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ISOLATED CARDIAC AMYLOIDOSIS: AN ENIGMA UNRAVELLED

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Abstract

Amyloidosis is a rare, multisystem disease characterized by deposition of fibrils in extracellular tissue involving kidney, liver, heart, autonomic nervous system, and several other organs. This report discusses a 75-year-old male who presented with worsening dyspnea on exertion, orthopnea, and lower-extremity edema. On physical exam, he had elevated jugular venous pressure and lower-extremity edema. Electrocardiogram depicted low voltage in limb leads and a prolonged PR interval. Echocardiogram revealed left ventricular hypertrophy, severe biatrial dilatation, and restrictive filling physiology. Coronary angiography showed absence of significant epicardial coronary artery disease. On right heart catheterization, a "dip-and-plateau sign" was noted on right ventricular pressure tracings. A diagnosis of cardiac amyloidosis was considered, but a complete hematology work-up for systemic amyloidosis was negative. Cardiac magnetic resonance imaging was pursued, showing delayed gadolinium enhancement, and this ultimately led to the myocardial biopsy confirming the diagnosis of isolated cardiac amyloidosis. Further genetic analyses confirmed isolated cardiac amyloid caused by mutant transthyretin protein (Val-122-Ile). Isolated cardiac amyloidosis is an extremely rare entity, and diagnosis may be difficult despite the use of multimodality imaging. If the index of suspicion is high, then myocardial biopsy should be considered.

Introduction

Amyloidosis refers to a group of diseases characterized by the deposition of fibrillary proteins in the extracellular compartment, leading to the loss of normal tissue architecture.[1] Based on the type of amyloid protein, it may be systemic or localized. Although cardiac involvement is frequently seen, isolated cardiac amyloidosis is extremely rare, and in these cases the diagnosis can be difficult due to minimal or absent extracardiac features. Characteristic findings of cardiac amyloidosis on electrocardiogram, echocardiogram, and cardiac magnetic

