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CASE REPORT

ADVANCED

CLINICAL CASE

Hereditary Apolipoprotein A-I–Associated Cardiac Amyloidosis

Importance of Endomyocardial Biopsy When Suspicion Remains High

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ABSTRACT

Cardiac amyloidosis has recently garnered substantial attention. Although the advent of noninvasive diagnostic algorithms revolutionized diagnosis, endomyocardial biopsy may still be considered in select cases to determine the amyloidosis subtype definitively. We report a case of a patients with a known mutation causing hereditary apolipoprotein A-I–associated cardiac amyloidosis. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1032–7)

HISTORY OF PRESENTATION

A 55-year-old White man presented with an insidious onset of dyspnea on exertion, fatigue, and lower extremity edema. Physical examination revealed the following: blood pressure, 104/82 mm Hg; regular heart rate of 65 beats/min; estimated jugular venous pressure, 16 cm H_2O; S_3 gallop; clear lung fields; and lower extremity edema. Handheld point-of-care ultrasound revealed grossly normal biventricular cavity size and left ventricular ejection fraction, no significant primary valve disease, and at least a small pericardial effusion. Given his physical and point-of-care ultrasound findings, a working diagnosis of heart failure with preserved ejection fraction (HFpEF) was made, and the patient was admitted to the hospital for further management.

LEARNING OBJECTIVES

- To recognize the wide variation in CA presentation and to highlight the pitfalls of noninvasive work-up.
- To recommend endomyocardial biopsy with LC MS/MS and appropriate reflex gene sequencing in select patients with suspected CA.

PAST MEDICAL HISTORY

History included hypertension, stage 2 chronic kidney disease, and class I obesity.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cardiac conditions included typical HFpEF related to hypertension and

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obesity, pericardial constriction, hypertrophic cardiomyopathy (HCM), cardiac amyloidosis (CA), or another form of restrictive cardiomyopathy. Hypervolemia related to renal insufficiency, liver disease, and thyroid disease were also considered as potential noncardiac causes.

INVESTIGATIONS

Initial remarkable laboratory tests revealed elevated the following (normal values are shown in parentheses): blood urea nitrogen, 42 mg/dl (7 to 20 mg/dl); creatinine, 1.8 mg/dl (0.7 to 1.2 mg/dl); high-sensitivity troponin I, 186 ng/l (0 to 30 ng/l); B-type natriuretic protein, 488 pg/ml (<100 pg/ml); alkaline phosphatase, 500 U/l (44 to 147 U/l); aspartate aminotransferase, 97 U/l (10 to 40 U/l); and alanine aminotransferase, 220 U/l (29 to 33 U/l). The complete blood count, albumin, and bilirubin were normal. A prominent cardiac silhouette was noted on the chest radiograph (**Figure 1A**). An electrocardiogram (**Figure 1B**) showed normal sinus rhythm, an intraventricular conduction delay, anterior and inferior Q waves, and normal voltage in limb leads (>5 mm) but low voltage in precordial leads (<10 mm). Transthoracic echocardiography (Video 1) demonstrated markedly increased biventricular thickness (interventricular septum, 1.7 cm; posterior wall, 1.6 cm; right ventricular free wall, 1 cm), preserved left ventricular ejection fraction, restrictive filling pattern, abnormal tissue Doppler findings (septal e′, 5.0 cm/s; lateral e′, 5.4 cm/s), and a large pericardial effusion without tamponade physiology.

Serum free light chains, serum, and urine immunofixation results were unremarkable. Urinalysis did not reveal any proteinuria or active sediment. A viral hepatitis panel and hepatic ultrasound scan were unremarkable. The hemoglobin A_{1c} value was 6.4 %. Lipid analysis revealed low high-density lipoprotein levels of 19 mg/dl (35 to 60 mg/dl) and elevated levels of total

