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Hereditary Cardiac Amyloidosis: A Case Report

Yu-hui Huang, MS*; Maya Viner, MD; Tushar Patel, MD; Radhika Sreedhar, MD, MS

***Yu-hui Huang, MS**

University of Illinois College of Medicine at Chicago, 808 S Wood St, Chicago, IL 60612-7314, USA

Abstract

Amyloidosis is a rare, multisystem disease characterized by the accumulation of protein fibrils in the extracellular tissue of organs, including the heart, liver, kidney, and autonomic nervous system. This report discusses a 79-year-old African American female who presented to a university hospital after a fall at home. Her past medical history was significant for non-ischemic cardiomyopathy secondary to cardiac amyloidosis. This was diagnosed by endomyocardial biopsy and genetic analysis revealed a mutant transthyretin protein (Val-122-Ile). The patient also had a history of orthostatic hypotension, pulmonary hypertension, chronic obstructive pulmonary disease, and chronic kidney disease. Significant physical examination findings on admission were elevated jugular venous pressure and lower extremity edema. An EKG showed low voltage readings in the limb leads with a pseudo-infarct pattern. Echo revealed left ventricular hypertrophy, bi-atrial dilation, and restrictive filling physiology. In light of these findings, the patient underwent coronary angiography, which was normal. Her case presents a unique medical challenge, as isolated cardiac amyloidosis is exceedingly rare and difficult to treat. We present a case of hereditary cardiac amyloidosis and discuss its diagnosis and management.

Keywords

cardiac amyloidosis; hereditary amyloidosis; restrictive cardiomyopathy; transthyretin protein.

Introduction

Amyloidosis is defined by the deposition of fibrillary proteins in the extracellular compartment, which progressively damages tissue structure and function [1]. The type of amyloid protein dictates whether deposition will be systemic or localized. The heart is a commonly affected organ in amyloidosis, but many patients are diagnosed because they present with a myriad of symptoms related to their damaged kidneys, liver and ANS. In the absence of such systemic signs of amyloidosis, isolated cardiac amyloidosis is often overlooked when assessing a patient who presents with non-ischemic heart failure. Clinical findings suggestive of cardiac amyloidosis in patients presenting with non-ischemic heart failure, include syncope and orthostatic hypotension. Other findings suggestive of cardiac amyloidosis include nephrotic range of proteinuria, a pseudo-infarct pattern with low voltage on electrocardiogram, a restrictive pattern on echocardiography, and delayed gadolinium enhancement on cardiac magnetic resonance imaging (CMR). A definitive diagnosis is made by a myocardial biopsy. This is required for genotyping of the amyloidosis, which can aid in determining optimal treatment [2, 3]. The patient we present underwent endomyocardial biopsy, which identified a mutant transthyretin protein

(Val-122-Ile) as the underlying factor. The patient is currently enrolled in a clinical trial of tafamidis for transthyretin cardiomyopathy and has been provided supportive treatment with diuretics.

Case Report

A 79-year-old African American female with a history of non-ischemic cardiomyopathy (status post implantable cardioverter defibrillator placement), pulmonary hypertension, chronic obstructive pulmonary disease, chronic kidney disease, and bilateral carpal tunnel syndrome (status post carpal tunnel release surgery on left hand) was admitted after a fall for further evaluation. She quit smoking tobacco 10 years ago with 15 pack years and denied alcohol or illicit drug use. Patient reported diabetes mellitus type 2 and congestive heart failure in her father and hypertension and cerebrovascular accident in her mother, but lacked awareness about other relatives' health information. Both of her parents died of cardiovascular disease in their sixties. On physical examination, she was afebrile but ill appearing, with a blood pressure of 98/64, heart rate of 62 beats per minute, and a respiratory rate of 18 breaths per minute (oxygen saturation of 97% on room air). Her jugular venous pressure was elevated at 12 cm with a positive hepatojugular reflux. Cardiac exam revealed a regular rate and rhythm with an audible third heart sound. On lung exam, she had diminished breath sounds at bases. She also had clubbing of nails and 1+ pitting edema bilaterally. The patient's medications included acetaminophen, albuterol, budesonide-formoterol, aspirin, amiodarone, torsemide, warfarin, and milrinone. A 12-lead electrocardiogram (Figure 1) showed low voltage in the limb leads, interventricular conduction delay, and pseudo-infarct pattern in the inferior and anterolateral leads. Patient's brain natriuretic peptide (BNP) was elevated at 744 pg/mL, compared with 431 pg/mL measured two months prior.

