ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Spontaneous Partial Rupture of the Long Proximal Biceps Tendon in a Patient with Variant Transthyretin Amyloid Cardiomyopathy Due to a Heterozygous c148G>A p.Val50Leu Mutation

c148G>A p.Val50Leu'nun Heterozigot Mutasyonuna Bağlı Varyant Transtiretin Amiloid Kardiyomiyopatisi Olan Bir Hastada Uzun Proksimal Biseps Tendonunun Spontan Kısmi Rüptürü

ABSTRACT

Variant transthyretin amyloid cardiomyopathy (ATTRv-CM) is a rare disease caused by a genetic mutation in the *ATTR* gene. Due to the pathogenic mutation, transthyretin tetramers lose their structural stability and misfold, leading to the accumulation of amyloid fibrils in various tissues, particularly in the heart. The clinical progression of ATTRv-CM varies depending on the specific mutation. Data on *ATTR* gene mutations in Türkiye are limited. This paper presents a case of spontaneous biceps tendon rupture, identified prior to diagnosis, in a patient with ATTRv-CM carrying a heterozygous c148G>A pVal50Leu mutation.

Keywords: Biceps tendon rupture, herediter amyloid, transthyretin, variant amyloid cardiomyopathy

ÖZET

Varyant transtretin amiloid kardiyomyopatisi (ATTRv-KM) nadir bir hastalıktır ve *ATTR* genindeki mutasyona bağlı gelişir. İlişkili patojenik mutasyon neticesinde transtretin terramerlerinin stabilliği bozulur ve yanlış katlanırlar. Bunun sonucunda amiloid fibrilleri başta kalp olmak üzere pek çok dokuda birikirler. ATTRv-KM hastalarında klinik seyir mutasyona bağlı olarak değişir. Türkiye görülen *ATTR* mutasyonları ile ilgili bilgiler çok sınırlıdır. Biz de bu yazıda, c148G>A p.Val50Leu heterozigot mutasyonu olan ATTRv-KM olgusunda tanıdan önce saptanmış olan spontan biseps tendonu rüptürü birlikteliğini sunduk.

Anahtar Kelimeler: Biseps tendon rüptürü, herediter amiloid, transtiretin, varyant amiloid kardiyomiyopati

CASE REPORT
OLGU SUNUMU

Belma Kalaycı[1]
Ezgi Polat Ocaklı[1]
Nur Aydınbelge Dizdar[2]
Esin Kurtuluş Öztürk[3]
Taha Bahsi[4]
Özlem Özmen[2]

[1]*Department of Cardiology, Ankara Etlik City Hospital, Ankara, Türkiye*
[2]*Department of Nuclear Medicine, Ankara Etlik City Hospital, Ankara, Türkiye*
[3]*Department of Radiology, Ankara Etlik City Hospital, Ankara, Türkiye*
[4]*Department of Medical Genetics, Ankara Etlik City Hospital, Ankara, Türkiye*

Corresponding author:
Belma Kalaycı
✉drbelma@hotmail.com

Received: April 26, 2024
Accepted: September 29, 2024

Cite this article as: Kalaycı B, Polat Ocaklı E, Aydınbelge Dizdar N, Kurtuluş Öztürk E, Bahsi T, Özmen Ö. Spontaneous Partial Rupture of the Long Proximal Biceps Tendon in a Patient with Variant Transthyretin Amyloid Cardiomyopathy Due to a Heterozygous c148G>A p.Val50Leu Mutation. *Turk Kardiyol Dern Ars.* 2025;53(5):362-366.

DOI: 10.5543/tkda.2024.71970

Transthyretin protein misfolding is caused by genetic, epigenetic, or oxidative factors, leading to the accumulation of amyloid fibrils between cells, which exert a cytotoxic effect. As a result, dysfunction develops in the affected organs. Variant transthyretin amyloid cardiomyopathy (ATTRv-CM) is caused by substitution or deletion mutations that lead to TTR misfolding.[1] Familial, mutant, and hereditary ATTR-CM are synonymous with ATTRv-CM. More than 130 known TTR variants have been associated with ATTR amyloidosis.[2] However, data on ATTR gene variants are still limited, and the most common variants in Türkiye remain unidentified. Although the association between ruptured distal biceps tendon and wild-type ATTR-CM is well established, there have been no reported cases of coexistence between a ruptured biceps tendon and ATTRv-CM. We present the first case of a spontaneous partial rupture of the proximal biceps tendon in a patient with ATTRv-CM.

