinopathy and nephropathy</td>
<td>Increased QRS voltage</td>
<td>Concentric LVH, (maximal wall thickness usually less than 16 mm)</td>
<td>Blood pressure measurement</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Typically absent</td>
<td>Increased QRS voltage</td>
<td>Asymmetrical LVH, LVOT obstruction, Systolic anterior motion of the mitral valve</td>
<td>Genetic testing‡</td>
<td>MYH7, MYBPC3, TNNT2, TPM1, MYL2, MYL3</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>AL amyloid</td>
<td>Presentation typically in sixth decade or later</td>
<td>Renal dysfunction, typically with albuminuria, Peripheral neuropathy, Hepatic dysfunction, Periportal ecchymosis, Carpal tunnel syndrome, Macroglia, May be asymptomatic</td>
<td>Decreased QRS voltage</td>
<td>Concentric LVH, Increased RV wall thickness, Biventricular enlargement, Systolic dysfunction in advanced disease</td>
<td>Cardiac MR, Endomyocardial biopsy, Fad pad biopsy, Bone marrow biopsy</td>
<td>---</td>
</tr>
<tr>
<td>Senile (WT TTR) amyloid</td>
<td>Indolent presentation in eighth decade or later</td>
<td>Clinically apparent extracardiac involvement is uncommon</td>
<td>Decreased QRS voltage</td>
<td>Concentric LVH, Increased RV wall thickness, Biventricular enlargement, Valvar thickening</td>
<td>Cardiac MR, Endomyocardial biopsy, 99mTc-DPD-SPECT/CT</td>
<td>---</td>
</tr>
<tr>
<td>Mutant TTR amyloid</td>
<td>Presentation in fourth decade or later</td>
<td>Sensorimotor and autonomic neuropathy</td>
<td>Decreased QRS voltage</td>
<td>Concentric LVH, Increased RV wall thickness, Biventricular enlargement, Valvar thickening</td>
<td>Cardiac MR, Endomyocardial biopsy, 99mTc-DPD-SPECT/CT, Genetic testing§</td>
<td>TTR</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>More pronounced features in men</td>
<td>Renal failure, Angiokeratoma, Angiodyrosis, Acroparesthesias, Increased QRS voltage, Short PR interval</td>
<td>Concentric LVH, Increased RV wall thickness</td>
<td>Cardiac MR, Endomyocardial biopsy, 99mTc-DPD-SPECT/CT, Genetic testing§</td>
<td>GLA</td>
<td>X-linked</td>
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<td>Danon disease</td>
<td>More pronounced features in men</td>
<td>Cognitive impairment, Skeletal myopathy, Ophthalmic disorders, Increased QRS voltage, Short PR interval</td>
<td>Marked LV thickness (2-6 cm), Systolic dysfunction in advanced disease</td>
<td>Cardiac or skeletal muscle biopsy in selected cases</td>
<td>LAMP2</td>
<td>X-linked</td>
</tr>
<tr>
<td>Friedrich ataxia</td>
<td>Initial presentation from first to sixth decades</td>
<td>Gait abnormality</td>
<td>Increased QRS voltage</td>
<td>Concentric LVH</td>
<td>Genetic testing§</td>
<td>FXN</td>
</tr>
<tr>
<td>PRKAG2-related cardiomyopathy</td>
<td>Present in adolescents and young adults</td>
<td>Not identified</td>
<td>Increased QRS voltage, Short PR interval</td>
<td>Concentric LVH</td>
<td>Genetic testing§</td>
<td>PRKAG2</td>
</tr>
</tbody>
</table>

99mTc-DPD-SPECT/CT indicates 99mTc-diphosphono-propanodicarboxylic acid single photon emission computed tomography; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MR, magnetic resonance; RV, right ventricle; TTR, transthyretin; and WT, wild type.