Two years earlier, the patient was initially diagnosed with amyloidosis when she presented with worsening heart failure and increasing fatigue. Her clinicians performed a transthoracic echocardiogram (Figure 2), which revealed moderate concentric left ventricular hypertrophy, mild right ventricular enlargement, moderate bi-atrial dilation, and an ejection fraction of less than 20%. Pulmonary artery systolic pressure was estimated to be 24 to 42 mmHg, assuming a right atrial pressure of 20 to 28 mmHg. Diagnostic angiography showed no evidence of coronary artery disease. Eventually, the patient underwent a right ventricular endomyocardial biopsy (Figure 3), which confirmed the presence of amyloid deposits. The specimen was sent for further characterization, and mutant transthyretin protein (Val-122-Ile) was identified via liquid chromatography tandem mass spectrometry. The patient was diagnosed with transthyretin (TTR) amyloidosis despite the lack of family history of amyloidosis. The patient was enrolled in a clinical trial of tafamidis for transthyretin cardiomyopathy and was provided supportive treatment with diuretics.

Discussion

Amyloidosis refers to a number of different disease entities that share in common the extracellular deposition of insoluble fibrillary proteins in organs and tissues [1]. Based on the type of amyloid protein, cardiac involvement in amyloidosis can be seen in the following five types: (1) amyloid light chain (AL) or primary amyloidosis, (2) TTR or familial/hereditary amyloidosis, (3) systemic senile amyloidosis, (4) isolated atrial amyloidosis, and (5) serum amyloid A (AA) or secondary amyloidosis [2]. The diagnostic evaluation in suspected cardiac amyloidosis includes electrocardiography echocardiography, CMR, and myocardial biopsy in certain cases.

The typical electrocardiographic findings in amyloidosis include low QRS voltage and a pseudo-infarct pattern. Low voltage is more commonly seen in AL amyloidosis compared to TTR amyloidosis, but a pseudo-infarct pattern is equally seen in both types [4-6]. Measurements of BNP and cardiac troponins serve as informative markers in AL amyloidosis, but their value in TTR amyloidosis is yet to be determined. BNP in general reflects high filling pressures, but amyloid deposits may have a local effect as BNP granules are found in higher quantities in myocytes adjacent to amyloid deposits [7]. Increased troponin concentrations are a marker of poor prognosis, but the mechanism remains unclear [8].

On echocardiogram (Figure 2), the characteristic features of cardiac amyloidosis include ventricular thickening with myocardial "speckled" appearance, decreased left ventricular volume, enlarged atria, and restrictive diastolic physiology [9]. These findings are similar in all types of amyloidosis [10]. In comparison, CMR gives better characterization of myocardial borders and 3-dimensional images for quantification of wall thickness and ventricular volumes. However, the key finding in CMR that helps in the diagnosis of amyloidosis is delayed gadolinium enhancement. In normal myocardium, gadolinium is not retained after administration, a phenomenon known as "nulling of myocardium." In cardiac amyloidosis, the distribution kinetics of gadolinium are impaired due to extracellular deposition of amyloid, leading to retained contrast that produces the characteristic late gadolinium enhancement [3].

A subcutaneous fat pad biopsy may identify amyloid deposition in about 70% of patients, but for conclusive diagnostics a myocardial biopsy is required and is the clinical standard. Unfortunately, a false negative biopsy remains a concern as the biopsy may miss the abnormal amyloid deposits and erroneously sample healthy tissue. According to the American Heart Association/American College of Cardiology guidelines, there is a Class II-a recommendation to perform endomyocardial biopsy in heart failure associated with unexplained restrictive cardiomyopathy [11]. Histological detection of amyloid deposits via Congo red stain and classic apple-green birefringence under polarized light confirms the diagnosis [1].

