Acta Cardiol Sin 2021;37:549–553
Letter to the Editor
doi: 10.6515/ACS.202109_37(5).20210422A

Transthyretin Amyloid Cardiomyopathy Associated with Ala81Val Transthyretin Mutation: A Case Report

HsinYu Tseng,[1] Cheng-Hsuan Tsai,[2] Chien-Boon Jong,[3] Sung-Tsang Hsieh,[4,5] Chia-Tung Shun[6,7] and Yen-Hung Lin[1]

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an important cause of heart failure but is frequently overlooked worldwide. Genetic testing is essential in the diagnosis sequence to differentiate the two major types of ATTR-CM: hereditary and wild type. Herein, we report a patient with an Ala81Val (A81V) transthyretin mutation presenting as isolated hereditary transthyretin amyloid cardiomyopathy. The patient had an initial presentation of heart failure, however, several "red flag" signs came to our attention. ATTR-CM was diagnosed by nuclear scintigraphy after the exclusion of light chain amyloidosis, and further confirmed by an endomyocardial biopsy with immunohistochemical staining. The A81V transthyretin mutation was detected in a genetic survey. In summary, we report a case of ATTR-CM with an A81V mutation. ATTR-CM is an important cause of heart failure, and the diagnosis requires a series of surveys. A high clinical suspicion of ATTR-CM is necessary when taking care of patients with heart failure.

Received: February 22, 2021 Accepted: April 22, 2021
[1]Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei; [2]Department of Internal Medicine, National Taiwan University Hospital, Jin-Shan Branch, New Taipei City; [3]Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, Hsinchu City; [4]Department of Neurology, National Taiwan University Hospital; [5]Department of Anatomy and Cell Biology, College of Medicine, National Taiwan University; [6]Department of Pathology, National Taiwan University Hospital; [7]Graduate Institute of Forensic Medicine, National Taiwan University College of Medicine, Taipei, Taiwan.
Corresponding author: Dr. Yen-Hung Lin, Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Zhongshan S. Rd., Zhongzheng Dist., Taipei 100, Taiwan. E-mail: austinr34@gmail.com

CASE

A 78-year-old Taiwanese man presented with progressive dyspnea for one year. He had no history of cardiac disease, renal disease, limb numbness or weakness. He had smoked for 30 years. His family history of cardiac or neurological disease was unremarkable. A physical examination revealed hypotension, jugular vein engorgement and bilateral leg pitting edema. An electrocardiogram showed normal sinus rhythm, QS wave in inferior leads and poor R wave progression (Figure 1A). A chest X-ray revealed marked cardiomegaly with bilateral pleural effusion (Figure 1B). The level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was significantly elevated to 2,147 pg/mL. Complete blood count and comprehensive metabolic panel were within normal limits. A transthoracic echocardiogram disclosed concentric left ventricular hypertrophy (LVH, 17 mm in the basal septum and 15 mm in the posterior wall) and bilateral atrial dilatation (49 mm in the left atrial dimension) (Figure 1C). Global hypokinesia with poor left ventricular contractility [left ventricular ejection fraction: 35%] and grade IV diastolic dysfunction were detected (Figure 1D). The global longitudinal strain was 11.3% with a cherry on top pattern (Figure 1E). In addition, a moderate amount of pericardial effusion was observed.

Clinically evident right heart failure and unexplained LVH with diastolic dysfunction suggested restrictive cardiomyopathy. Cardiac amyloidosis was highly suspected based on the specific echocardiography pattern. Technetium-99m pyrophosphate (^{99m}Tc-PYP) scintigraphy was arranged and serum/urine monoclonal proteins were checked. ^{99m}Tc-PYP scintigraphy showed moderate cardiac uptake equal to bone, which was classified as grade 2 according to the Semi-quantitative Visual Grading of Myocardium system (Figure 1F & 1G). A heart to contralateral ratio (H/CL ratio) of 1.6517 was recorded