*Compiled from select references.2–8
†Mucopolysaccharidosis, familial nontransthyretin amyloid, cardiac oxalosis, Pompe disease, glycogen storage disease IV, and mitochondrial disease (eg, MELAS) are exceedingly rare causes of increased LV wall thickness.
‡Good Positive predictive value, poor negative predictive value.
§Good positive and negative predictive value.
on echocardiography in patients with cardiac amyloidosis has been described as speckled. However, most echocardiography machines now use harmonic imaging, which makes this finding nonspecific. Disabling harmonic imaging on most machines is simple and can be undertaken for obtaining several select images to help support the diagnosis.

This degree of echocardiographic hypertrophy, without increased voltages, points to cardiac amyloid. It is notable that several storage cardiomyopathies are associated with increased QRS voltages (eg, Danon and Fabry diseases).8

**Patient presentation (continued):** Given the initial and ongoing instability of the patient, central access was obtained and the patient was transferred to an intensive care unit for closer monitoring. The patient was begun on intravenous diuretic with dopamine infusion at an initial dose of 2 μg/kg/min. Measurement of intracardiac filling pressures with a pulmonary artery catheter demonstrated a mean right atrial pressure of 21 mm Hg, a pulmonary artery pressure of 59/36 (mean 45) mm Hg, and pulmonary artery wedge occlusion pressure of 38 mm Hg (Figure 3).

The cardiac output by Fick calculation was 3.2 L/min, with a cardiac index of 1.7 L/min/m2. Systemic vascular resistance was 1313 dyn-s-cm⁻⁵, and pulmonary vascular resistance was 2.2 Woods units.

**Figure 2.** Transthoracic echocardiographic (A) parasternal long-axis and (B) short-axis views demonstrate right ventricular thickening, severe left ventricular thickening, a speckled appearance to the left ventricle, and left atrial enlargement (Movie I in the online-only Data Supplement). End diastolic interventricular septal and posterior wall thickness was 1.9 cm 1.7 cm, respectively. There was grade III diastolic dysfunction, evidenced here by E dominant mitral inflow and rapid mitral valve E deceleration time of 110 ms (C).

Dr Neal K. Lakdawala: Appropriate clinical stabilization of the patient is underway. The elevated left- and right-sided filling pressures and depressed cardiac output measured by the pulmonary artery catheter are consistent with our clinical assessment. Among patients with advanced heart failure, there is a 70% to 80% concordance between elevated right atrial pressure (≥10 mm Hg) and elevated pulmonary artery wedge occlusion pressure (≥22 mm Hg).10,11 During the bedside evaluation it is important to be mindful of causes of elevated right atrial pressure in the absence of high left-sided filling pressures, such as pulmonary arterial hypertension. The elevated right ventricular end diastolic pressures are suggestive of a restrictive cardiomyopathy but are relatively nonspecific. Other hemodynamic findings characteristic of restriction can be obtained using simultaneous left and right ventricular pressure recordings, and include pulmonary hypertension, an early ventricular diastolic dip-and-plateau (square root sign), and near-equilibration of diastolic pressures, although the diastolic left ventricular pressure is frequently slightly higher than the right ventricular diastolic pressure.12 Additionally, in patients with restrictive cardiomyopathy, there is often simultaneous decrease of LV and right ventricular pressure during inspiration, referred to as ventricular concordance. This latter finding contrasts with the changes in pressure with respiratory variation seen in constrictive pericarditis, wherein pressures are discordant (ie, right ventricular pressure increases on inspiration and the LV pressure decreases).13

Before sending this patient to the cardiac catheterization laboratory, two important questions should be considered a priori. First, does this patient require invasive hemodynamic support with intra-aortic balloon pump or percutaneous ventricular assist device? The placement of these hemodynamic support devices is increasingly recognized as an important short-term bridge for hemodynamic support in patients with cardiogenic shock while recovery or more definitive therapies can be pursued.14 Studies of these devices to date support their role in augmenting hemodynamics in patients with cardiogenic shock compared with intra-aortic balloon pump, but have not yet shown an effect on mortality.15–17 Perhaps owing to the small number of patients studied or the heterogeneous population of patients with cardiogenic shock enrolled. Additionally, it is important to consider that surgical VAD placement may be impossible in some patients with cardiac amyloid or other infiltrative diseases as a result of insufficient chamber dimensions to accommodate the device’s inflow conduit. Nonetheless, in patients in whom inadequate perfusion is observed, these devices deserve consideration where available.