The TTR gene is located on the long arm of chromosome 18 and consists of 5 introns and 4 exons [12]. More than 100 different mutations have been isolated in transthyretin-associated amyloidosis. Val-30-Met is the most common mutation worldwide, followed by Val-122-Ile, which is the most frequent mutation in the United States. Other less common transthyretin mutations include Thr-60-Ala, Ser-77-Tyr, and Ile-84-Ser [1, 2]. These mutations are usually found in geographic or ethnic clusters and appear to exhibit an autosomal dominant pattern of inheritance. TTR geno-positivity has been reported in approximately 4% of the African American population in the United States, while it is virtually undetectable in Caucasians [13-15]. Since the disease has an incomplete penetrance, the clinical phenotype can be quite variable [16]. However, there is still a strong association between the carrier status and development of heart failure, with a reported relative risk of 2.6 [17]. According to statistics from the U.S. Census, as many as 1.5 million African Americans carry the Val-122-Ile mutation [18]. Data from the Beta-Blocker Evaluation in Survival Trial revealed that around one-tenth of all African Americans over the age of sixty are carriers of Val-122-Ile mutation [19]. Therefore, unrecognized cardiac amyloidosis may account for several cases of nonischemic cardiomyopathy in the African American population.

Cardiac amyloidosis in general has a poor prognosis, but this differs according to amyloid type and response to therapy. Treatment may be classified as supportive therapy with modified heart-failure treatment including device therapy, therapies that suppress respective amyloid fibril precursor protein production such as chemotherapy in AL amyloidosis, and novel strategies to inhibit amyloid fibril formation. TTR dissociation inhibitors such as tafamidis, which is currently undergoing phase 3 clinical trial, may be the first medication to treat amyloidosis [20]. Although rarely feasible, cardiac transplantation can be successful in select patients [21]. Since our patient was enrolled in a clinical trial of tafamidis for transthyretin cardiomyopathy, she was provided supportive treatment with diuretics and recommended follow-up with her cardiologist.

Conclusion

Although the initial presentation with classic electrocardiographic, echocardiographic, and cardiac catheterization findings was suggestive of amyloidosis in our patient, the absence of any other organ involvement made the diagnosis and management difficult. Isolated cardiac amyloidosis with no evidence of systemic organ involvement is rare and may require endomyocardial biopsy to delineate the diagnosis. As treatment ultimately depends on the cause of amyloid deposition, it is important that clinicians consider the various types of systemic amyloidosis before initiating therapy.

