THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Mutant p.Val114Ala Transthyretin-Related Cardiac Amyloidosis with Heart Failure and Right Bundle Branch Block

CASE REPORT

Selda Murat[1]
Sinem Kocagil[2]
İlknur Ak Sivrikoz[3]
Hava Üsküdar Teke[4]
Halit Emre Yalvaç[5]
Rabia Okumuş[1]
Oğuz Çilingir[2]
Yüksel Çavuşoğlu[1]

[1]Department of Cardiology, Eskişehir Osmangazi University, Faculty of Medicine, Eskişehir, Türkiye
[2]Department of Medical Genetic, Eskişehir Osmangazi University, Eskişehir, Türkiye
[3]Department of Nuclear Medicine, Eskişehir Osmangazi University, Eskişehir, Türkiye
[4]Department of Internal Medicine, Division of Hematology, Eskişehir Osmangazi University, Eskişehir, Türkiye
[5]Department of Cardiology, Eskişehir City Hospital, Eskişehir, Türkiye

Corresponding author:
Selda Murat
✉ selda.eraslan@hotmail.com

Cite this article as: Murat S, Kocagil S, Ak Sivrikoz İ, et al. Mutant p.Val114Ala transthyretin-related cardiac amyloidosis with heart failure and right bundle branch block. *Anatol J Cardiol.* 2025;29(7):371-374.

DOI:10.14744/AnatolJCardiol.2025.5150

INTRODUCTION

Transthyretin (TTR) cardiac amyloidosis is an increasingly recognized cause of heart failure and mortality worldwide.[1,2] Cardiac amyloidosis appears in 2 distinct forms: hereditary and wild-type. Hereditary TTR amyloidosis (ATTRm) is a rare disease caused by TTR gene mutations. More than 150 TTR gene pathogenic variants that cause autosomal dominant ATTRm have been described.[1-3] There is a lack of data on the mutations that cause ATTRm and appear to be common in Türkiye. The present case is a case diagnosed with ATTRm as the etiology of heart failure with preserved ejection fraction. In addition, a detailed genetic study and pedigree analysis was presented. The phenotype in the patients with the p.Val114Ala variant is characterized by a late-onset predominantly cardiac phenotype with right bundle branch block on electrocardiogram (ECG) and cardiac symptoms and signs of heart failure at diagnosis. To the authors' knowledge, this is the first ATTRm case due to this mutation described in Türkiye.

CASE REPORT

A 70-year-old male patient was admitted to the cardiology outpatient clinic with gradually worsening dyspnea on exertion and lower extremity edema for the last 3 months. The patient's functional capacity was New York Heart Association class III. It was learned that the patient was diagnosed with bilateral carpal tunnel syndrome 5 years ago. He had no additional chronic disease. There was no medication he used. There is no known cardiac disease in his family. On physical exam, his blood pressure was 115/70, heart rate 72 beats/min with regular rhythm. He had a grade 2/6 systolic murmur and severe pretibial edema. For 3 years, he has also reported paresthesia in the feet and hands.

Electrocardiogram revealed sinus rhythm, right bundle branch block, left anterior hemiblock (Figure 1). Echocardiography showed a significantly increased left ventricular (LV) wall thickness of 21 mm for the septum and 20 mm for the posterior wall, stage II diastolic dysfunction, thickened valve leaflets, small pericardial effusion, and granular sparkling (Figure 2A). Left ventricular ejection fraction was 60%, LV global longitudinal strain was –7.0% with apical sparing (Figure 2B), left atrial reservoir strain was 9.6%. Increased right ventricular wall thickness was also seen. His blood tests (complete blood count, liver enzymes, urea, and blood glucose) and urine sediment test yielded normal results. The glomerular filtration rate was 80.7 mL/min/1.73 m^2. N-terminal pro brain natriuretic peptide (NT-proBNP) evaluated at the time of diagnosis was 22 662 pg/mL, and troponin T was 0.178 ng/mL. On neurological examination, no muscle atrophy or weakness was present. Pain and temperature sensations were decreased bilaterally in the hands and feet. The clinical, ECG, and echocardiographic findings led us to suspect cardiac amyloidosis. Technetium pyrophosphate (99mTc-PYP) bone scintigraphy was conducted, showing an H/CL ratio of 1.9 and grade 3 myocardial uptake on the SPECT/CT, confirming a higher myocardial uptake of the bone tracer (Figure 2C, 2D). No monoclonal gammopathy was detected on serum and urine immunofixation, and the free kappa/lambda ratio was normal. Genetic testing for TTR mutations in

