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A novel genotype–phenotype overlap: transthyretin cardiac amyloidosis with a pathogenic CTNNA3 truncating variant presenting with malignant ventricular arrhythmias

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Case Report

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Abstract

Background:

Transthyretin cardiac amyloidosis (ATTR-CM) may mimic hypertrophic cardiomyopathy and, in rare cases, coexist with genetic cardiomyopathies, potentially increasing arrhythmic risk.

Methods:

An 82-year-old man with atrial fibrillation presenting with progressive heart failure symptoms underwent comprehensive clinical, electrocardiographic, echocardiographic, hematologic, and nuclear imaging evaluation. Genetic testing was performed to investigate a potential underlying cardiomyopathic substrate.

Results:

Electrocardiography demonstrated low QRS voltage and a pseudo-infarction pattern. Echocardiography revealed marked left ventricular hypertrophy with a small cavity and restrictive filling. Hematologic evaluation excluded light-chain amyloidosis. Tc-99m pyrophosphate scintigraphy showed Grade 3 myocardial uptake, confirming ATTR-CM. Genetic analysis identified a pathogenic truncating CTNNA3 variant. Despite initiation of tafamidis therapy, the patient developed non-sustained ventricular tachycardia followed by ventricular fibrillation and died.

Conclusions:

This case suggests a previously underrecognized high-risk arrhythmogenic phenotype arising from the coexistence of infiltrative and genetic cardiomyopathies, in which structural and electrical substrates may synergistically contribute to malignant ventricular arrhythmias and adverse outcomes.

Introduction

Cardiac amyloidosis is a progressive infiltrative cardiomyopathy characterized by extracellular amyloid deposition within the myocardium [1]. Transthyretin cardiac amyloidosis (ATTR-CM) is increasingly recognized, particularly in elderly patients, and often presents with a phenotype resembling hypertrophic cardiomyopathy [2]. Non-invasive diagnostic approaches using bone scintigraphy and hematologic testing have improved early detection [3].

Arrhythmogenic cardiomyopathies are genetically mediated diseases associated with ventricular arrhythmias and sudden cardiac death [4]. The CTNNA3 gene, encoding αT-catenin, has been implicated in arrhythmogenic cardiomyopathy, although the level of evidence remains limited [5].

The coexistence of infiltrative and genetic cardiomyopathies is rare but may significantly affect clinical outcomes [6]. However, data regarding their combined arrhythmic risk and clinical implications remain limited. Increasing evidence suggests that multiple cardiomyopathic substrates may coexist in elderly patients, potentially modifying arrhythmic risk and clinical outcomes.

Case presentation

An 82-year-old man with a known history of atrial fibrillation and previously documented left ventricular wall thickening presented to the cardiology outpatient clinic with progressively worsening dyspnea, orthopnea, and bilateral lower extremity edema. At initial presentation, he reported progressively worsening symptoms over several months, including limited exercise tolerance, and was classified as New York Heart Association (NYHA) functional class III.

On physical examination, he appeared dyspneic at rest. Bilateral basal crackles were auscultated over the lung fields, and marked pretibial edema was observed. Blood pressure was noted to be relatively low compared to his previous records. Of particular clinical relevance, the patient described intolerance to previously prescribed antihypertensive therapy, specifically a combination of ramipril and hydrochlorothiazide, which had been discontinued due to recurrent symptomatic hypotension. This feature was considered an important clinical red flag suggestive of cardiac amyloidosis.

Electrocardiography demonstrated atrial fibrillation with low QRS voltage in the limb leads (< 5 mm) and a pseudo-infarction pattern (Fig. 1). These findings were discordant with the degree of left ventricular wall thickening and raised suspicion for an infiltrative cardiomyopathy.

Transthoracic echocardiography revealed preserved left ventricular systolic function with an ejection fraction of 60% and no regional wall motion abnormalities. However, there was marked concentric left ventricular hypertrophy, with an interventricular septal thickness of 20 mm and a posterior wall thickness of 18 mm. The left ventricular cavity was relatively small (LV end-diastolic diameter 40 mm), consistent with a restrictive physiology.