Case Report

A 77-year-old man presented with progressively worsening exertional dyspnea and fatigue over the past six months. He also reported symptoms of orthostatic

hypotension. On physical examination, mild bilateral pretibial edema was observed, with no crackles auscultated in the lungs. His medical history included hypertension, diabetes mellitus, and bilateral carpal tunnel syndrome. He had undergone surgery for spinal stenosis eight years prior. There was a family history of heart failure—his brother had experienced thickening of the heart walls. His current medications included irbesartan-hydrochlorothiazide and metformin. Electrocardiography showed no rhythm abnormalities but revealed a pseudoinfarct pattern in leads V1 and V2 (Figure 1). Transthoracic echocardiography demonstrated concentric left ventricular hypertrophy, measuring 17 mm in the parasternal long-axis image (Figure 2A, Video 1). Left ventricular systolic function remained within normal limits. The apical view confirmed left ventricular hypertrophy and revealed a mild pericardial effusion during end-diastole (Figure 2B, Video 2). Diastolic dysfunction, classified as Grade 1, was identified based on tissue Doppler imaging of the lateral and septal mitral annulus, as well as mitral inflow pulse wave Doppler findings (Figure 3A-C). The thickness of the right ventricular wall was measured at 6 mm, with no thickening of the interatrial septum observed. The strain study revealed a reduced global longitudinal strain (GLS) of -13.1% and an apical "cherry-on-top" pattern (Figure 3D). Laboratory findings showed mildly elevated high-sensitivity troponin-T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at 24 ng/L and 385 pg/mL, respectively. To exclude immunoglobulin light chain (AL) amyloidosis, serum immunofixation electrophoresis, 24-hour urine immunofixation electrophoresis, and a serum free light chain assay were performed. All results were within normal limits, with a kappa/lambda light chain ratio of 0.82, showing no evidence of gammopathy. Simultaneously with the blood and urine tests, technetium-labeled pyrophosphate (Tc-PYP) scintigraphy was performed using both planar and single-photon emission computed tomography-computed tomography (SPECT-CT) nuclear imaging. Planar images obtained one hour after injection demonstrated increased myocardial activity, with a heart-to-contralateral lung ratio of 1.54 and a visually assessed Perugini Grade 2. SPECT-CT imaging further confirmed

ABBREVIATIONS

AL	Amyloidosis
ATTR-CA	Transthyretin cardiac amyloidosis
ATTRv-CM	Variant transthyretin amyloid cardiomyopathy
GLS	Global longitudinal strain
h-ATTR	Hereditary ATTR
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RBT	Ruptured distal biceps tendon
SPECT-CT	Single-photon emission computed tomography-computed tomography
Tc-PYP	Technetium-labeled pyrophosphate
wt-ATTR	Wild-type ATTR