ABBREVIATIONS AND ACRONYMS

AApo A-I = amyloid apolipoprotein A-I

AL = immunoglobulin light chain

ATTR = amyloid transthyretin

CA = cardiac amyloidosis

CMR = cardiac magnetic resonance

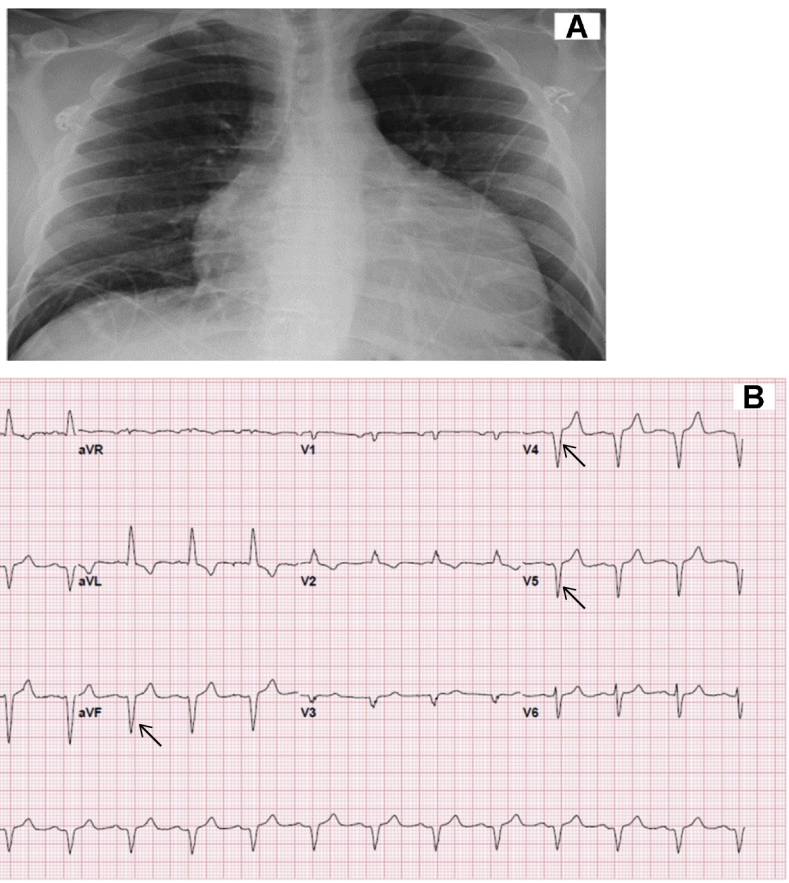
EMB = endomyocardial biopsy

HCM = hypertrophic cardiomyopathy

HFpEF = heart failure with preserved ejection fraction

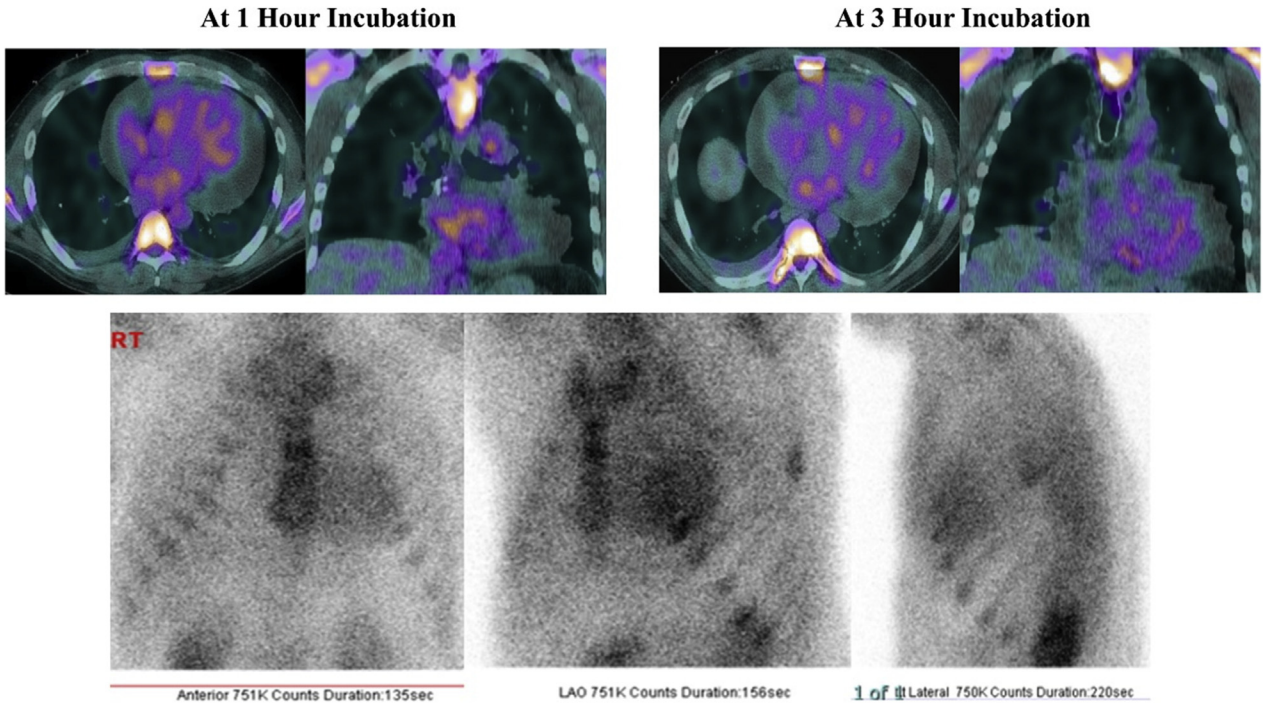
LC MS/MS = liquid chromatography tandem mass spectrometry