Diastolic function assessment demonstrated a restrictive filling pattern. Mitral inflow showed an E wave velocity of 79 cm/s, while tissue Doppler imaging revealed a septal e' velocity of 3.9 cm/s and a lateral e' velocity of 5.5 cm/s. The calculated E/e' ratio was 24, indicating significantly elevated left ventricular filling pressures and consistent with grade III diastolic dysfunction. Additional echocardiographic findings included biatrial enlargement, thickening of both mitral and aortic valves, moderate mitral regurgitation, and a small pericardial effusion (~ 5 mm). Taken together, these findings were highly suggestive of an infiltrative cardiomyopathy, particularly cardiac amyloidosis.

Laboratory evaluation revealed markedly elevated high-sensitivity troponin I (317.4 ng/L) and BNP (466.2 ng/L), indicating ongoing myocardial injury and increased intracardiac pressures. Mild anemia, slight renal impairment, and elevated liver enzymes were also noted, consistent with systemic congestion and advanced cardiac involvement.

Given the high clinical suspicion for cardiac amyloidosis, a comprehensive hematologic work-up was performed. Serum free light chains and serum/urine immunofixation studies were negative. Serum protein electrophoresis demonstrated no monoclonal spike (Supplementary Fig. 1), and bone marrow biopsy did not reveal evidence of plasma cell dyscrasia, effectively excluding light-chain (AL) amyloidosis. Serum free light chain analysis demonstrated a normal kappa/lambda ratio, and no monoclonal protein was detected on serum or urine immunofixation, effectively excluding AL amyloidosis.

Subsequently, Tc-99m-labeled cardiac scintigraphy was performed and demonstrated intense myocardial uptake exceeding bone uptake (Grade 3), confirming the diagnosis of transthyretin cardiac amyloidosis in the absence of monoclonal gammopathy (Wild-type) (Fig. 3). This combination of findings established a non-invasive diagnosis of ATTR-CM according to current diagnostic criteria. Following confirmation of the diagnosis, disease-modifying therapy with tafamidis (61 mg once daily) was initiated, and the patient was subsequently enrolled in regular outpatient follow-up.

To further evaluate the etiology, genetic testing was performed. While no pathogenic variants were detected in the transthyretin gene, a heterozygous pathogenic truncating variant in the CTNNA3 gene (c.160del, p.Arg54GlyfsTer6) was identified. This finding raised suspicion for an additional arrhythmogenic cardiomyopathy substrate.

Cardiac magnetic resonance imaging was subsequently performed and demonstrated late gadolinium enhancement involving the right ventricular free wall, particularly in the subepicardial region, suggestive of arrhythmogenic right ventricular involvement. In addition, asymmetric septal hypertrophy and hypertrophic myocardial appearance of the left ventricle were observed, further supporting the coexistence of a complex cardiomyopathic phenotype (Fig. 4).

Approximately one month after the initial hospitalization, the patient presented to the emergency department with palpitations and worsening dyspnea. Electrocardiography revealed a wide-complex tachycardia at approximately 190 beats per minute, consistent with prolonged NSVT (Fig. 2). He was admitted to the intensive care unit, where rhythm control was achieved with medical therapy, and the rhythm reverted to atrial fibrillation.

Given the high risk of malignant ventricular arrhythmias, implantation of a cardioverter-defibrillator (ICD) was planned. However, the procedure was deferred due to the development of sepsis during hospitalization. After clinical stabilization, the patient was discharged with continuation of tafamidis therapy and a plan for elective ICD implantation.

Approximately three weeks after discharge, the patient was found unconscious at home and was brought to the emergency department by emergency medical services. Upon arrival, ventricular fibrillation was documented. Despite successful defibrillation and aggressive intensive care management, including mechanical ventilation and inotropic support, the patient’s condition deteriorated, and he died two days later.

This clinical course highlights the aggressive nature of advanced cardiac amyloidosis and the potential contribution of an additional arrhythmogenic substrate in determining outcomes.

Discussion

In this patient, confirmed transthyretin cardiac amyloidosis coexisted with a pathogenic CTNNA3 truncating variant and was associated with a malignant arrhythmic course.

The coexistence of an infiltrative cardiomyopathy and a genetic arrhythmogenic substrate may have further increased the risk of malignant ventricular arrhythmias in this patient. Importantly, cardiac magnetic resonance imaging further strengthened the suspicion of an arrhythmogenic substrate by demonstrating right ventricular late gadolinium enhancement, a finding commonly associated with arrhythmogenic cardiomyopathy. The concomitant presence of hypertrophic left ventricular morphology and infiltrative features may reflect a complex overlap phenotype involving infiltrative, hypertrophic, and arrhythmogenic remodeling. While ATTR-CM alone is associated with conduction abnormalities and atrial arrhythmias, the presence of a pathogenic CTNNA3 truncating variant may have further destabilized myocardial electrical integrity, predisposing to ventricular tachyarrhythmias and sudden cardiac death.