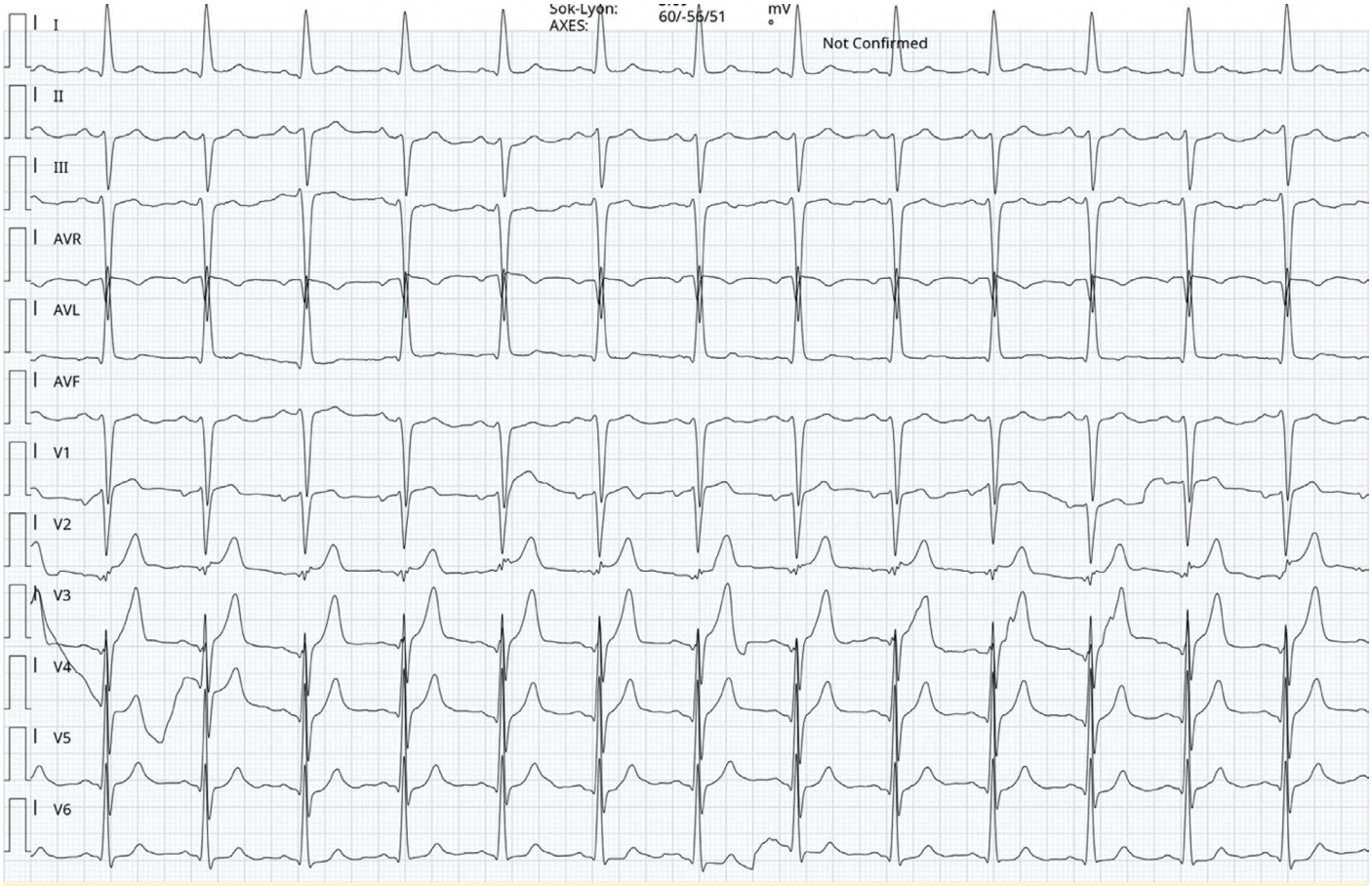

Figure 1. Electrocardiogram showing normal sinus rhythm and a pseudoinfarct pattern in leads V1 and V2.

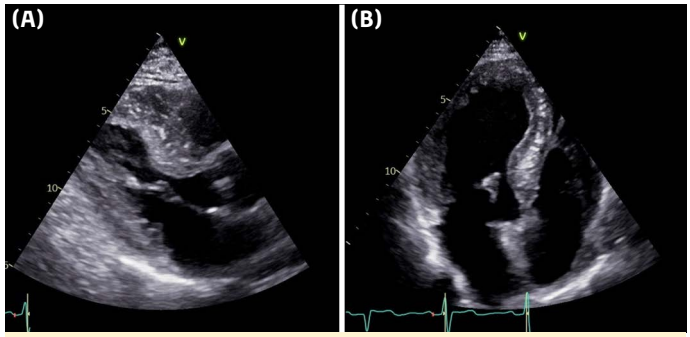

Figure 2. (A) Parasternal long-axis transthoracic echocardiography image demonstrating significant left ventricular hypertrophy. (B) Apical four-chamber image showing biatrial enlargement and left ventricular hypertrophy.