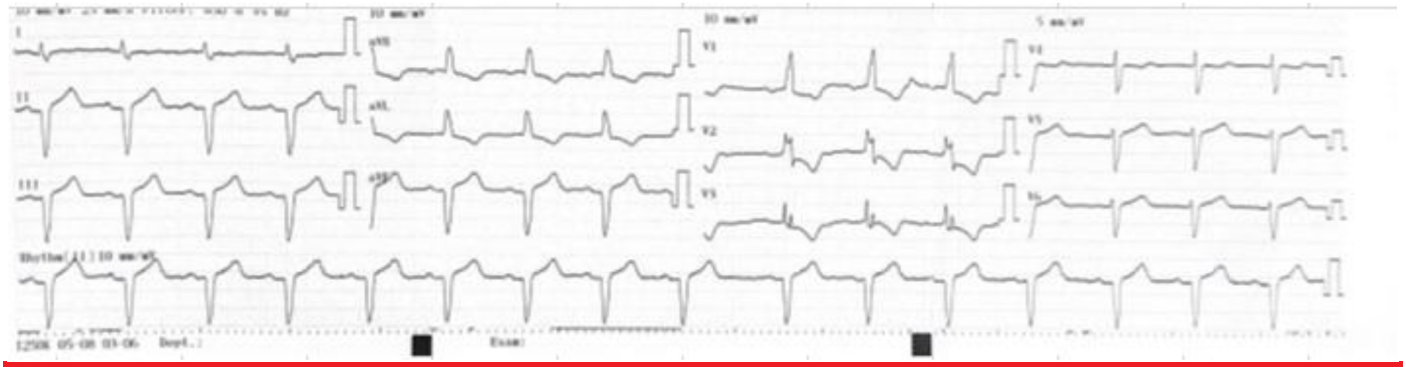

Figure 1. The patient's 12-lead electrocardiogram. Electrocardiogram: sinus rhythm, right bundle branch block, left anterior hemiblock.

the proband revealed a heterozygous pathogenic TTR variant (NM_000371.4):c.341T>C p.(Val114Ala) (Figure 3). With the current findings, the patient was diagnosed with ATTRm. Treatment with tafamidis 61 mg has been initiated, together with torasemide, spironolactone, and empagliflozin.

The patient had 2 healthy siblings and 2 children. Pedigree analysis was performed (Figure 4). For genetic testing, clinical exome sequencing was used in both siblings and the offspring. Peripheral venous blood was collected from 17 members of the affected family and performed clinical exome sequencing. Mutation was detected in 5 of the family members (II-4, II-9, III-4, III-5, III-13). Demographic and clinical characteristics of the index case and affected family members are presented in Table 1.

DISCUSSION

The phenotype in the patients with the p.Val114Ala variant is characterized by a late-onset predominantly cardiac phenotype with right bundle branch block on ECG and cardiac symptoms and signs of heart failure at diagnosis, along with mild neurological involvement. ATTRm is a rare disease caused by TTR gene mutations. The clinical presentation of ATTRm varies depending on the type of mutation and

