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Case Reports

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### **Advanced systolic heart failure in undiagnosed cardiac amyloidosis**

David Gelovani

Zachary Demertzis

Gillian Grafton

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## Introduction

- Transthyretin (TTR) amyloidosis is characterized by extracellular deposition of hepatocyte derived TTR with hereditary and acquired variants.
- Of the >120 genetic mutations in the TTR gene, only a few are responsible for hereditary amyloidosis<sup>[1]</sup>.
- The most common mutation in African-Americans is Val142Ile substitution, occurring with a frequency of 3.5%<sup>[2]</sup>.
- Accumulation of misfolded TTR within the myocardium results in cardiac restriction and dysfunction, most commonly presenting as heart failure with preserved ejection fraction.
- Delay of diagnosis is associated worsening patient in a potentially treatable and reversible disease<sup>[3]</sup>.
- Our case describes a patient who presented with advanced non-ischemic systolic heart failure with subsequent diagnosis of hereditary TTR cardiac amyloidosis.

## History

- EP is a 72 year old African-American male with a past medical history of worsening non-ischemic heart failure diagnosed 20 years ago status post AICD placement in 2016 for low EF.
- Symptoms: worsening fatigue, generalized weakness, and exertional dyspnea limiting ambulation without assistance for two weeks prior to presentation.
- Family history: father and uncle died of heart failure.

## Physical Exam and Laboratory Findings

- Vital Signs: Afebrile, SBP 70-80s, MAP 60s, HR 80-90, RR 16.
- Physical Exam: Thin, frail appearing male with JVD, bibasilar crackles and 3+ pitting lower extremity edema.
- BNP: 2,443 pg/mL.
- EKG: low-voltage tracings (Figure 1).
- Transthoracic Echocardiogram: left ventricular wall hypertrophy with biatrial enlargement and ejection fraction of 25% (Figures 2, 3).

## Hospital Course

- Hypotension did not improve with dobutamine and norepinephrine was started.
- Genetic testing identified a valine to isoleucine substitution at position 142 (Val142Ile) in the TTR protein.
- Goals of care were discussed with family who decided to pursue comfort measures and the patient was discharged home.

## Radiographic and Clinical Images

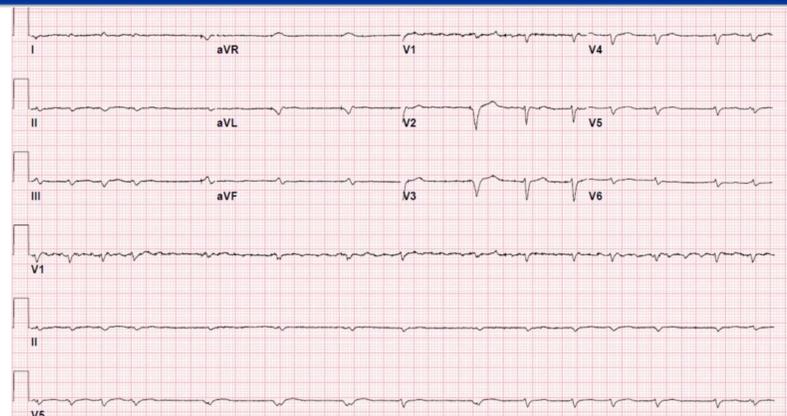


Figure 1. 12 Lead EKG demonstrating low voltage sinus arrhythmia without evidence of left ventricular hypertrophy.