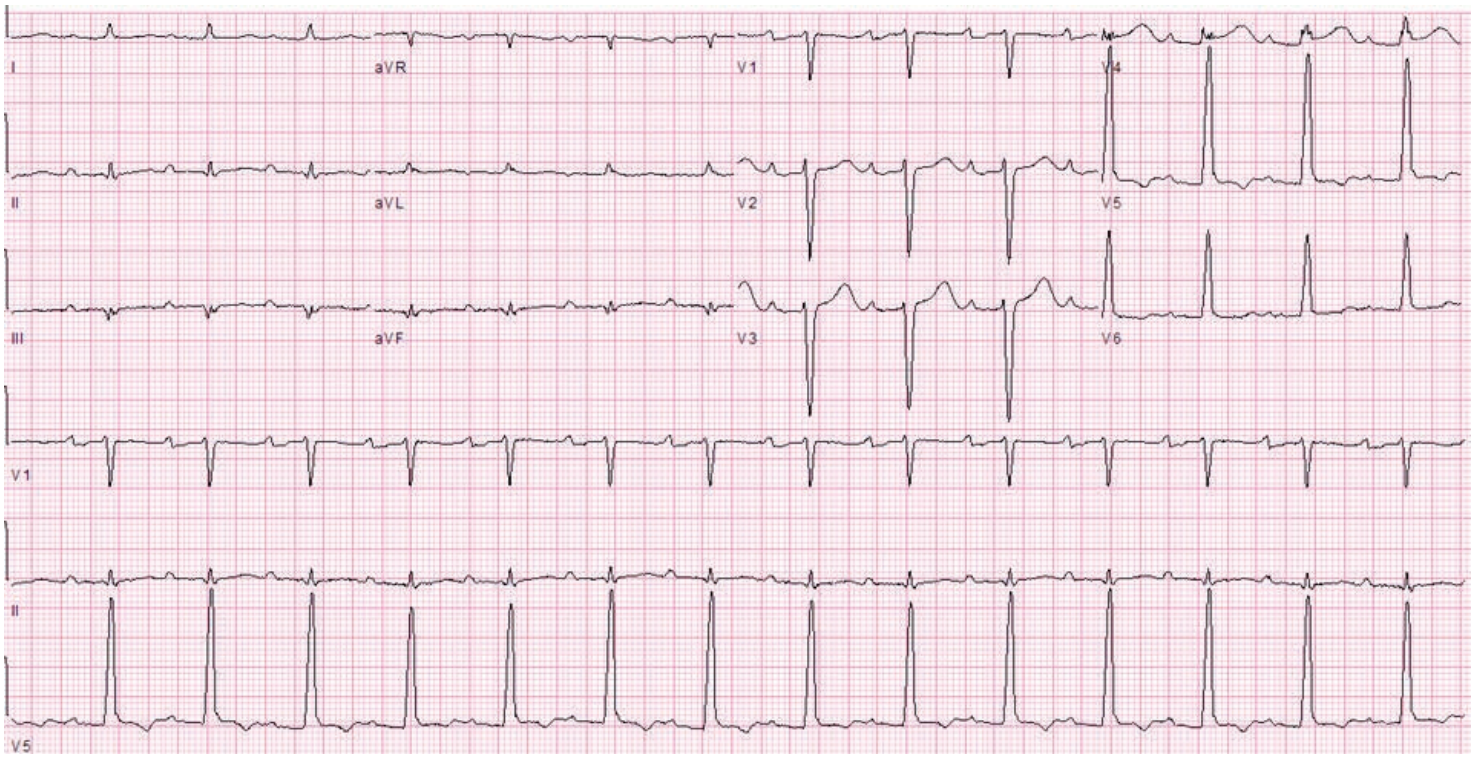

Figure 1. 12-lead electrocardiogram demonstrating low voltage in limb leads and prolonged PR interval.