In this patient, a trial of inotropic support is reasonable before pursuing invasive mechanical circulatory support. Studies have not shown a long-term mortality benefit with inotropic therapy, and indeed these therapies may increase mortality.18 Among patients with acute heart failure and renal dysfunction, a recent study found that neither low-dose dopamine nor nesiritide improved renal function or adequacy of diuresis.19 Patients in cardiogenic shock, as presented here, were excluded from this trial, and inotropic therapy remains commonly used in this setting to support hemodynamics, assist diuresis, and temporize to further therapy such as mechanical support, or transplantation. The use of inotropes is limited by the provocation of dysrhythmia or ischemia.

The second consideration is whether endomyocardial biopsy (EMB) is indicated at this stage. In the most recent American Heart Association Scientific Statement regarding
the indications for EMB, heart failure associated with unexplained restrictive cardiomyopathy was given a class Ila (level of evidence C) recommendation. Indeed, there are circumstances in which EMB is required to establish the diagnosis. However, before undertaking this procedure, it must be recalled that if there is clinical suspicion for cardiac amyloid, as there is here, fat pad aspirate is an easy, safe, first-line diagnostic procedure. Rectal biopsy is an alternative if fat pad is unrevealing. Furthermore, advanced imaging can help elucidate an etiology of cardiac amyloidosis. For example, in addition to the echocardiographic features above, myocardial strain and strain rate imaging may help differentiate cardiac amyloidosis from hypertrophic cardiomyopathy. In cardiac amyloidosis, there is greater restriction of basal compared with apical motion, and indeed mean left ventricular basal strain has been shown to be an independent predictor of cardiac and all-cause mortality. Cardiac MRI can demonstrate global subendocardial late gadolinium enhancement and associated abnormal myocardial and blood-pool gadolinium kinetics. Finally, nuclear scintigraphy is emerging as a novel method for detecting visceral amyloid using 99mTc-DPD. This method appears to be highly sensitive for detecting transthyretin cardiac amyloid, but is only positive in 30% of patients with light chain (AL) amyloid. Thus, EMB biopsy should be considered when there is clinical suspicion but histological confirmation from noncardiac tissue is lacking, concomitant paraproteinemias confuses the diagnosis of possible systemic amyloid, when there is suspicion of senile cardiac amyloid (generally confined to the heart), or before undertaking orthotopic heart transplant. Overall, there are limited data on safety of EMB specifically in cardiac amyloid, but overall the reported rate of complications of EMB is low. In a prospective study of patients with unexplained cardiomyopathy, the rate of biopsy procedure-related complications—including cardiac tamponade, ventricular arrhythmia, heart block, and damage to the tricuspid valve—was reported at 3.3% and the rate of vascular access complications at 2.7%, although the rate of the latter is likely to be lower in the era of ultrasound-guided sheath insertion.

**Patient presentation (continued):** Serum protein electrophoresis revealed an IgM lambda monoclonal protein at 20.8% of total protein (1.60 g/dL) with markedly elevated serum free lambda (λ) light chains and decreased kappa (κ):lambda light chain ratio (free κ:λ ratio of 0.02). Fat pad and bone marrow biopsies were obtained. The fat
pad biopsy stained positively for amyloid with Congo red (Figure 4), which demonstrated apple-green birefringence under polarized light. The bone marrow aspirate demonstrated trilinear hematopoiesis and was 85% cellular with a diffuse lymphoplasmacytic infiltrate constituting 39% of total cellularity (Figure 5). Flow cytometry of the aspirate revealed IgM surface positive, λ light chain producing cells which were positive for CD19, CD20, and CD79a and negative for CD5 and CD10 (Figure 6).

