Journal of Community Hospital Internal Medicine Perspectives

COACTION PUBLISHING

CASE REPORT

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

Gabriela Molina O, MD[1]*, Daniel Judge, MD[2], Wayne Campbell, MD[3], Harjit Chahal, MD[4] and Marc Mugmon, MD, FACC[5]

[1]Department of Internal Medicine, Medstar Union Memorial Hospital, Baltimore, MD, USA; [2]Center for Inherited Heart Disease, Johns Hopkins University, Baltimore, MD, USA; [3]Department of Internal Medicine, Division of Infectious Diseases, Medstar Union Memorial Hospital, Baltimore, MD, USA; [4]Department of Internal Medicine, Medstar Union Memorial Hospital, Baltimore, MD, USA; [5]Department of Cardiology, Medstar Union Memorial Hospital, Baltimore, MD, USA

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*

*Correspondence to: Gabriela Molina O, Department of Internal Medicine, 201 E University Parkway, Baltimore, MD 21218, USA, Email: maria.g.molina@medstar.net

Received: 18 July 2014; Revised: 2 September 2014; Accepted: 10 September 2014; Published: 25 November 2014

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

Citation: Journal of Community Hospital Internal Medicine Perspectives 2014, **4**: 25500 - http://dx.doi.org/10.3402/jchimp.v4.25500

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 $SatO_2$ 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.

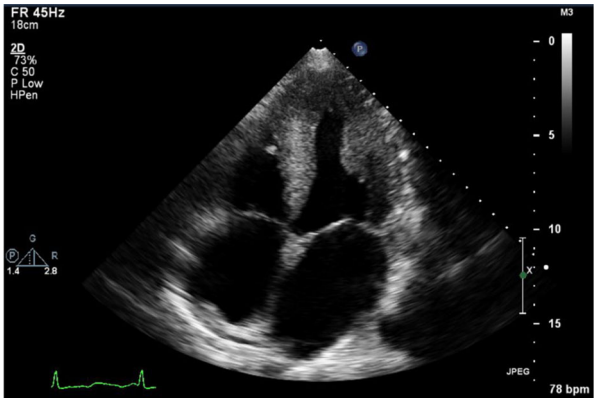

Fig. 1. A four-chamber apical view echocardiogram showing bi-atrial dilatation, valve thickening, thick ventricular walls, and interventricular septum with speckled appearance.

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).

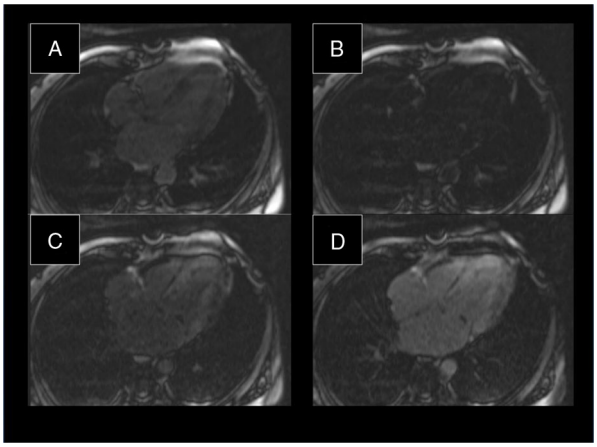

Fig. 2. (A–D) Inversion sequence trying to determine optimal inversion time to assess for late gadolinium enhancement. Inversion time (TI) = 97.5, 125, 152.5, and 180 ms, respectively. There is no optimal delineation of myocardial nulling relative to the myocardial blood pool. (C) TI of 152.5 demonstrate 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.

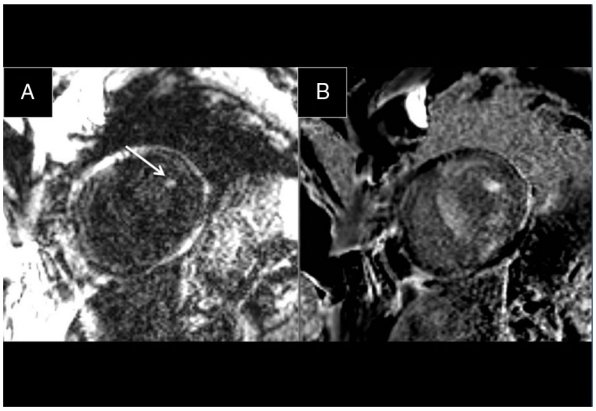

Fig. 3. Inversion recovery images demonstrating late gadolinium enhancement throughout the myocardium. Diffuse infiltration of myocardium with amyloid results in technical difficulty in myocardial nulling. (A) In this case, abnormal enhancement of the papillary muscle (arrow) acts as a reference to normal myocardial relaxation time on magnitude images. (B) Subsequent phase sensitive inversion recovery images demonstrate the extent of myocardial abnormality.