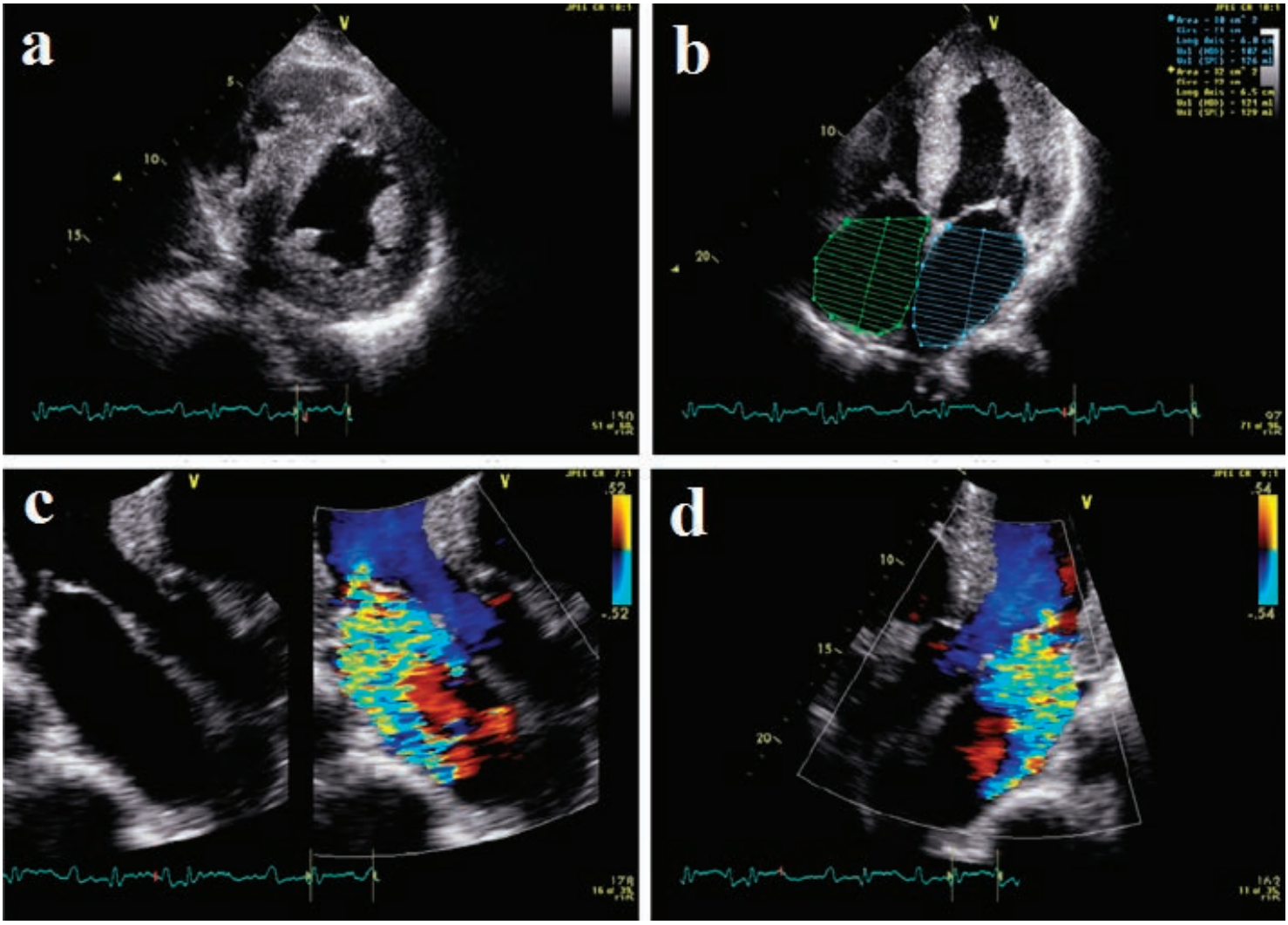

Figure 2. Transthoracic echocardiogram showing the following: (a) severe concentric left ventricular hypertrophy with moderately dilated left ventricular size (93 ml/m^2); (b) massively dilated atria; and (c, d) moderate to severe mitral regurgitation.

resonance imaging (CMR) can assist in diagnosis. In a selected group of patients, a myocardial biopsy is imperative to reach a conclusive diagnosis.[2,3] We hereby report a unique case of isolated cardiac amyloidosis caused by mutant transthyretin protein (Val-122-Ile).

Case History

A 75-year-old male with a history of hypertension presented with worsening dyspnea on exertion, orthopnea, and lower-extremity edema that had persisted for the past 6 months. He reported several members of his family having "heart problems," including a niece who died in her 20s with an "enlarged heart." He denied any history of smoking or alcohol/drug abuse and was not on any medications. Physical examination revealed a 3/6 holosystolic murmur in the mitral area, elevated jugular venous pressure of 17 cm, fine bibasilar crackles, and 1+ pitting edema bilaterally. Initial laboratory data was unremarkable. A 12-lead electrocardiogram (Figure 1) revealed low voltage in limb leads and first-degree atrioventricular block (PR interval > 200 ms). A transthoracic echocardiogram (Figure 2) revealed moderate concentric left ventricular hypertrophy, a moderately