**Dr Jacob P. Laubach:** These findings support a diagnosis of Waldenstrom macroglobulinemia with secondary light chain amyloidosis involving the myocardium. Systemic amyloidosis is a heterogeneous disorder characterized by extracellular deposition of 8 to 10 nm fibrils derived from a range of low-molecular-weight proteins circulating in plasma. AL amyloidosis can occur as a primary disorder or secondary to a hematologic malignancy such as multiple myeloma or Waldenstrom macroglobulinemia, as in the patient described, wherein there is production of an amyloidogenic light chain. The Institutes of Medicine have concluded that there is evidence to suggest that exposure to Agent Orange is a risk factor for the development of AL amyloidosis.26

**Figure 4.** Fat pad biopsy with positive Congo red stain. Confirmatory testing with polarized light demonstrated apple-green birefringence.

**Patient presentation (continued):** Despite ongoing diuretic and inotropic support, the patient remained critically ill. He was deemed too unstable to undergo chemotherapy, with a Karnofsky Performance Score of 20. Mechanical circulatory support as a bridge to sequential cardiac transplantation and stem cell transplant was considered. However, when the prognosis and anticipated forthcoming clinical course was presented to the patient, he chose to focus care on comfort care and expired peacefully shortly thereafter.

**Drs Neal K. Lakdawala and Jacob P. Laubach:** As illustrated here, the prognosis for individuals with severe organ dysfunction may be poor, and interventions aimed at supporting the patient’s comfort and care goals are often prioritized. This case highlights the complexities and challenges in managing patients with amyloidosis, particularly in the setting of multiple organ involvement and limited treatment options. Further research and improved therapeutic strategies are needed to improve outcomes for this population.
compromise related to primary or secondary AL amyloidosis remains guarded. However, patients with limited organ dysfunction at the time of diagnosis fare considerably better and are most likely to benefit from chemotherapy with long-term progression-free and overall survival. This highlights the importance of appropriate diagnostic evaluation in patients whose presentation suggests amyloidosis as a possible diagnosis, and timely initiation of chemotherapy when a diagnosis of AL amyloidosis is confirmed. Unfortunately for this patient, identification of his underlying disease came too late in his overall clinical course.

Discussion

Cardiac amyloid is an uncommon, albeit increasingly recognized, cause of heart failure. Systemic amyloidosis generally results from dystrophic deposition of misfolded protein precursors, including free light chains (AL amyloidosis), amyloidogenic mutant transthyretin (ATTR), and wild-type senile transthyretin, arising from heterogeneous underlying conditions. Amyloid deposition leads to abnormalities of myocardial structure and function, either through infiltration of the myocardium causing a restrictive cardiomyopathy, and, in the case of AL amyloidosis, through direct myocardial toxicity. Differentiating the types of cardiac amyloidosis is essential to guiding treatment and prognosis. Common amyloid features include the finding of apple-green birefringence under polarized light when stained with Congo red, as well as a distinctive green color when stained with sulfated Alcian blue. Multiple organ systems—including cardiac, neural, renal, and hepatic—can be affected, although the pattern of organ involvement varies with the cause of amyloidosis.

Primary AL amyloidosis results from dysregulated production of either mutant immunoglobulin kappa or lambda light chain by a clonal population of bone marrow plasma cells. Likewise, AL amyloidosis may be related to dysregulated production of either mutant kappa or lambda light chain, in the setting of a B-cell malignancy such as multiple myeloma, Waldenstrom macroglobulinemia (as in the patient described), or other non-Hodgkin lymphoma. When these amyloid-forming light chains deposit systemically, organ toxicity arises, including neuropathy (peripheral or autonomic), nephropathy (including light chain nephropathy), hepatopathy, and cardiomyopathy.

Cardiomyopathy manifests most commonly as a restrictive cardiomyopathy, wherein fibril infiltration causes increased ventricular mass and wall thickness and abnormal myocardial relaxation. Unlike other causes of amyloidosis, light chain amyloidosis results in direct myocardial toxicity. In experimental studies, when adult rat cardiomyocytes were exposed to free light chains from purified urine of patients with AL amyloid, a decrease in fractional cardiomyocyte shortening was seen.