Figures

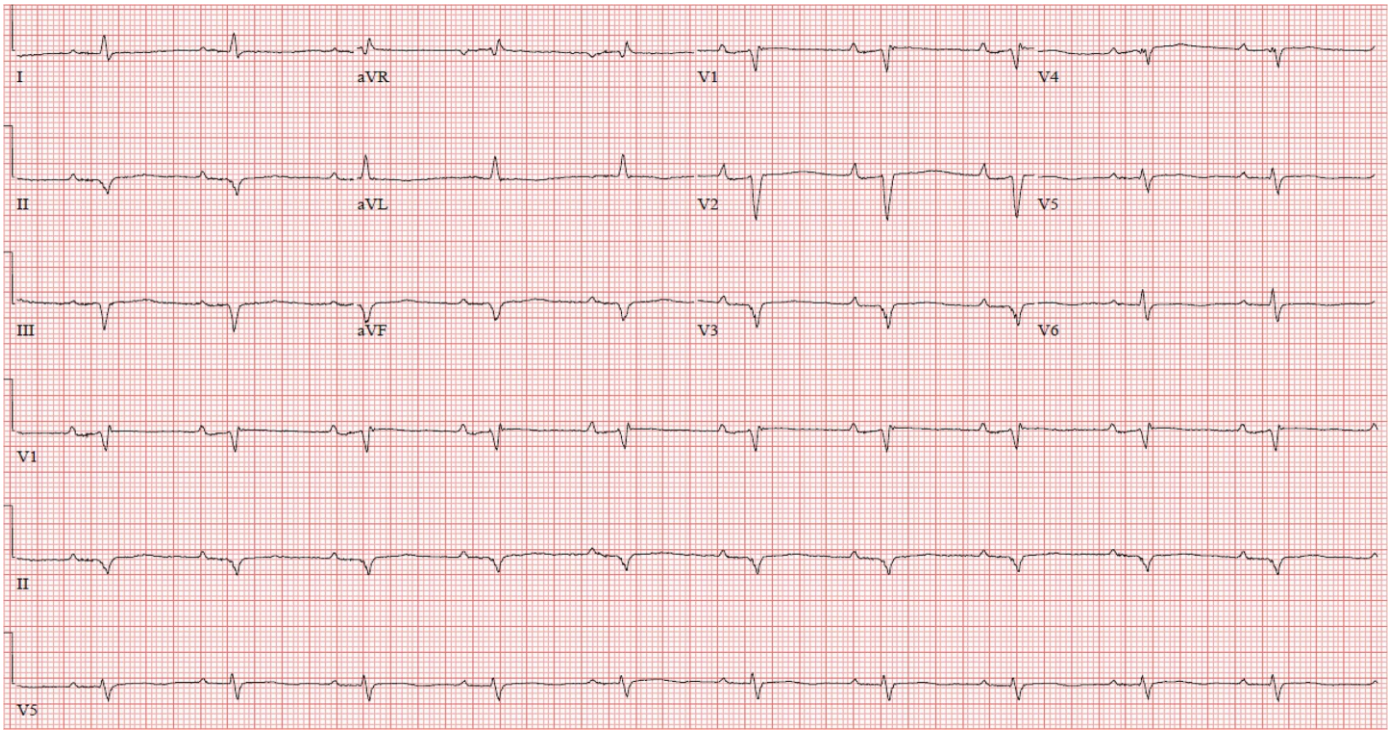

Figure 1: 12-lead electrocardiogram demonstrating low voltage in limb leads, interventricular conduction delay, and pseudo-infarction pattern in the inferior and anterolateral leads.

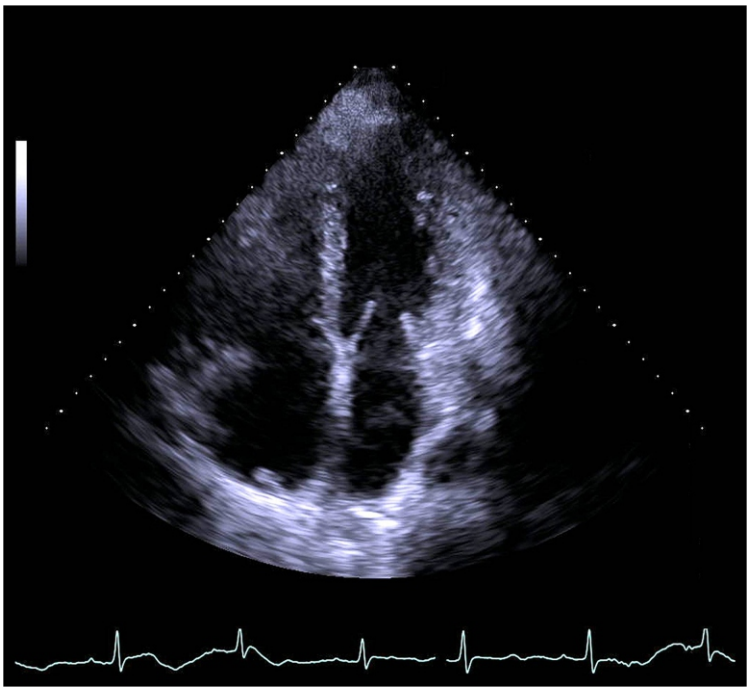

Figure 2: Transthoracic echocardiogram showing moderate concentric left ventricular hypertrophy with myocardial "speckled" appearance and moderately dilated atria.