dilated left ventricular cavity (93 mL/ml^2), and severe biatrial dilation. Ejection fraction exhibited significant beat-to-beat variation between 30% and 45%. Impaired relaxation and elevated filling pressures with restrictive mitral inflow pattern were consistent with severe diastolic dysfunction. Also noted was moderate to severe mitral regurgitation. Pulmonary artery systolic pressure was estimated to be 38 to 48 mm Hg assuming a right atrial pressure of 10 to 20 mmHg. Diagnostic angiography revealed no epicardial coronary artery stenosis. In addition to elevated pulmonary arterial pressures, right heart catheterization (Figure 3) revealed the dip-and-plateau sign noted on right ventricular pressure tracings. A diagnosis of cardiac amyloidosis was considered, and he was referred to hematology clinic. However, a complete work-up for systemic amyloidosis including serum protein electrophoresis, 24-hour urine protein electrophoresis, and free light chain ratio was negative. The patient underwent a minor salivary gland biopsy that was also negative for amyloid deposits. Since cardiac findings were strongly suggestive for amyloidosis, CMR was pursued (Figure 4), which depicted delayed post gadolinium enhancement of myocardium in a heterogeneous pattern that suggested amyloid deposition in the myocardium. The patient finally underwent an endomyocardial biopsy (Figure 5), which confirmed the presence of amyloid deposits. The