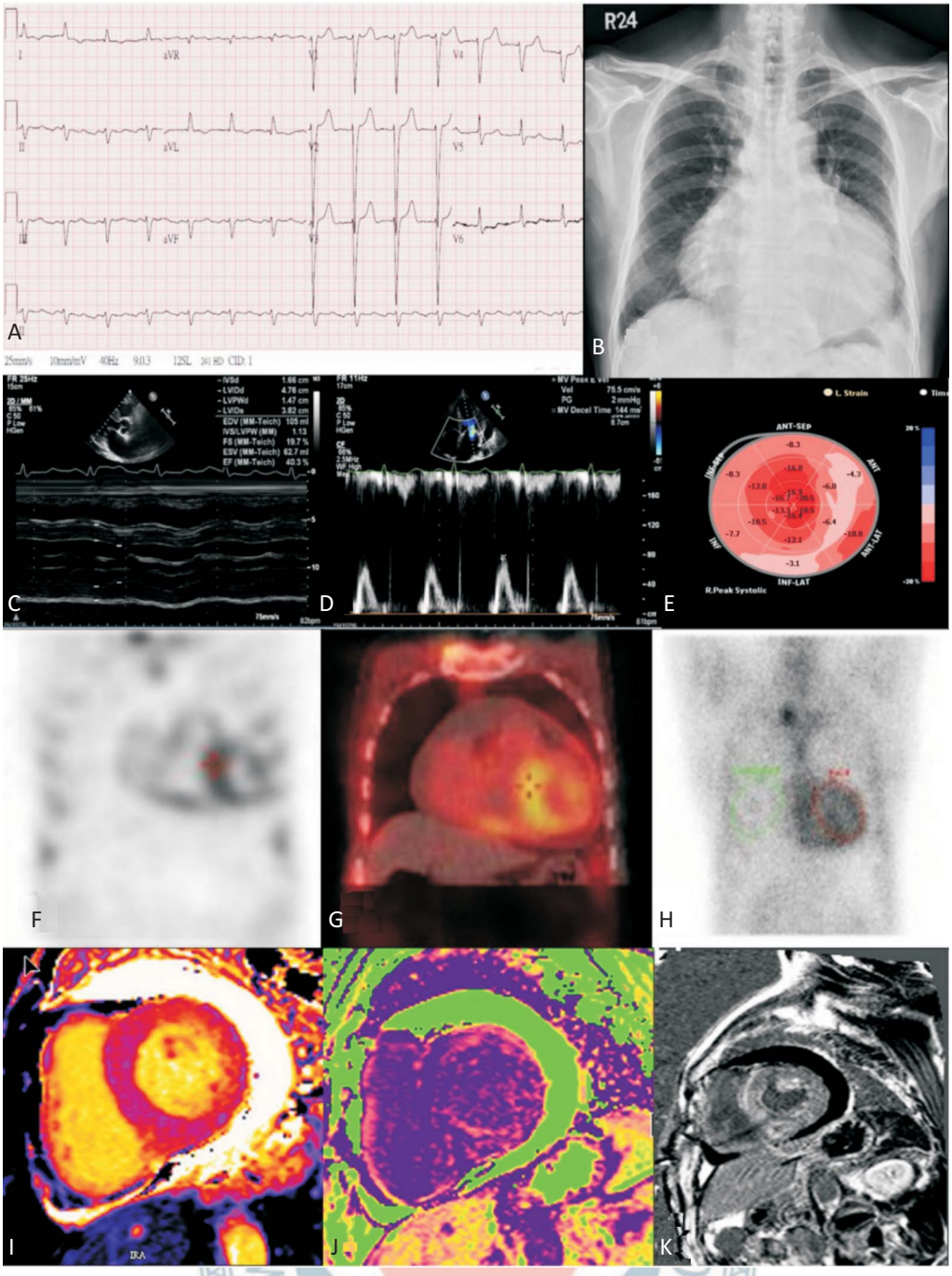

Figure 1. *(A) Electrocardiogram showed normal sinus rhythm, left axis deviation, QS wave in inferior leads and poor R wave progression. (B) Chest X-ray revealed marked cardiomegaly with bilateral pleural effusion. (C) Transthoracic echocardiogram of parasternal long axis view with M-mode showed left ventricular hypertrophy (LVH, 17 mm in the basal septum and 15 mm in the posterior wall). (D) Duplex of mitral inflow showed MV peak E 75.5 cm/s with no visible A wave, indicating severe diastolic dysfunction. (E) Global longitudinal strain showed reduced longitudinal systolic strain with apical sparing. (F) Technetium-99m pyrophosphate (^{99m}Tc-PYP) scintigraphy (SPECT) showed moderate cardiac uptake equal to bone with mildly attenuated bone uptake, which was classified as grade 2 according to the Semi-quantitative Visual Grading of Myocardium system. (G) ^{99m}Tc-PYP scintigraphy with SPECT/CT confirmed radiotracer uptake in the myocardium. (H) The heart to contralateral ratio (H/CL ratio) was 1.6517. (I) Cardiac magnetic resonance (CMR) with pre-contrast T1 image of short axis view showed a significantly elevated T1 signal to 1,154 ms. (J) CMR with extracellular volume fraction (ECV) maps of short axis view showed increased ECV to 64%. (K) CMR with post-contrast image showed diffuse subendocardial late gadolinium enhancement.*

(Figure 1H). No monoclonal gammopathy was detected on serum and urine immunofixation, and the free kappa/lambda ratio was normal. Cardiac magnetic resonance confirmed LVH and thicker inferoseptal segments. T1 mapping showed a significantly elevated T1 signal to 1,154 ms (Figure 1I), and the extracellular volume (ECV) was 64% (Figure 1J). Furthermore, subendocardial late gadolinium enhancement (LGE) of bilateral ventricular myocardium was detected (Figure 1K).