FIGURE 1 Initial Imaging



(A) Chest radiograph showing prominent cardiac silhouette. **(B)** A 12-lead electrocardiogram showing normal sinus rhythm, an intraventricular conduction delay, anterior and inferior Q waves, and low voltage in leads V_1 to V_6.

FIGURE 2 Technetium-99m Pyrophosphate Myocardial Scan



No myocardial technetium uptake is noted on planar imaging. Single-photon emission computed tomography combined with computed tomography images **(top row)** with little focal uptake, unlike vertebrae **(yellow),** seen at 1 h and, to a lesser degree, at 3 h, show minimal myocardial uptake that is not enough to be diagnostic. Planar images in the **bottom row** (anterior, left anterior oblique [LAO], and lateral views) show minimal tracer uptake (dark if positive) not suggestive of amyloid transthyretin amyloidosis.

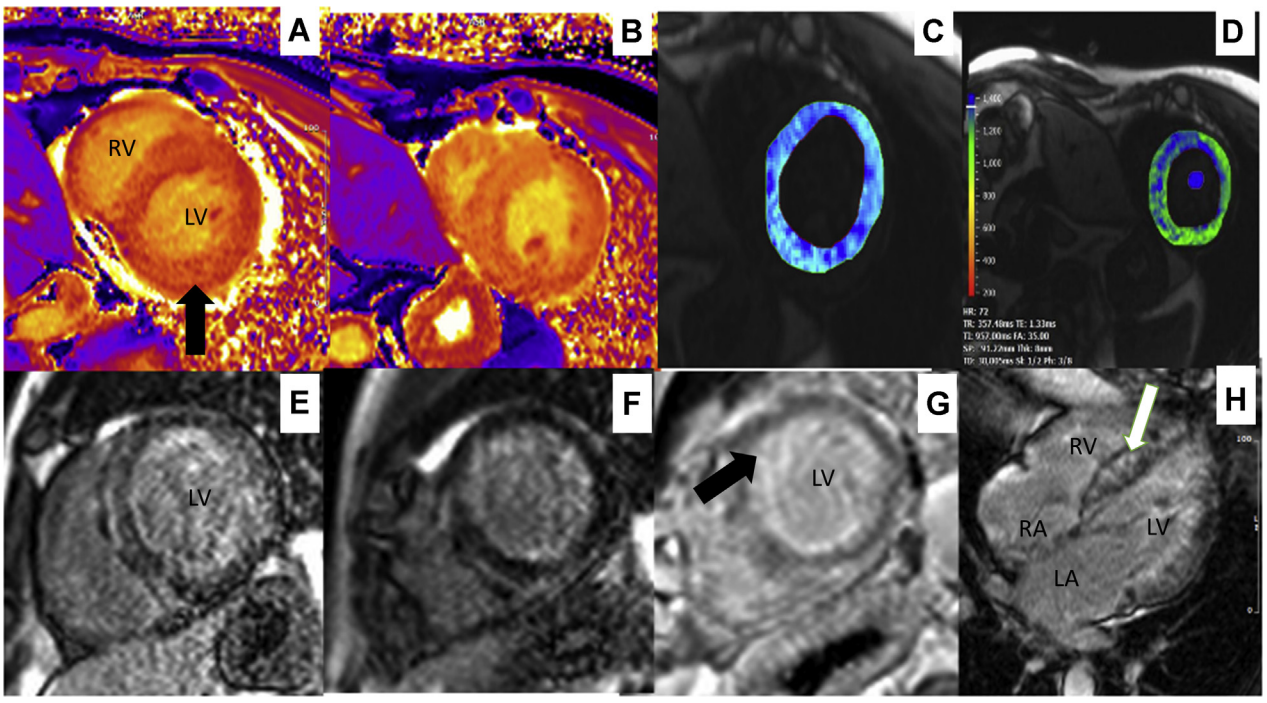
cholesterol of 233 mg/dl (150 to 200 mg/dl), LDL 173 mg/dl (80 to 150 mg/dl). and triglycerides 206 mg/dl (50 to 150 mg/dl). His TSH was an elevated at 98 μIU/ml (0.35 to 5.00 μIU/ml) with undetectable free T4.

