CASE REPORT

Transthyretin cardiac amyloidosis: an under-diagnosed cause of heart failure

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Introduction: Cardiac amyloidosis is the most common cause of infiltrative cardiomyopathy and is associated with a poor prognosis. Transthyretin cardiac amyloidosis, particularly the type caused by the mutation that replaces the amino acid valine with the amino acid isoleucine at position 122 (Val122Ile), is most common among African Americans above 65 years of age. Evidence suggests that this mutation is an important, though under-diagnosed, cause of heart failure in this population.

Case presentation: A 74-year-old African American male with a diagnosis of non-ischemic cardiomyopathy for several years, presented with gradually worsening dyspnea on exertion and lower extremity edema. There is no known cardiac disease in his family. An echocardiogram was done showing a decrease in ejection fraction to 30% from 45% in the span of a year. An endomyocardial biopsy analysis identified transthyretin amyloid with the Val122Ile mutation, confirming the diagnosis of familial transthyretin cardiomyopathy.

Discussion: Systemic amyloidosis is a group of diseases caused by the deposition of an abnormally folded, insoluble protein that can accumulate in multiple organs causing progressive and irreversible dysfunction. The mutations that most commonly induce variant transthyretin cardiac amyloidosis are Val122Ile, Val30Met and Thr60Ala. The Val122Ile mutation has been found to be present in 3–4% of the African American/Caribbean population.

Conclusions: Familial amyloid cardiomyopathy is an uncommonly recognized cause of heart failure in the population, and patients may wait several years before accurate diagnosis, risking additional significant irreversible deterioration. Patients that meet the high-risk profile criteria (male gender, age 65 years and older, heart failure symptoms, symmetric left ventricular (LV) hypertrophy, and moderately depressed LV function) should likely undergo additional testing for cardiac amyloidosis.

Keywords: amyloid; cardiomyopathy; transthyretin; cardiac amyloidosis; familial amyloid cardiomyopathy; TTR amyloidosis

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Systemic amyloidosis is a group of diseases caused by an abnormally folded insoluble protein that can accumulate in multiple organs, leading to their progressive dysfunction. The particular precursor protein that misfolds defines the amyloid type and predicts the patient’s clinical course (1). Early identification and accurate classification of the type of amyloid are keys to establish the prognosis and treatment, given that several novel therapies are on the near horizon.

Cardiac amyloidosis is the most common cause of infiltrative cardiomyopathy, and compared with other etiologies (such as sarcoid and hemochromatosis) is associated with a worse prognosis (2). In general, amyloid infiltration of the heart causes both mechanical and electrochemical disruption of cardiac function, manifesting itself as ventricular thickening and restrictive abnormalities, with both diastolic and systolic dysfunction. All cardiac tissues are susceptible, and conduction and valvular abnormalities as well as vascular infiltration (1) can lead to death.

There are two types of amyloid that commonly infiltrate the heart. The first is Immunoglobulin light chain (AL or primary amyloidosis). The second is transthyretin amyloidosis (TTR), which includes both mutant or variant transthyretin (familial amyloid cardiomyopathy...
and familial amyloidotic polyneuropathy) and a non-genetic disease caused by wild-type transthyretin (senile systemic amyloidosis) (1).

Among the variants of TTR that affect the heart, the one with the valine-to-isoleucine substitution at position 122 (Val122Ile) is particularly prevalent among African Americans above 65 years of age (3). Evidence suggests that this mutation is an important, though under-diagnosed, cause of heart failure in the elderly black community, with virtually undetectable prevalence in the white population (4).

Case presentation
A 74-year-old African American male with history of cardiomyopathy was hospitalized with progressive dyspnea on exertion and lower extremity edema. One week prior to admission he had worsening lower extremity edema, orthopnea, and paroxysmal nocturnal dyspnea unresponsive to an increase in his usual dose of oral furosemide, over which time he noted an 8-pound weight gain. NT-proBNP was 8,080 pg/ml, and troponin I was 0.151 ng/ml. Past medical history includes Type 2 diabetes mellitus, hypertension, chronic kidney disease, dyslipidemia, benign prostatic hyperplasia, sleep apnea, cataracts, glaucoma, right and left carpal tunnel syndrome status post release surgery 3 and 8 years ago, respectively, and several surgeries for stenosing tenosynovitis.

There was no family history of heart disease. There was a remote history of smoking, and he used alcohol rarely, and denied using illicit drugs. Medications included aspirin, valsartan, furosemide, metolazone, simvastatin, spironolactone, metoprolol, glipizide, and latanoprost ophthalmic.