Aggressive treatment of AL amyloidosis has been shown to improve prognosis. In patients with primary AL amyloidosis, melphalan and prednisone was for many years the standard approach, but regimens incorporating the proteasome inhibitor bortezomib are now more widely used based on higher levels of hematologic response. Moreover, bortezomib therapy has been associated with improved surrogate cardiac measures, including LV wall thickness, N-terminal brain naturtic peptide, and New York Heart Association functional class. There are data for the use of the immunomodulatory agents lenalidomide and pomalidomide as well. Treatment options remain limited by advanced organ dysfunction or poor functional class. In these patients, sequential orthotopic heart transplant followed by stem cell transplantation has shown clinical promise, although prognosis remains guarded and organ availability in most areas is a limitation. Overall, early and rapid referral of patients to an experienced center is crucial to assuring optimal outcomes.

Amyloidosis from mutant amyloidogenic transthyretin (ATTR) arises from mutations in the tissue transthyretin (TTR) gene, which cause production of misfolded TTR in hepatocytes, and causes neuropathy and cardiomyopathy. Interestingly, hepatic accumulation is minimal, and hepatic failure is uncommon. Nonetheless, liver transplant is the definitive treatment in ATTR. Inheritance of ATTR is autosomal dominant with variable expression but high penetrance. The prognosis is considerably more favorable than AL amyloidosis. Although >70 mutations have been implicated in ATTR, 1 of the most common mutations is a substitution of isoleucine for valine at position 122 (V122I). V122I heterozygosity occurs in ≈4% of blacks and can result in late-onset cardiomyopathy in both men and women. Differentiating this from hypertensive heart disease in this population relies on recognition of clinical clues as illustrated in the case presentation.

Unlike mutant transthyretin, amyloidosis attributable to wild-type transthyretin—senile systemic amyloidosis—occurs as a result of aberrant deposition of normal transthyretin in the myocardium, and occurs almost exclusively in elderly men. This course is more slowly progressive, and the prognosis more favorable than AL amyloidosis: median
survival from the onset of heart failure is 7.5 years versus 15 months in patients with AL amyloidosis, for an identical degree of left ventricular thickening. Extra-cardiac involvement in senile systemic amyloidosis is rare, and hence EMB is often required. However, fibril infiltration may be patchy reducing the sensitivity of EMB. Additionally, the finding of transthyretin fibrils on EMB occurs in a number of patients without clinical amyloidosis as a benign consequence of aging, reducing the specificity of EMB. Ruling out underlying AL amyloidosis is essential. Care should be undertaken here, too, because 3% to 5% of these elderly patients will have an incidentally found monoclonal gammopathy of unknown significance, with paraproteinemia which is unrelated to cardiac amyloidosis. In these patients biopsy or advanced imaging modalities are key to making this distinction.

Diagnostic approaches to suspected cardiac amyloid were illustrated in the case presentation above. Differentiation of various types of amyloidosis is critical to determining treatment options and prognosis. In assessing for AL amyloidosis, the most common form of amyloid, serum, or urine electrophoresis with immunofixation as well as serum-free light chain assay should be performed. A bone marrow evaluation that includes an aspirate, core biopsy, cytogenetics, and Congo red staining is suggested as well. The sensitivity of bone marrow Congo red staining is limited, and thus, if negative, biopsy of the abluminal fat pad, rectum, or organ in which there is suspected amyloid involvement should be pursued. Amyloid subtyping by mass spectrometry proteomic analysis can be considered in selected patients where there is uncertainty regarding the specific amyloid type. Advanced imaging has promise to play an increasingly important role in facilitating the diagnosis. Overall, a number of diagnostic algorithms have been proposed. A modification of these algorithms is presented (Figure 7).

In conclusion, cardiac amyloidosis is a heterogeneous group of clinical conditions manifesting as heart failure with important overlapping and differentiating features. Early interspecialty collaboration is essential for prompt diagnosis and effective management.

Disclosures

None.

References


Key Words: amyloid □ cardiomyopathies
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SUPPLEMENTAL MATERIAL
**Movie Legend**

**Movie 1.** Transthoracic echocardiographic parasternal long axis views demonstrating right ventricular thickening and hyokinesis, severe left ventricular thickening and hyokinesis, a speckled appearance to the left ventricle, and significant left atrial enlargement. Best viewed with Windows Media Player.