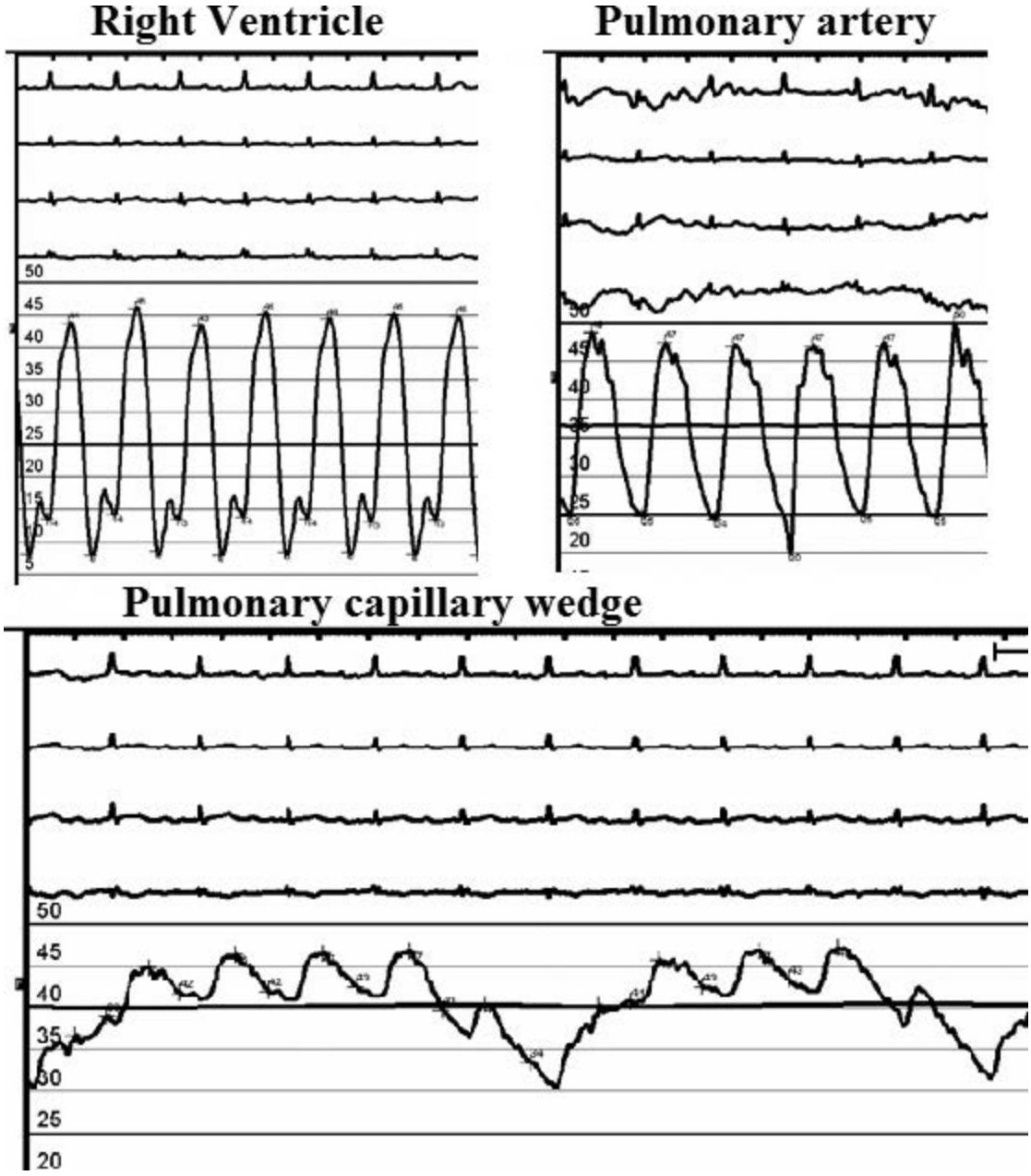

Figure 3. Right heart catheterization revealing elevated pulmonary artery pressure, elevated pulmonary artery wedge pressures, and dip-and-plateau on right ventricular pressure tracing.

specimen was sent for further genetic characterization, and mutant transthyretin protein was identified via liquid chromatography tandem mass spectrometry (Val-122-Ile).

Discussion

Amyloidosis is a rare, multisystem disease characterized by deposition of fibrils in extracellular tissue that involves the kidney, liver, heart, autonomic nervous system, and several other organs.[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) transthyretin (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, and CMR and in certain cases requires a myocardial biopsy.

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 the types.[4-6] On echocardiography, the characteristic features of amyloid heart include ventricular thickening with myocardial "speckled" appearance, decreased left ventricular volume, enlarged atria, and restrictive diastolic physiology.[7] These findings are similar in all types of amyloidosis.[8] 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 amyloid heart, the distribution kinetics of gadolinium are altered due to extracellular deposition of amyloid,