the increased cardiac uptake and helped distinguish myocardial uptake from blood pool radiotracer signal (Figure 4). As a result of the Grade 2 PYP scintigraphy findings and the absence of gammopathy, a diagnosis of transthyretin cardiac amyloidosis (ATTR-CA) was confirmed. Subsequently, a genetic test using Sanger sequencing was performed to differentiate between wild-type ATTR (wt-ATTR) and hereditary ATTR (h-ATTR). The genetic analysis revealed a c148G>A pVal50Leu heterozygous mutation in exon 2, confirming the diagnosis of ATTRv-CM. During further history-taking, it was discovered that the patient had undergone a magnetic resonance imaging (MRI) two years earlier due to right shoulder pain. Review of the imaging revealed a partial rupture of the long proximal biceps tendon, identified two years prior to the diagnosis of ATTRv-CM (Figure 5). Based on clinical findings suggestive of ATTR cardiac amyloidosis, the diagnosis was confirmed as summarized in Table 1. Following diagnosis, we planned to discontinue hydrochlorothiazide due to orthostatic hypotension and initiate tafamidis as a specific treatment for ATTR cardiac amyloidosis.

Discussion

Musculoskeletal findings may develop 5 to 15 years before the onset of other symptoms in patients with ATTR-CM.[3,4] Carpal tunnel syndrome is the most common non-cardiac manifestation in patients with either wt-ATTR-CM or ATTRv-CM, often occurring several years prior to diagnosis.[5] A recent study reported that 10.2% of patients with bilateral