ATTR-CM was impressed. An endomyocardial biopsy was performed of the right ventricle, and the pathology showed hypertrophic myocardium with homogeneous deposition in the interstitium. Congo red staining disclosed apple-green birefringence in the interstitium (Figure 2A), thereby confirming cardiac amyloidosis. Immunohistochemistry with transthyretin (TTR)-specific antibodies further confirmed TTR deposition in the myocardium (Figure 2B & 2C), thus confirming the diagnosed of ATTR-CM. DNA sequencing was showed a C to T point mutation at nucleotide 5496, corresponding to an amino acid change from Ala to Val (A81V). A neurological evaluation showed no evidence of polyneuropathy or autonomic dysfunction. Hereditary transthyretin amyloid cardiomyopathy (hATTR-CM) without neuropathy was finally diagnosed.

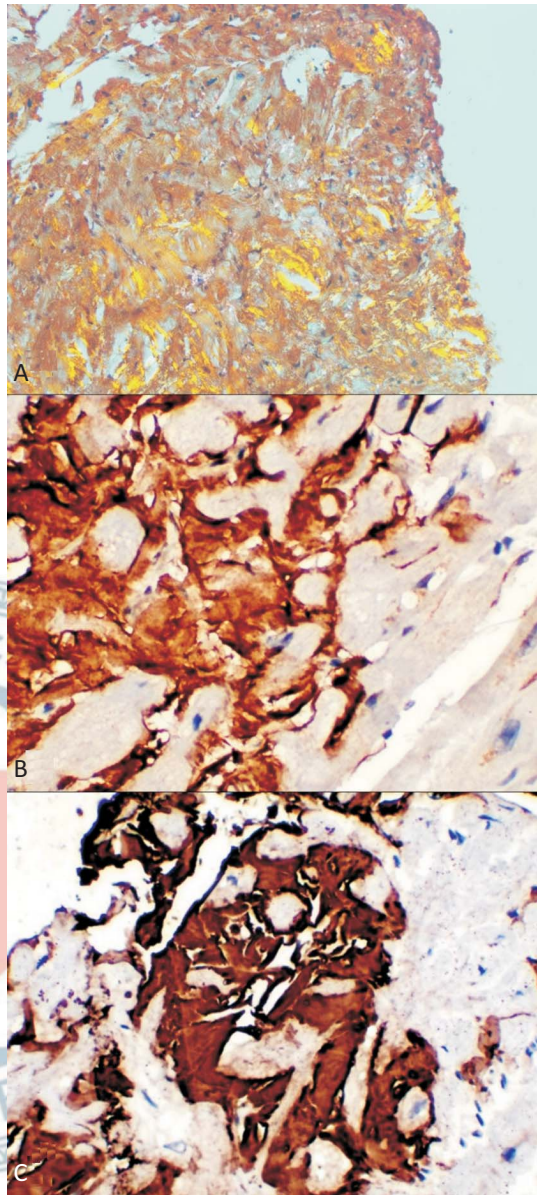

Figure 2. *Endomyocardial biopsy of the right ventricular was done. (A) Congo red staining with polarizing microscopy revealed the typical apple-green appearance of amyloid protein. (B) Immunohistochemistry of Rabbit Transthyretin (Sigma) revealed transthyretin deposition in the myocardium. (C) Immunohistochemistry of monoclonal-transthyretin (TTR) (Santa Cruz) also confirmed transthyretin deposition in the myocardium.*

DISCUSSION

ATTR-CM is an important cause of heart failure in the elderly but is frequently overlooked worldwide. The actual prevalence rate is unknown due to various diagnostic methods and different patient populations. We report a patient presenting with amyloid cardiomyopathy, and a genetic test detected an A81V transthyretin mutation. To the best of our knowledge, this mutation has only been reported once in a poster presentation in a congress.[1] However, there was no clear description of the clinical manifestation (ex. neurological, cardiac, or both) in that presentation. Our patient had an A81V transthyretin mutation that was associated with isolated amyloid cardiomyopathy without neurological involvement.