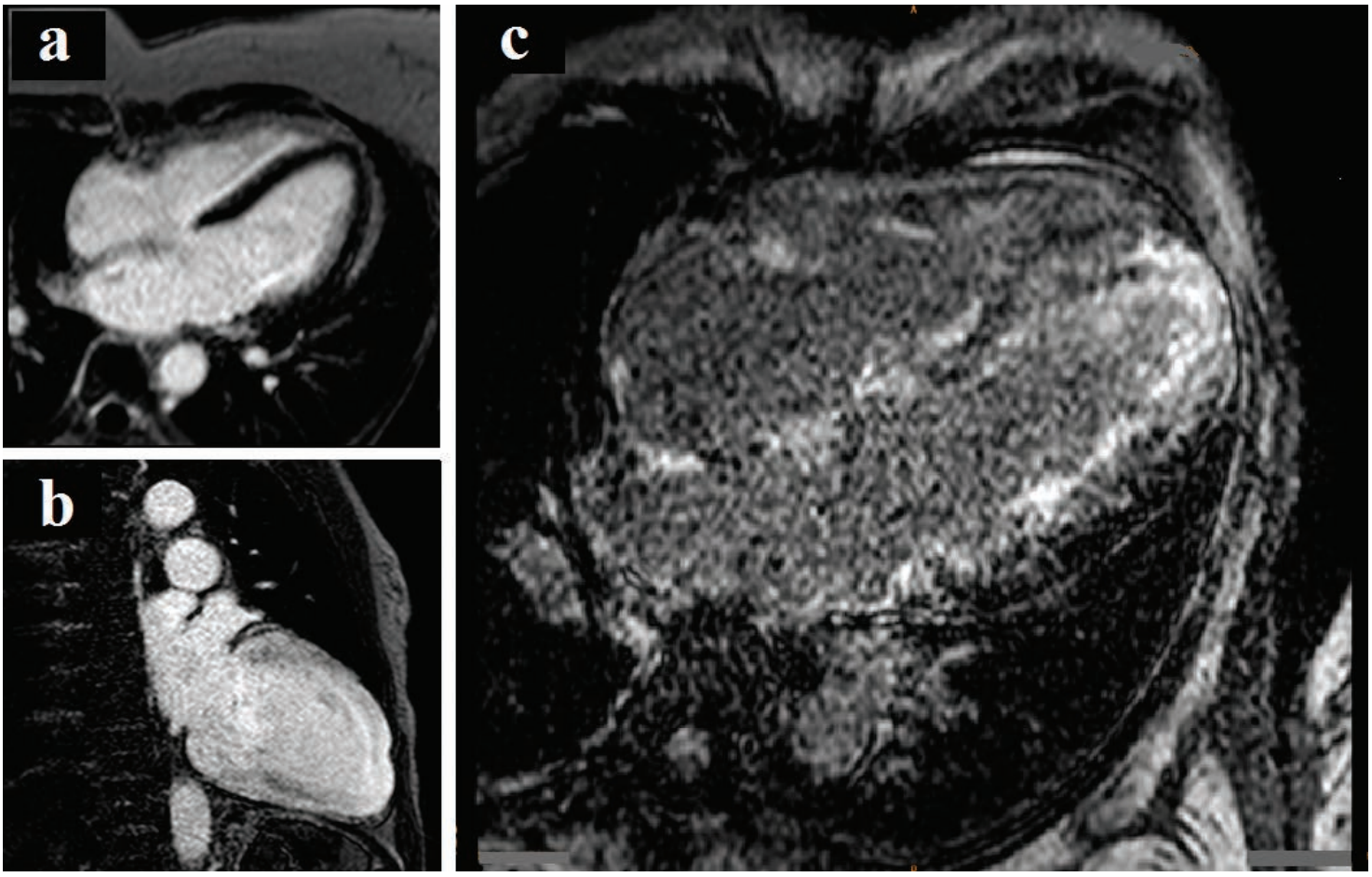

Figure 4. Magnetic resonance of the heart showing (a) an example of normal heart with "nulling" of myocardium; (b) gadolinium-enhanced cardiac magnetic resonance imaging showing inability to suppress (null) myocardial signal despite changing the inversion time; and (c) postgadolinium delayed enhancement image (4-chamber view) showing diffuse heterogeneous enhancement

leading to retained contrast that produces the characteristic late gadolinium enhancement.[3]

While abdominal fat pad biopsy may reveal the diagnosis in about 70% of patients, the gold standard for diagnosis remains the myocardial biopsy. Unfortunately, it is still not uncommon to miss the abnormal amyloid deposits in the biopsy sample, resulting in false negative results. 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.[9] 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.[10] 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 one 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. Interestingly enough, TTR genopositivity has been reported in approximately 4% of the African American population in the United States, while in Caucasians it is virtually undetectable.[11-13] The disease penetrance is not 100%, and hence the clinical phenotype is quite variable.[14] However, there is still a strong association between the carrier status and development of heart failure, with a reported relative risk of 2.6.[15] According to statistics from the U.S. Census, as many as 1.5 million African Americans carry the Val-122-Ile mutation.[16] Data from the Beta-Blocker Evaluation in Survival Trial revealed that around one-tenth of all African Americans aged > 60 years are carriers of Val-122-Ile mutation.[17] Therefore, unrecognized cardiac amyloidosis may account for several cases of nonischemic cardiomyopathy in the African American population—for example, several family members of our patient who died of unknown cause of cardiomyopathy.

Conclusion

Although the initial presentation with classic electrocardiographic, echocardiographic, and right heart catheterization findings was suggestive of amyloidosis in our patient, the absence of any other organ involvement—including a negative salivary gland biopsy—made the diagnosis difficult. Isolated cardiac amyloidosis with no evidence of systemic organ involvement is extremely rare and may require magnetic resonance imaging and endomyocardial biopsy to delineate the diagnosis.