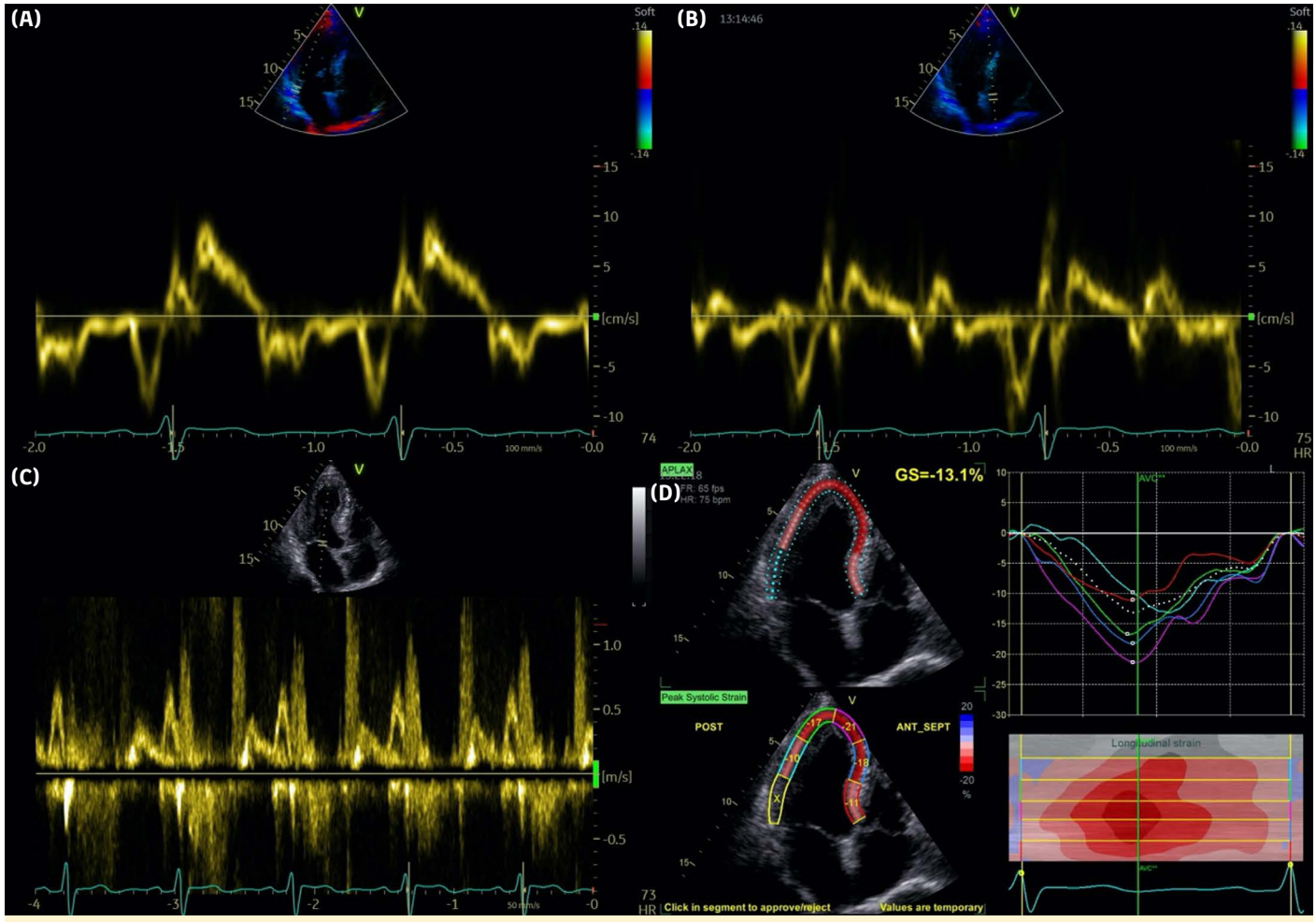

Figure 3. Left ventricular diastolic function assessment. Lateral (A) and septal (B) mitral annulus tissue velocity, and mitral inflow pulse wave Doppler (C) images reveal Grade 1 diastolic dysfunction. Global longitudinal strain study shows the "cherry-on-top" pattern (D).