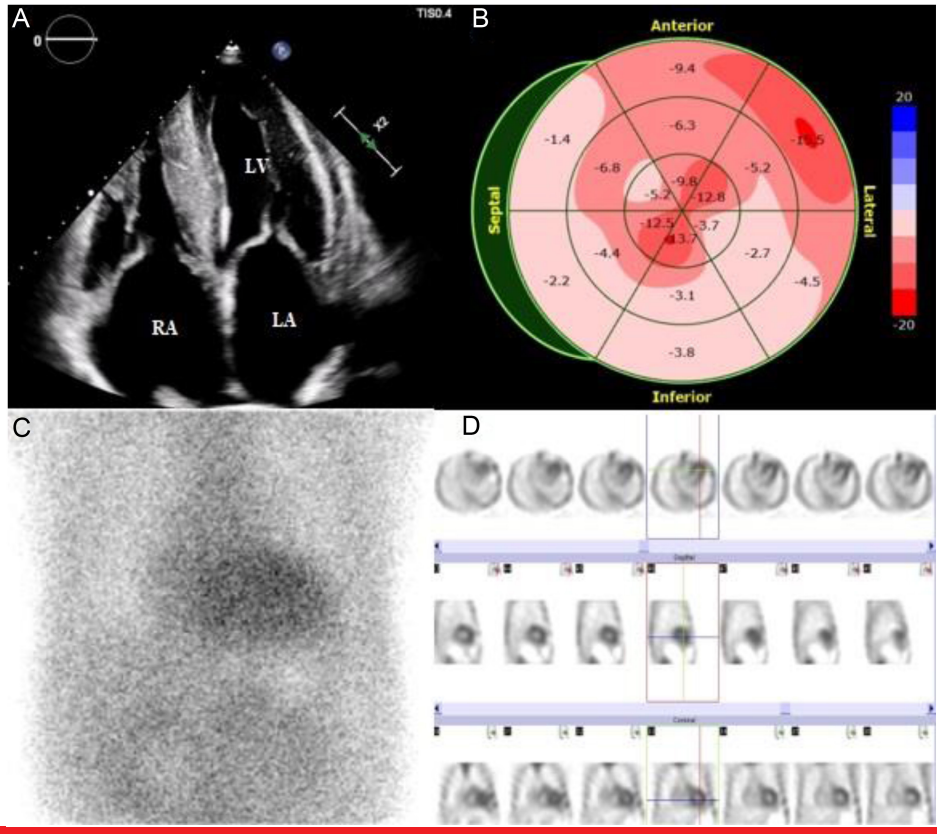

Figure 2. The patient's echocardiography and bone scintigraphy with SPECT/CT images. A: Apical 4-chamber transthoracic echocardiographic view, interventricular septum thickness, biatrial dilatation. B: Left ventricular global longitudinal strain, bull's eye map. C and D: 99mTc-pyrophosphate (99mTc-PYP) bone scintigraphy with SPECT/CT images.

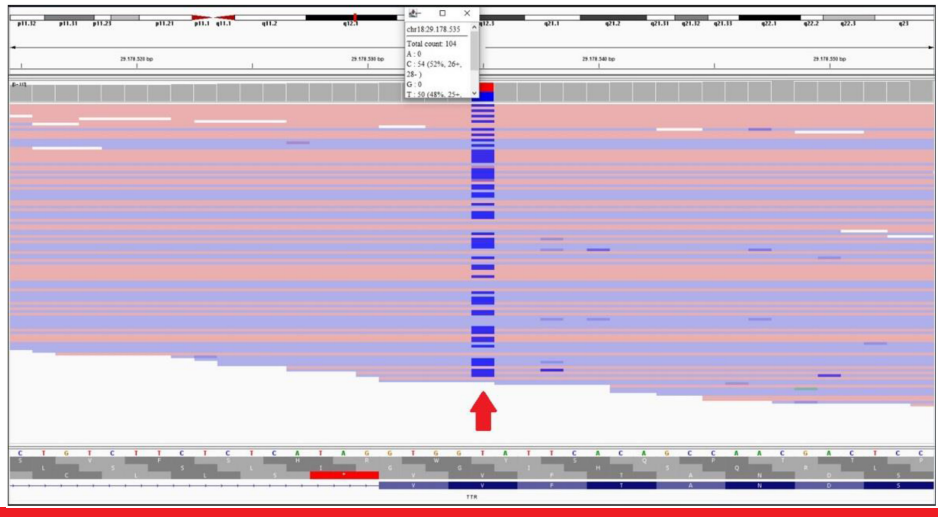

Figure 3. Image of mutation.

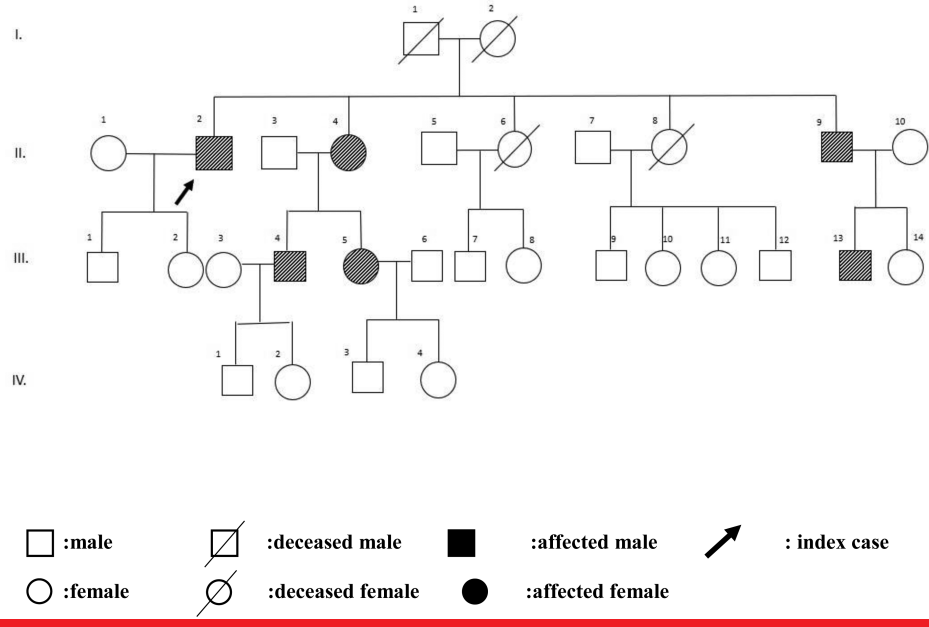

Figure 4. Pedigree analysis of the proband.