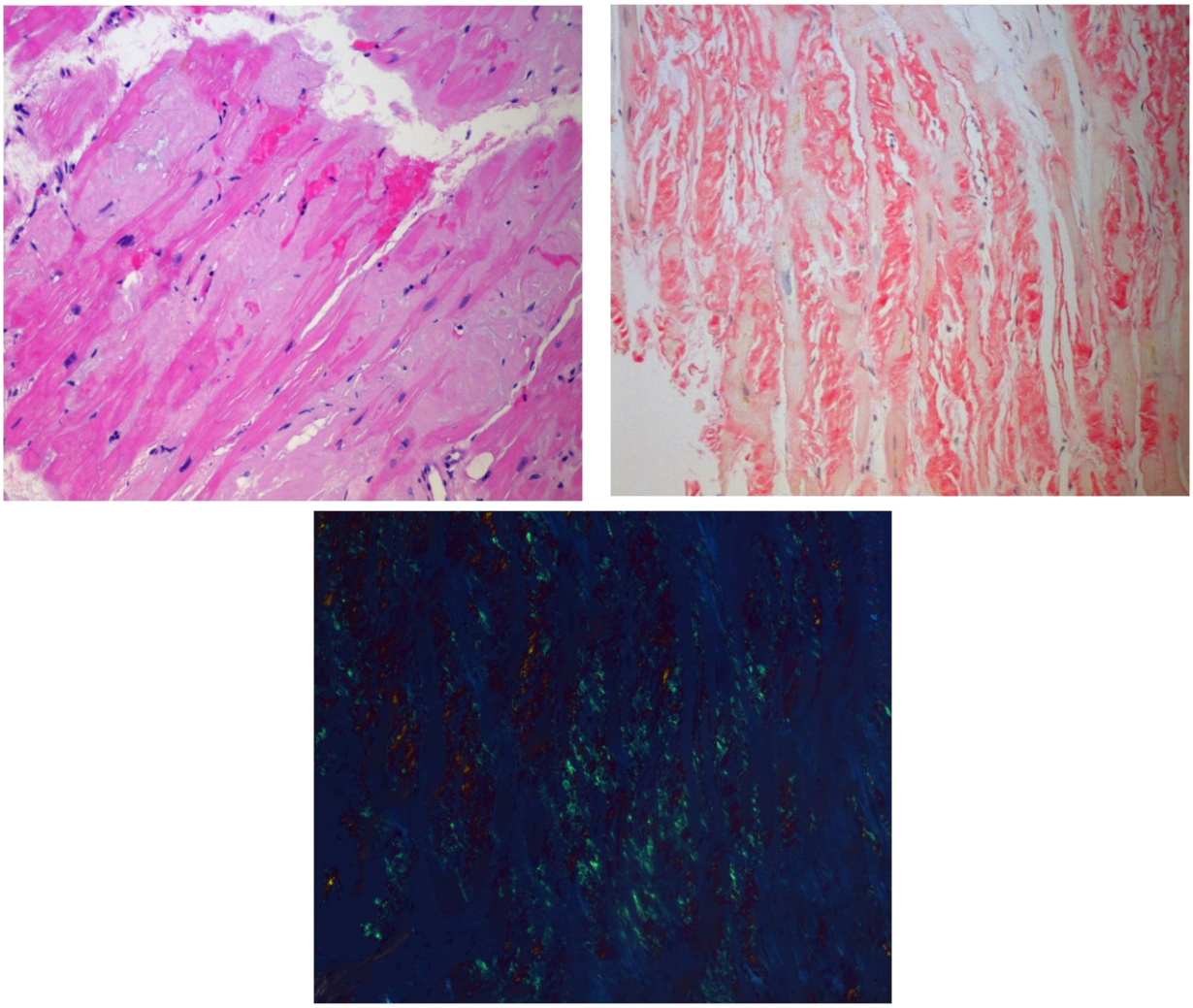

Figure 3: Endomyocardial biopsy demonstrating (a) cardiac myocyte hypertrophy and deposition of amorphous eosinophilic material within the tissue (Hematoxylin and Eosin, 20x); (b) amyloid deposits confirmed by a positive Congo red stain (Congo red, 20x); and (c) amyloid deposits exhibiting characteristic apple-green birefringence under polarized light (Congo red under polarized light, 20x).

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