On physical examination the patient was not in distress. Blood pressure was 97/61, respiratory rate was 22 per minute, heart rate was 69 bpm, and SatO₂ was 100% on room air. Significant jugular venous distention was noted. Minimal bibasilar crackles were present. Point of maximal impulse (PMI) was displaced laterally, but no murmurs or gallops were noted. Abdomen was slightly distended, without organomegaly or ascites, and 3+ pitting edema extended to the thighs and scrotum. Electrocardiogram (EKG) showed low voltage in limb leads, Q waves compatible with prior inferior infarction, left anterior fascicular block, and prolonged QTc. Chest x-ray revealed no infiltrates or cardiomegaly.

Non-ischemic cardiomyopathy was diagnosed 3 years prior to this admission. Cardiac catheterization revealed no coronary artery disease, mild global left ventricular (LV) hypokinesis, and ejection fraction of 45%. He had two prior admissions to the hospital for congestive heart failure exacerbation, each time responding to intravenous diuretics. A recent echocardiogram demonstrated a drop in ejection fraction to 30% with global hypokinesis, with marked echogenicity of the LV myocardium (Fig. 1). Pulmonary artery systolic pressure was estimated to be 55 mmHg.

Evaluation for amyloidosis revealed serum protein electrophoresis (SPEP) to be negative for monoclonal gammopathy. His serum free kappa light chain was twice the normal level, and there was very mild serum lambda elevation. Immunofixation electrophoresis revealed no evidence of monoclonal gammopathy. An abdominal fat pad biopsy was positive for amyloid deposits by Congo red staining and the presence of apple green birefringence under polarized light. Cardiac MRI demonstrated diffuse LV hypertrophy and significant infiltrative process involving the entire myocardium (Figs. 2 and 3).

**Fig. 1.** A four-chamber apical view echocardiogram showing bi-atrial dilatation, valve thickening, thick ventricular walls, and interventricular septum with speckled appearance.

**Fig. 2.** (A–D) Inversion sequence trying to determine optimal inversion time to assess for late gadolinium enhancement. Inversion time (TI) = 97.5, 125, 152.5, and 180 ms, respectively. There is no optimal delineation of myocardial nulling relative to the myocardial blood pool. (C) TI of 152.5 demonstrate areas of increased signal within the myocardium which have increased relaxivity related to the blood pool which is opposite normal relaxation parameters and suggestive of diffuse infiltration of the myocardium, characteristic of amyloidosis.
Because of continued concern about AL amyloidosis (despite the absence of detectable monoclonal gammopathy), endomyocardial biopsy was performed and mass spectrometry analysis identified transthyretin amyloid with the Val122Ile mutation, confirming the diagnosis of familial amyloid cardiomyopathy. TTR genetic testing showed that he is heterozygous for this mutation.

Treatment with aggressive intravenous diuretics was started. Weight decreased and edema resolved. At discharge, the patient was euvoletic but he still had NYHA class III symptoms. His beta blocker and angiotensin II receptor blocker were discontinued and he remained on a high dose of furosemide.

**Discussion**

Systemic amyloidosis is a group of diseases caused by the deposition of an abnormally folded, insoluble protein that can accumulate in multiple organs causing progressive and irreversible dysfunction. More than 27 different precursor proteins have the propensity to form amyloid fibrils (5). TTR is caused by a misfolding in the hepatic-derived transthyretin in to amyloid and is the most common hereditary amyloidosis.

The mutations that most commonly induce variant TTR cardiac amyloidosis are Val122Ile, Val30Met, and Thr60Ala. Similarly to our patient, most individuals develop a late-onset cardiac amyloidosis and the Val122Ile mutation has been found to be present in 3–4% of the African American/Caribbean population (4, 6). The allele frequency of Val122Ile in the United States is 0.44% for Caucasians and 0% for Hispanics (4).

Diagnosis requires identification of pathologic amyloid deposition. This can be done by Congo red staining, with the characteristic apple green birefringence under polarized light. The particular precursor protein can be identified by immunohistochemical staining, immunogold electron microscopy, or mass spectrometry, which confers the greatest sensitivity and specificity for amyloid typing (7, 8).

An abdominal fat biopsy can identify amyloid deposits in ~70% of those with variant TTR such as Val122Ile disease (9), but cardiac biopsy it is the gold standard for the diagnosis of amyloid cardiomyopathy.