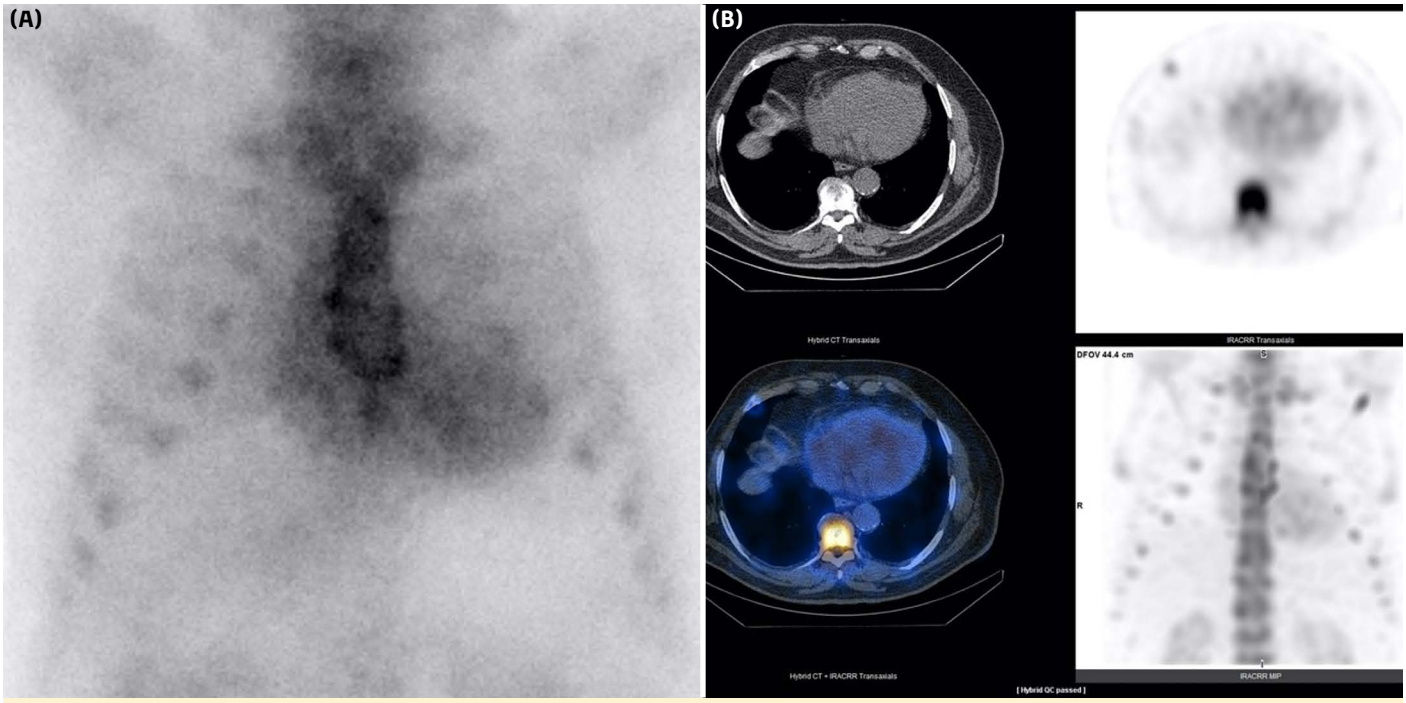

Figure 4. (A) Planar image of the patient obtained one hour after injection, showing increased myocardial activity. (B) Single-photon emission computed tomography-computed tomography (SPECT-CT) image demonstrating increased cardiac uptake in a patient with suspected transthyretin cardiac amyloidosis (ATTR-CM).

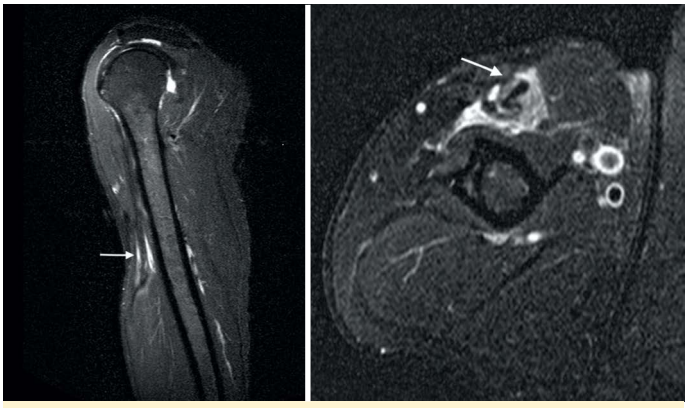

Figure 5. Sagittal T2-weighted fat-suppressed (T2 FS) and axial T2 FS images showing a partial rupture of the proximal biceps tendon.

carpal tunnel syndrome were found to have amyloid deposits.[6] In a Japanese family, the coexistence of trigger finger and carpal tunnel syndrome was also reported in association with ATTRv amyloidosis.[7] Additionally, several studies have identified a clinical history of lumbar spinal stenosis in patients with both wt-ATTR and ATTRv amyloidosis.[7,8]

Geller et al.[9] investigated the frequency of ruptured distal biceps tendon (RBT) in 111 patients with wt-ATTR, diagnosed either through endomyocardial biopsy or technetium pyrophosphate scintigraphy in the absence of gammopathy. In this study, RBT was observed in 37 patients (33.3% [95% confidence interval (CI), 24.7%-42.9%]), with the rupture occurring in the dominant arm in 35 patients (95% [95% CI, 82%-99%]). The incidence of RBT was significantly higher in the wt-ATTR group compared to the control group with heart failure from non-amyloid etiologies (33.3% vs. 2.5%). Hick et al.[10] also reported two cases of ATTR amyloidosis presenting with spontaneous distal biceps tendon rupture, commonly referred to as the "Popeye sign."