includes significant heterogeneity, ranging from primarily cardiac, primarily neuropathic, or mixed cardiac and neuropathic disease. Data on cardiac and extra-cardiac manifestations regarding the p.Val114Ala TTR variant are limited. This condition was previously described in a few patients in Germany, Crete, and Austria.[4-6] In Crete, the most common mutation among 30 ATTRm patients was the p.Val50Met mutation, while the second most common mutation was

Table 1. Demographic and Clinical Characteristics of the Index Case and Affected Family Members

Patient No.	Age/Gender	LVWT	GLS	PYP Grade H/CL ratio	NT-proBNP	Troponin T	Neurologic Signs
II-2 index case	70 years/male	18 mm	−9.1%	III H/CL: 2.5	17219 pg/mL	0.118 ng/mL	PNP+
II-4	74 years/female	16 mm	−14.8%	II/III H/CL: 2.1	1500 pg/mL	0.019 ng/mL	Bilateral CTS
II-9	69 years/male	18 mm	−16.4%	I H/CL: 1.1	253 pg/mL	0.013 ng/mL	PNP+
III-4	52 years/male	12 mm	−20.4%	–	57 pg/mL	0.010 ng/mL	Normal examination
III-5	50 years/female	12 mm	−17%	I H/CL:1.3	132 pg/mL	0.005 ng/mL	Paresthesia in the hand
III-13	38 years/male	14 mm	−18%	–	24 pg/mL	0.008 ng/mL	Chronic diarrhea

CTS, carpal tunnel syndrome; GLS, global longitudinal strain; H/CL ratio, heart/contralateral lung ratio; LVWT, left ventricular wall thickness; NT-proBNP, N-terminal pro brain natriuretic peptide; PNP, Polyneuropathy; PYP, 99mtechnetium-pyrophosphate scintigraphy.

p.Val114Ala.[4] This variant has been previously described in a patient from Germany who presented with cardiac involvement and later developed sensorimotor polyneuropathy, autonomic dysfunction, and diarrhea as extra-cardiac findings.[5] The disease was also late-onset in this patient, with the patient's age at diagnosis being 63.[5]

Another important point of this case report is that a genetic study was performed covering the entire family. One of the major challenges of genetic screening is that all TTR variants show incomplete penetrance and variable expressivity, and therefore an individual may carry a relevant variant but show no evidence of the associated phenotype. It is difficult to comment on the incomplete penetrance and expressivity in the family members of this case due to the age-dependent manifestation of the disease. However, incomplete penetrance and variable expressivity data can be obtained with long-term follow-up of these cases. The 2023 ACC Expert Consensus Decision Pathway on Cardiac Amyloidosis recommends cascade testing of first-degree relatives. As a result of cascade testing, mutations were detected in 5 cases in the relatives of this case. Phenotypic features of the disease were also evident in one of the siblings and tafamidis was started for this sibling as a result of the diagnostic process.

To the authors' knowledge, this is the first ATTRm case due to this mutation described in Türkiye. Additionally, it is also a family medical history in which all family members at risk are identified through genetic study, and guideline recommendations are reflected in the diagnostic process. Revealing the clinical manifestations of TTR mutation types is important to ensure early diagnosis of the disease and to increase awareness. Unfortunately, there is a lack of genetic data on TTR variants in Türkiye. It would be valuable to conduct an ATTRm survey to reveal the genetic spectrum in Türkiye.

Artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLM], chatbots, or image creators) were not utilized in the production of this case report.

Informed Consent: Detailed written informed consent was obtained from the patient for the publication of this case.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study received no financial support.

REFERENCES

1. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;42(16):1554-1568. [CrossRef]
2. Writing Committee, Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology solution set oversight committee. *J Am Coll Cardiol*. 2023;81(11):1076-1126 [ePub]. Erratum in: *J Am Coll Cardiol*. 2023;81(11):1135.
3. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44(37):3503-3626. [CrossRef]
4. Tzagournissakis M, Foukarakis E, Samonakis D, et al. High hereditary transthyretin-related amyloidosis prevalence in Crete: genetic heterogeneity and distinct phenotypes. *Neurol Genet*. 2022;8(5):e200013. [CrossRef]
5. Kristen AV, Ehlermann P, Helmke B, et al. Transthyretin valine-94-alanine, a novel variant associated with late-onset systemic amyloidosis with cardiac involvement. *Amyloid*. 2007;14(4):283-287. [CrossRef]
6. Auer-Grumbach M, Rettl R, Ablasser K, et al. Hereditary ATTR amyloidosis in Austria: prevalence and epidemiological hot spots. *J Clin Med*. 2020;9(7):2234. [CrossRef]