Although profound hypothyroidism could have contributed to his imaging findings, given the totality of his cardiac studies, concomitant CA or HCM were still considered. Therefore, cardiac magnetic resonance (CMR) was attempted; however, claustrophobia leading to poor image quality rendered the study inconclusive. Unfortunately, the patient refused a repeat attempt at that time. The α-galactosidase level, iron studies, and creatinine kinase results were all unremarkable. Family history was not revealing. Subsequently, he underwent technetium-99m pyrophosphate scanning (Figure 2), and the findings were not consistent with transthyretin CA. The patient was decongested with diuretic therapy, given a diagnosis of Hashimoto disease, and treated with thyroid supplementation.

On follow-up, his pericardial effusion and fatigue improved significantly with thyroid supplementation, although his dyspnea on exertion persisted despite a euthyroid state. Given our continued suspicion of infiltrative disease, CMR was reattempted (Figures 3A to 3H). This time, excellent imaging quality demonstrated diffuse subendocardial enhancement with late gadolinium enhancement and increased extracellular volume with T_1 mapping suggestive of CA. His extracellular volume was elevated at 55% (25.3 ± 3.5%) with native T_1 of 1,263 ms (957 ± 30 ms). Subsequent neurological evaluation and electromyography studies confirmed occult upper extremity neuropathy and subclinical spinal stenosis.

Subsequent endomyocardial biopsy (EMB) showed deposition of noncollagenous, amorphous, acellular material between cardiomyocytes, which showed aberrant birefringence with a faint apple-green color in Congo red stained sections under polarized light, consistent with CA (Figures 4A to 4D). Results of liquid chromatography tandem mass spectrometry (LC MS/MS) were positive for AApo A-I deposition. Consistent with this, LC MS/MS detected an amino acid sequence abnormality in the AApo A-I protein (HGVS p.Leu99Pro). Genetic sequencing of this patient (Figure 5) confirmed an *AAPOA1* gene mutation,

FIGURE 3 Cardiac Magnetic Resonance



(A to H) Late gadolinium imaging demonstrating diffuse transmural enhancement **(arrow; top row). (C and D)** Normal signal intensity is **green,** whereas **blue** represents increased T_1 values suggestive of diffuse infiltration. T_1 mapping revealed increased extracellular volume suggestive of amyloid infiltration and increased signal intensity suggesting diffuse infiltration or fibrosis (extracellular volume, 55%). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

heterozygous for a c.296T>C transition resulting in p.Leu99Pro substitution.