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 euvolemic 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 digitalis 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. Diflunisal and tafamidis are medications that stabilize transthyretin monomers, although the non-steroidal anti-inflammatory properties of diflunisal make this medication less appealing for individuals with heart failure (19). In addition, new drugs are in clinical trials to silence the TTR gene, reducing production of this protein by the liver (20).

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.

Acknowledgements

We thank Dr. Dawn Kershner, Department of Cardiology, Medstar Union Memorial Hospital, Baltimore, MD, and Dr. Jean Jeudy, Cardiothoracic Imaging, Department of Diagnostic Radiology & Nuclear Medicine at University of Maryland Medical Center, Baltimore, MD.

Conflict of interest and funding

The authors have no conflict of interest.

References

1. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation 2012; 126(10): 1286–300. doi: 10.1161/CIRCULATIONAHA.111.078915.
2. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000; 342(15): 1077–84.
3. Jacobson DR, Pastore RD, Yaghoubian R, Kane I, Gallo G, Buck FS, Buxbaum JN. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. N Engl J Med 1997; 336(7): 466–73.
4. Yamashita T, Asl KH, Yazaki M, Benson MD. A prospective evaluation of the transthyretin Ile122 allele frequency in an African-American population. Amyloid 2005; 12: 127–30.
5. Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid 2010; 17: 101–4.
6. Jacobson DR, Pastore R, Pool S, Malendowicz S, Kane I, Shivji A, et al. Revised transthyretin Ile 122 allele frequency in African–Americans. Hum Genet 1996; 98: 236–38.
7. Lavatelli F, Vrana JA. Proteomic typing of amyloid deposits in systemic amyloidoses. Amyloid 2011; 18: 177–82.
8. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood 2009; 114: 4957–59.
9. Connors LH, Prokaeva T, Lim A, Theberge R, Falk RH, Doros G, et al. Cardiac amyloidosis in African Americans: Comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. Am Heart J 2009; 158: 607–14.
10. Bhuiyan T, Helmke S, Patel AR, Ruberg FL, Packman J, Cheung K, et al. Pressure–volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122I mutations and wild-type transthyretin: Transthyretin Cardiac Amyloid Study (TRACS). Circ Heart Fail 2011; 4: 121–28.
11. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. J Am Coll Cardiol 2007; 50: 2101–10.
12. Dungu JN, Valencia O, Pinney JH, Gibbs SD, Rowczenio D, Gilbertson JA, et al. CMR-based differentiation of AL and ATTR amyloidosis. JACC Cardiovasc Imaging 2014; 7(2): 133–42.
13. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 1998; 91: 141e57.
14. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: Disease profiles and clinical courses of the 3 main types. Circulation 2009; 120: 1203e12.

15. Skinner M, Lewis WD, Jones LA, Kasirsky J, Kane K, Ju ST, et al. Liver transplantation as a treatment for familial amyloidotic polyneuropathy. Ann Intern Med 1994; 120(2): 133–34.
16. Gertz MA, Falk RH, Skinner M, Cohen AS, Kyle RA. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. Am J Cardiol 1985; 55: 1645.
17. Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. Chest 1993; 104: 618–20.
18. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. Circulation 1981; 63: 1285–88.
19. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: A randomized, controlled trial. Neurology 2012; 79(8): 785–92. doi: 10.1212/WNL.0b013e3182661eb1.
20. Coelho T, Adams D, Silva A, Lozeron P, Hawkins PN, Mant T, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. N Engl J Med 2013; 369(9): 819–29. doi: 10.1056/NEJMoa1208760.
21. Estep JD, Bhimaraj A, Cordero-Reyes AM, Bruckner B, Loebe M, Torre-Amione G. Heart transplantation and end-stage cardiac amyloidosis: A review and approach to evaluation and management. Methodist Debakey Cardiovasc J 2012; 8(3): 8–16.
22. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady PA. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. J Cardiovasc Electrophysiol 2013; 24(7): 793–98. doi: 10.1111/jce.12123.