Echocardiography remains the most useful non-invasive imaging modality for identifying and monitoring this disease (1). There are no established echocardiographic criteria for TTR disease; most of the available data are based on the AL population. In general, amyloid infiltration in the heart presents as thick-walled ventricle with a speckled appearance of the myocardium, diminished LV chamber volume, valve thickening, atrial enlargement, and signs of elevated filling pressures caused by diastolic heart failure (1). Among patients with TTR with cardiac involvement, a LV ejection fraction of less than 50% is associated with reduced survival (10).

Increased wall thickness remains a major diagnostic criterion of cardiac amyloidosis. The combination of LV wall thickening with a low-voltage EKG is suggestive of an infiltrative cardiomyopathy, and has a sensitivity of (72–79%) and specificity (91–100%) for amyloidosis (11).

Cardiac MRI with gadolinium enhancement may play an important role in differentiating and identifying cardiac amyloidosis, as it has been proposed that it can distinguish between AL amyloidosis and TTR with good diagnostic accuracy (12).

The overall survival of TTR amyloidosis is significantly better than AL with cardiac involvement (6). Cardiac AL amyloidosis has a high mortality with a life span of 6–12 months from diagnosis (13). In contrast, it has been reported that hereditary TTR has a 98% two-year survival and wild-type TTR has a 100% two-year survival (14). Death commonly results from progressive heart failure or sudden cardiac death.

Clinical management and prognosis differ among the different types of cardiac amyloidosis. A thorough workup to distinguish AL amyloidosis from the TTR type is imperative to prevent inappropriate treatment, like chemotherapy for systemic AL amyloidosis.

Liver transplantation has been reported to halt the progression of clinical manifestations of familial TTR amyloidosis (15). Medical treatment focuses on alleviating the symptoms of heart failure and slow or stop progressive amyloid deposition.

Amyloid infiltration in the heart impairs diastolic filling, reducing stroke volume, leading to compensatory
tachycardia to preserve stroke volume. Beta blockers should therefore be avoided (1). Optimization of fluid status with diuretics is key in management. Calcium channel blockers and digitals are contraindicated in cardiac amyloidosis because they bind to the amyloid fibrils and have the potential of causing toxicity (16–18). Angiotensin receptor antagonists or converting enzyme inhibitors may be beneficial in low doses to improve cardiac output by reducing afterload, especially when there is coexisting hypertension (1).

New treatments provide alternatives to liver transplant. Diffusinal and tafamidis are medications that stabilize transthyretin monomers, although the non-steroidal anti-inflammatory properties of diffusinal make this medication less appealing for individuals with heart failure (19).

In addition, new drugs are in clinical trials to silence transthyretin fibrils and have the potential of causing toxicity (16–18). Diflunisal and tafamidis are medications that stabilize transthyretin fibrils, although the non-steroidal anti-inflammatory properties of diflunisal make this medication less appealing for individuals with heart failure (19).

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Death usually results from intractable heart failure, or sudden cardiac death due to the predisposition of these patients to suffer ventricular dysrhythmias and conduction abnormalities. Implantable cardiac defibrillators have not been widely used in patients with amyloidosis (21). It is well known that implantable cardioverter defibrillator therapy improves survival in patients with cardiomyopathy due to other etiologies, but its benefit in patients with cardiac amyloidosis is unclear, and the consensus opinion is that they do not prolong survival with cardiac amyloidosis (22).

**Conclusion**

Hereditary TTR is an uncommonly recognized cause of heart failure in the population and patients may wait several years before an accurate diagnosis, leading to additional significant and irreversible deterioration. Misdiagnosis is common due to misinterpreting LV infiltration as hypertensive heart disease or other entities that produce ventricular thickening.

The patient presented had the diagnosis of non-ischemic cardiomyopathy for several years and had been treated multiple times in the past for volume overload due to decompensated heart failure, but the etiology of his cardiomyopathy was never established or probably was attributed to his history of hypertension.

A high index of clinical suspicion for TTR is necessary to make the diagnosis, especially when evaluating the elderly African American/Caribbean population with CHF and LV thickening without a clear etiology.

In summary, we should have a low threshold for investigative workup in these patients due to the promise of new therapies for TTR and the positive impact that an early diagnosis could have in the treatment and prognosis. In addition, recognition of a genetic form of cardiomyopathy may also help with recognition of amyloidosis among relatives who carry the same genetic predisposition.

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The authors have no conflict of interest.

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