MANAGEMENT

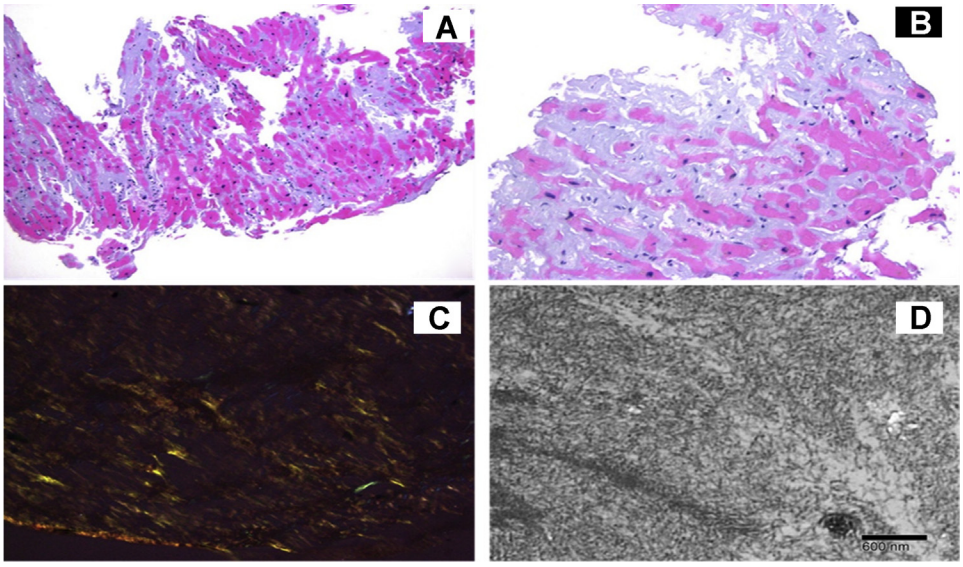
Unlike and immunoglobulin light chain (AL) and amyloid transthyretin (ATTR) CA, there is no effective targeted therapy for AApo A-I CA. Supportive management with diuretic agents is the current mainstay of treatment. Cardiac transplantation may be an option in well-selected patients. Additionally, family members should be referred to genetic counselors for genetic testing.

DISCUSSION

By far the most common causes of CA are ATTR and AL. That said, more than 30 proteins can form amyloid fibrils. AApo A-I CA is a rare hereditary form of amyloidosis caused by mutations in the *AAPOA1* gene. Mutations in the amino terminal portion of *APOA1* are associated with renal disease leading to proteinuric kidney disease largely from interstitial and medullary deposition, whereas mutations from residue 90 onward typically manifest with laryngeal, cutaneous, and cardiac deposition. AApo A-I amyloidosis is the second most common cause of "hereditary" amyloidosis and may also be associated with low levels of high-density lipoprotein, which was seen in our patient. Genetic sequencing of the *AAPOA1* gene (Figure 5) confirmed an *AAPOA1* gene mutation, heterozygous for a c.296T>C transition resulting in p.Leu99Pro substitution. We also suspect that this mutation was responsible for the patient's dyslipidemia. Different amino acid substitutions lead to variable organ involvement, and only isolated case reports of this specific mutation have been described, with different organ involvement (1).

The advent of noninvasive diagnostic algorithms using radionuclide scintigraphy or CMR, in conjunction with serum and urine testing for a monoclonal protein, revolutionized the diagnosis of CA (2). Contemporary diagnostic algorithms address the 2 most common forms of CA well; however, a thorough understanding of the algorithms' individual diagnostic testing characteristics is necessary for appropriate use. CMR using conventional sequences may lack sensitivity for early disease (3), and it can also pose a challenge in claustrophobic patients and

FIGURE 4 Endomyocardial Biopsy



(A) Deposition of amorphous acellular material between cardiomyocytes (hematoxylin and eosin, 100× original magnification). **(B)** Amorphous acellular material between cardiomyocytes (hematoxylin and eosin, 400× original magnification). **(C)** Congo red stain shows apple-green and aberrant birefringence under polarized light. **(D)** Electron microscopy showing amyloid fibrils.

patients with prosthetic hardware, as well as in centers without the necessary equipment or expertise. Radionuclide scintigraphy, paired with a negative monoclonal protein work-up, had excellent reported sensitivity and specificity for ATTR amyloidosis in early pivotal studies (2). However, with expanded real-world use, varying degrees of diagnostic accuracy may be appreciated in certain hereditary ATTR subtypes (4,5). Equivocal technetium-99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) pyrophosphate results may occur in early ATTR or in AL amyloidosis (6), and inappropriate use in the setting of abnormal monoclonal protein may not be uncommon because up to 40% of older adult patients who are ultimately found to have ATTR amyloidosis will have abnormal serum or urine monoclonal protein testing (7). Additionally, Apo CA itself can lead to cardiac uptake on nuclear scintigraphy scans, thus mimicking ATTR CA. Finally, one must not forget that even with appropriate noninvasive testing, patients with unrevealing or conflicting results still require EMB if significant clinical suspicion remains. Distracting findings, such as the hypothyroidism found in our patient, should not preclude pursuing CA testing. EMB can establish a definitive diagnosis and may uncover uncommon forms of CA, such as our case of AApo A-I CA.