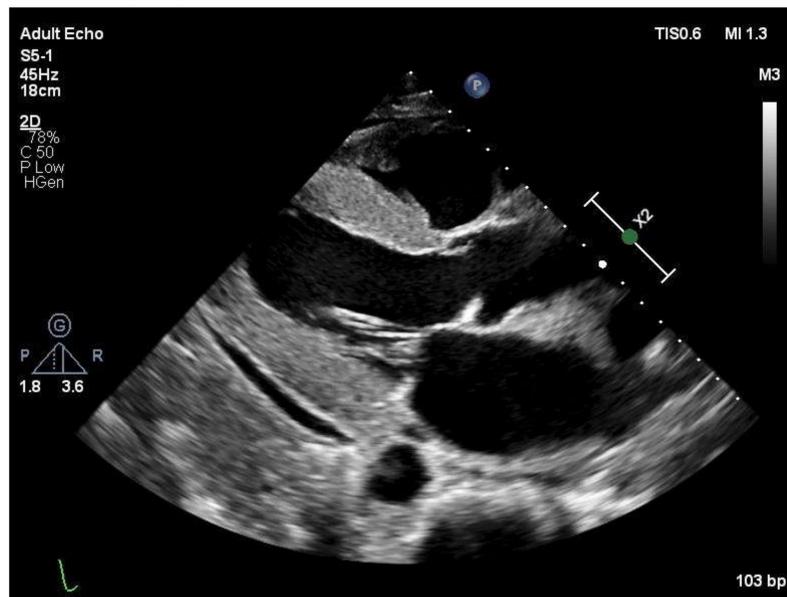


Figure 2. Transthoracic echocardiogram in parasternal long axis demonstrating increased myocardial thickness with speckled pattern.

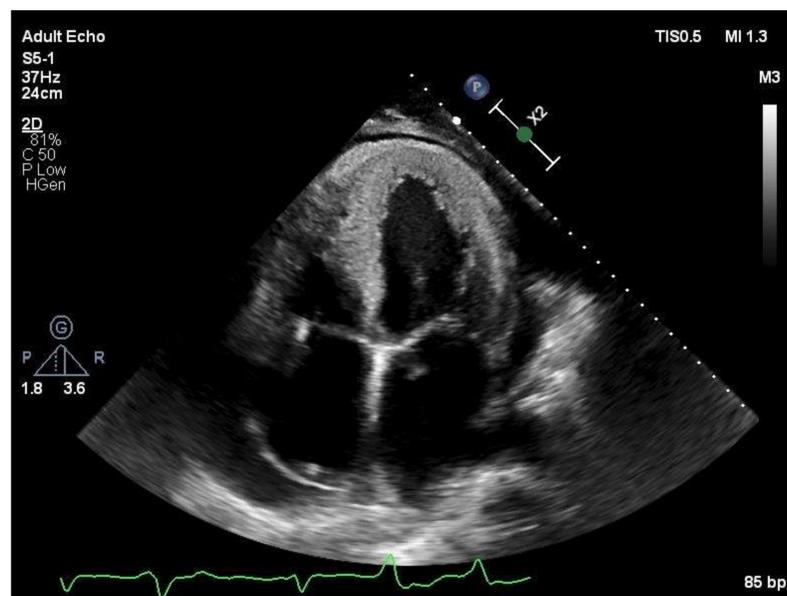


Figure 3. Transthoracic echocardiogram in 4 chamber view demonstrating increased myocardial thickness and biatrial enlargement.

## Discussion

- TTR cardiac amyloidosis is the hereditary or acquired extracellular deposition of misfolded TTR proteins in the myocardium.
- Results in restriction and dysfunction, commonly presenting as heart failure with preserved ejection fraction<sup>[1]</sup>.
- Val142Ile mutation has a frequency of approximately 3.5% in African-Americans and is likely to be underdiagnosed<sup>[2]</sup>.
- Subtle clinical and imaging signs include a constellation of ventricular hypertrophy with a low amplitude voltage EKG, biatrial enlargement, heart failure with preserved ejection fraction, and arrhythmias.
- <sup>99</sup>Tc-pyrophosphate scintigraphy is the most sensitive and specific test for cardiac amyloidosis. Genetic testing has become more accessible if there is an index of suspicion.
- Tafamidis was approved by the FDA in 2019 and prevents progression of disease by stabilizing misfolded protein fibrils<sup>[4]</sup>.
- Liver transplantation is the definitive therapy in patients diagnosed early in the disease course.
- Delay in diagnosis is associated with elevated BNP, troponins, development of systolic heart failure, fatal arrhythmias, or progressive heart failure<sup>[3]</sup>.
- Our case is an example of late diagnosis with systolic heart failure.
- Clinical cues include ventricular wall thickness alongside reduced ejection fraction with absence of ventricular dilation inconsistent with non-ischemic cardiomyopathy.
- Low voltage EKG tracings, family history, and genetic testing further confirmed the diagnosis.

## Conclusion

- With advancements in genetic testing, early detection of transthyretin amyloidosis could improve patient outcomes due to novel medical therapies and transplantation, preventing worsening heart failure and fatal arrhythmias.
- Cardiac amyloidosis should be considered in patients with worsening heart failure symptoms despite appropriate medical therapy with clinical findings associated with the disease.

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