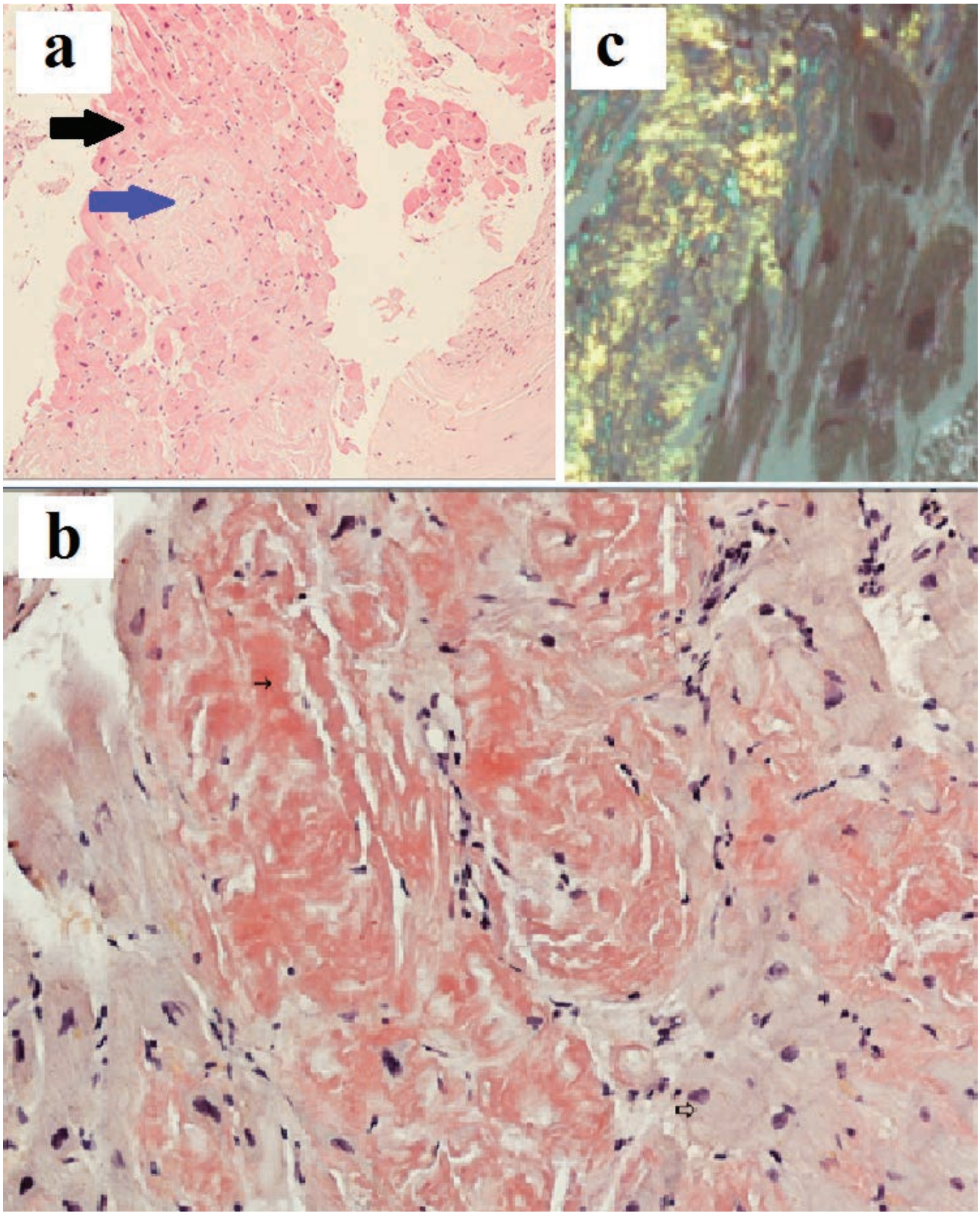

Figure 5. Endomyocardial biopsy demonstrating (a) hypertrophic myocytes (black arrow) and abundant deposits of pink amorphous material (blue arrow) within the tissue (Hematoxylin and Eosin, 100x); (b) amyloid deposits are confirmed by a positive Congo red stain, which gives the characteristic salmon-pink color (arrow) (Congo red, 400x); and (c) amyloid deposits exhibiting characteristic apple-green birefringence under polarized light (Congo red under polarized light 400x).

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Keywords: amyloidosis, restrictive cardiomyopathy, transthyretin-related amyloid fibril protein

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