FOLLOW-UP

The patient is following up with heart failure specialists, and given the lack of specific therapy, supportive management is provided.

CONCLUSIONS

A high index of suspicion is crucial for the recognition of CA. In patients with suspected HFpEF or HCM, infiltrative cardiomyopathies including CA should be considered. Multiparametric clinical assessment and multimodal imaging are necessary. Contemporary noninvasive diagnostic algorithms are helpful, but no single approach or test within these algorithms is without limitation. It is not uncommon to have initially ambiguous or discordant findings during the work-up for CA. If a high index of suspicion exists following unrevealing noninvasive approaches, definitive diagnosis with endomyocardial biopsy is often needed. Tissue subtyping with mass spectrometry is particularly important for less common types of amyloid infiltration.

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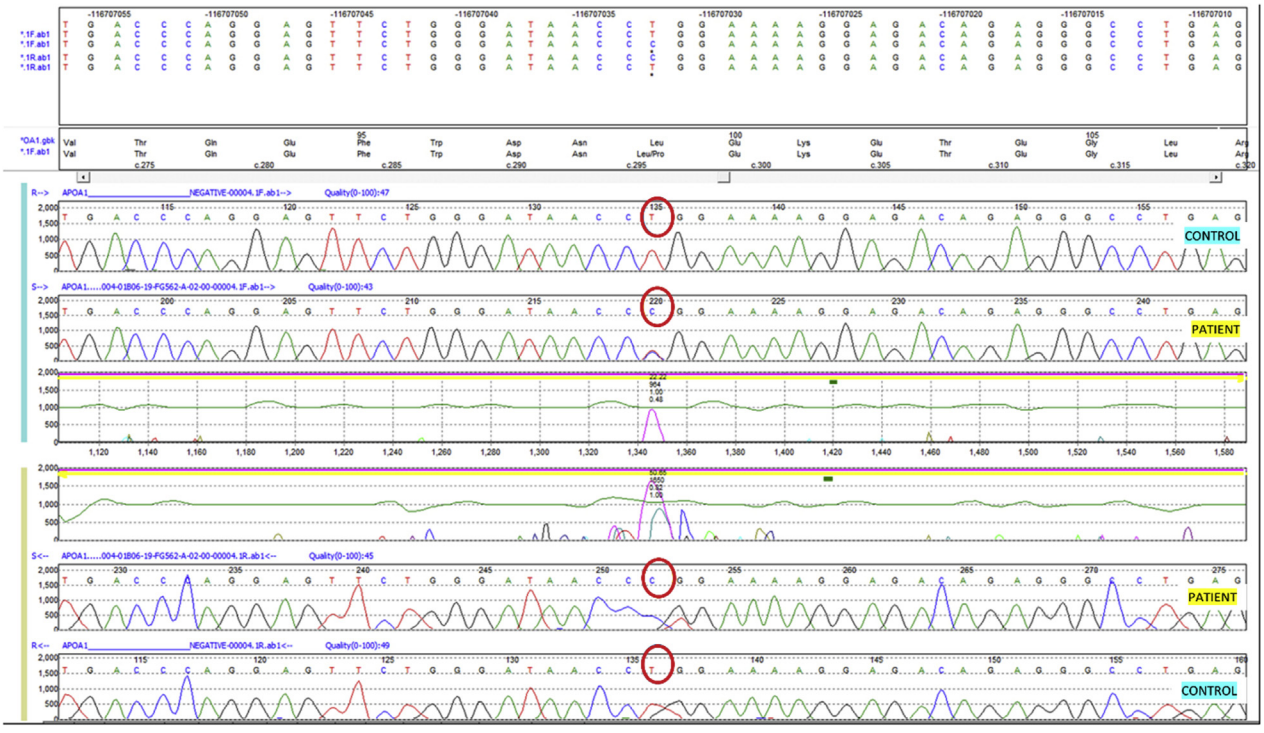
FIGURE 5 ***AAPOA1*** **Gene Sequencing**



Note the aberrant T>C change **(red circles)** at nucleotide position 296 in the patient tracing compared with the control.

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KEY WORDS apolipoprotein, endomyocardial biopsy, infiltrative cardiomyopathy

APPENDIX For a supplemental video, please see the online version of this article.