Amyloidosis is a systemic disease caused by extracellular deposition of insoluble amyloid fibrils, which are commonly formed by immunoglobulin light chain aggregation or misfolded transthyretin.[2] The former is referred to as light chain amyloidosis (AL) and the latter as transthyretin amyloidosis (ATTR). ATTR can be further classified into the wild type ATTR (wtATTR) or the hereditary transthyretin amyloid (hATTR) according the absence or presence of TTR gene mutations. Deposition

can take place in the heart, nerves, kidneys, gastrointestinal tract, soft tissue, and other organs. Two common clinical presentations of ATTR are ATTR-CM and familial amyloid polyneuropathy (FAP).[3]

More than 120 amyloidogenic mutations can result in hATTR.[4] Val30Met is the most common genetic variant found in endemic areas such as Portugal, Sweden, and Japan.[4] In the United States, Val122Ile is the most common mutation,[5] and Ala97Ser is the most frequently reported mutation in Taiwan.[6] The genotype and phenotype have certain degrees of correlation. Val30Met predominately presents as early onset neurologic disease, whereas Val122Ile, Thr60Ala, Leu111Met and Ile68Leu exclusively manifest as cardiomyopathy.[3] The A81V transthyretin mutation was first reported with four other novel variants by Rowczenio et al.[1] in a poster presentation at the First European Congress on Hereditary ATTR amyloidosis. However, they did not present a detailed description of the clinical presentations, and it is not known which system amyloidosis affects most. Our case showed that A81V is associated with amyloid cardiomyopathy without obvious neurological involvement.

The natural history of ATTR-CM is ventricular hypertrophy, followed by heart failure with preserved ejection fraction (HFpEF), and finally resulting in heart failure with reduced ejection fraction (HFrEF).[2] Both HFpEF and HFrEF can be presentations of ATTR-CM. The clinical clues to diagnose ATTR-CM can be classified as cardiovascular abnormalities and non-cardiovascular manifestations. Cardiovascular abnormalities include hypotension with intolerance to anti-hypertensive medications, conduction abnormality, low electrocardiographic voltage with discordance of wall thickness, and unexplained increased ventricular and/or atrial wall thickness. Non-cardiovascular manifestations include a history of carpal tunnel syndrome, lumbar spinal stenosis, or spontaneous biceps tendon rupture. In addition, the presence of unexplained peripheral or autonomic neuropathy warrants a suspicious of ATTR-CM and requires further surveys.[6]

The diagnosis of ATTR-CM used to be challenging, and the importance of an early diagnosis cannot be overemphasized due to emerging therapies that improve outcomes. Traditionally, an endomyocardial biopsy was the gold standard. Congo red staining combined with polarized light causes amyloid protein to produce an apple green birefringence. In routine practice, further classification of amyloid protein relies on immunohistochemistry. However, panels have been designed to detect only three typical amyloid types – amyloid A (AA), transthyretin amyloid (ATTR), and amyloid light chain (AL). Novel techniques include mass spectrometry (MS) and immunoelectron microscopy (EM). MS has been reported to type amyloidosis successfully in 98.1%-100% of cases,[7,8] compared to 91.6% for EM.[7] A combination of both techniques can further increase the diagnostic classification to 100%.[7] However, the accessibility of MS and EM limits their clinical application.

Recently, nuclear scintigraphy using bone-avid radiotracers such as ^{99m}Tc PYP scintigraphy, technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy (^{99m}Tc DPD) or ^{99m}Tc-labeled-hydroxymethylene diphosphonate (^{99m}Tc HMDP) have been reported to have excellent diagnostic accuracy for ATTR-CM.[9] By applying a semiquantitative visual score according to different degrees of uptake and quantitative analysis with heart corrected for contralateral counts and calculating a heart to contralateral ratio, AL and ATTR-CM can be differentiated.[10] Grade 2 or 3 tracer uptake or an H/CL ratio > 1.5 in conjunction with no evidence of monoclonal gammopathy by serum/urine testing can serve as an alternative diagnosis of ATTR-CM with 100% specificity and 74% sensitivity.[9] Both endomyocardial biopsy and nuclear scintigraphy in combination with immunofixation are accepted diagnostic approaches for ATTR-CM.[2] Our case received both diagnostic methods, which confirmed the diagnosis of A81V-related ATTR-CM.

In conclusion, we report a rare TTR gene mutation, A81V, in a patient who presented with typical amyloid cardiomyopathy without polyneuropathy. This case broadens our understanding of the very rare TTR-amyloidosis genotype and its clinical presentations. Further studies are warranted to investigate the genetic penetration of this mutation, the natural course of the disease, and its clinical impact to determine the timing of further interventions.

LEARNING POINTS

ATTR-CM is under-recognized but an important cause of heart failure. A high clinical suspicion of ATTR-CM is necessary when taking care of patients with heart fail-

ure. Specific patterns on echocardiography and cardiac magnetic resonance imaging should raise suspicion. A positive ^{99m}Tc PYP scan (grade 2 or 3 tracer uptake or an H/CL ratio > 1.5), along with blood and urine tests to rule out other forms of amyloidosis, can confirm the diagnosis of ATTR-CM without the need for a heart biopsy.

ACKNOWLEDGMENTS

No funding to declare.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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