Table 1. Clues Suggesting a Diagnosis of Cardiac Amyloidosis in the Patient

Clinical	Fatigue
	Heart failure symptoms
	Family history of heart failure (brother)
Electrocardiographic	Pseudoinfarct pattern
Imaging	Increased left ventricular wall thickness
	Abnormal longitudinal strain with apical sparing (GLS -13%)
	Right wall thickness of 6 mm
Laboratory	Persistently low-level elevation of troponin
	Elevated N-terminal pro-B-type natriuretic peptide
	Kappa/lambda light chain ratio: 0.82
	Estimated glomerular filtration rate (eGFR): 82 mL/dk/1.73 m^2
	Normal hemogram indices
Musculoskeletal	Bilateral carpal tunnel syndrome
	Lumbar spinal stenosis
	Spontaneous biceps tendon rupture
Neurologic	Orthostatic hypotension

The patient presented in this report had a history of bilateral carpal tunnel syndrome, prior spinal stenosis surgery, and a partial rupture of the long proximal biceps tendon—musculoskeletal manifestations accompanying a pathogenic ATTR mutation. Current studies have described that biceps tendon rupture and carpal tunnel syndrome can precede a diagnosis of cardiac amyloidosis by several years.[9] As previously mentioned, the association between distal biceps tendon rupture and wt-ATTR-CM is well established; however, the coexistence of spontaneous biceps tendon rupture with ATTRv-CM has not been reported before. It is uncertain whether spontaneous rupture of the proximal biceps tendon is directly related to ATTRv-CM. Additional case reports are needed to clarify this potential association. We believe that this case may provide insight into future instances of ATTRv-CM and spontaneous proximal biceps tendon rupture, potentially influenced by the specific mutation type.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient.

Conflict of Interest: The authors have no conflicts of interest to declare.

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

Use of AI for Writing Assistance: None declared.

Author Contributions: Concept – B.K., E.P.O., N.A.D., E.K.Ö., T.B., Ö.Ö.; Design – B.K., E.P.O., N.A.D., E.K.Ö., T.B., Ö.Ö.; Supervision – B.K., E.P.O., Ö.Ö.; Data Collection and/or Processing – B.K., E.P.O., N.A.D., E.K.Ö., T.B., Ö.Ö.; Analysis and/or Interpretation – B.K., E.P.O., N.A.D., E.K.Ö., T.B., Ö.Ö.; Literature Review – B.K., E.P.O., N.A.D., E.K.Ö., T.B., Ö.Ö.; Writing – B.K., E.P.O., N.A.D., E.K.Ö., T.B., Ö.Ö.; Critical Review – B.K., E.P.O., N.A.D., E.K.Ö., T.B., Ö.Ö.

Peer-review: Internally peer-reviewed.

Video 1. Parasternal long-axis transthoracic echocardiography view.

Video 2. Apical four-chamber echocardiography view.

References

1. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2020: Update and recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. *Amyloid*. 2020;27(4):217-222. [CrossRef]
2. Castaño A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38(38):2879-2887. [CrossRef]
3. Papoutsidakis N, Miller EJ, Rodonski A, Jacoby D. Time course of common clinical manifestations in patients with transthyretin cardiac amyloidosis: Delay from symptom onset to diagnosis. *J Card Fail*. 2018;24(2):131-133. [CrossRef]
4. Donnelly JP, Hanna M, Sperry BW, Seitz WH Jr. Carpal tunnel syndrome: A potential early, red-flag sign of amyloidosis. *J Hand Surg Am*. 2019;44(10):868-876. [CrossRef]
5. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68(2):161-172. [CrossRef]
6. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol*. 2018;72(17):2040-2050. [CrossRef]
7. Sueyoshi T, Ueda M, Jono H, et al. Wild-type transthyretin-derived amyloidosis in various ligaments and tendons. *Hum Pathol*. 2011;42(9):1259-1264. [CrossRef]
8. Yanagisawa A, Ueda M, Sueyoshi T, et al. Amyloid deposits derived from transthyretin in the ligamentum flavum as related to lumbar spinal canal stenosis. *Mod Pathol*. 2015;28(2):201-207. [CrossRef]
9. Geller HI, Singh A, Alexander KM, Mirto TM, Falk RH. Association between ruptured distal biceps tendon and wild-type transthyretin cardiac amyloidosis. *JAMA*. 2017;318(10):962-963. [CrossRef]
10. Hicks C, Cei L, Fan Q, et al. Biceps tendon rupture as an early manifestation of hereditary transthyretin amyloidosis. Ann Intern Med: *Clin Cases*. 2024;3(3):e231130. [CrossRef]