Cardiac amyloidosis frequently mimics hypertrophic cardiomyopathy, particularly in elderly patients [2]. Several well-established red flags—including increased wall thickness with low QRS voltage, small ventricular cavity, restrictive filling pattern, and valvular thickening—are highly suggestive of this diagnosis [7, 8]. Our patient exhibited all of these features, which were further supported by Grade 3 myocardial uptake on scintigraphy, allowing a non-invasive diagnosis of ATTR-CM in accordance with current guidelines [3].

Previous studies, including that of Yalvaç et al., have highlighted the importance of integrating clinical, electrocardiographic, and echocardiographic red flags in raising suspicion for cardiac amyloidosis [7]. The present case strongly aligns with these findings.

Notably, in many clinical settings, advanced imaging modalities such as strain echocardiography or cardiac magnetic resonance imaging may not be readily available. In such scenarios, a high index of suspicion based on conventional echocardiographic parameters, electrocardiographic findings, and clinical features remains crucial. The combination of increased left ventricular wall thickness with disproportionately low QRS voltage, restrictive diastolic filling, biatrial enlargement, and characteristic clinical features such as intolerance to antihypertensive therapy can strongly suggest cardiac amyloidosis even in the absence of advanced imaging techniques [3, 7, 8]. Therefore, recognition of these readily available findings is essential for early diagnosis, particularly in resource-limited settings or centers without access to advanced imaging.

Although atrial fibrillation and conduction abnormalities are common in ATTR-CM, ventricular arrhythmias are less frequently observed [9]. However, in advanced stages, the risk of ventricular

arrhythmias and sudden cardiac death increases significantly [10]. The occurrence of both NSVT and ventricular fibrillation in our patient reflects this advanced arrhythmic phenotype.

Importantly, the identification of a pathogenic truncating variant in CTNNA3 suggests an additional arrhythmogenic substrate. CTNNA3 has been implicated in arrhythmogenic cardiomyopathy, although current evidence remains relatively limited [5, 12]. Truncating variants may lead to loss of protein function, impairing cellular adhesion and contributing to electrical instability. The coexistence of myocardial infiltration and genetic susceptibility may explain the severe arrhythmic manifestations observed in this case. Although the pathogenic role of CTNNA3 variants in arrhythmogenic cardiomyopathy remains incompletely established, truncating variants are generally considered more likely to be clinically significant due to loss-of-function effects. The occurrence of malignant ventricular arrhythmias in our patient further supports a potential contributory role of this variant.

Biomarkers also play a critical role in prognosis. Elevated troponin and natriuretic peptide levels reflect myocardial injury and hemodynamic stress and are associated with worse outcomes in ATTR-CM [13]. The markedly elevated levels observed in this patient are consistent with advanced disease and poor prognosis.

The most likely cause of death in this case is sudden cardiac death due to ventricular arrhythmia. Although rhythm documentation at the exact time of death was unavailable, the recent occurrence of NSVT and ventricular fibrillation strongly supports this mechanism.

These findings further emphasize the importance of early diagnosis and timely intervention. Implantable cardioverter-defibrillator therapy was planned but could not be performed due to clinical deterioration, which may have contributed to the fatal outcome. This case further emphasizes the need to consider a dual pathological substrate in patients with disproportionate arrhythmic burden, even when a primary diagnosis has already been established.

Our findings suggests that the coexistence of an infiltrative cardiomyopathy and a genetically determined arrhythmogenic substrate may represent a distinct high-risk phenotype, in which structural and electrical remodeling synergistically contribute to malignant ventricular arrhythmias. These findings highlight the importance of considering a combined phenotypic and genotypic evaluation in patients with unexplained hypertrophy and disproportionate arrhythmic burden.

Limitations

This case has several limitations. Strain echocardiography, which may provide additional diagnostic information such as apical sparing, was not available in our center. Although cardiac magnetic resonance imaging demonstrated late gadolinium enhancement suggestive of arrhythmogenic involvement, comprehensive tissue characterization and mapping sequences could not be fully performed due to the patient’s clinical deterioration. In addition, functional validation of the CTNNA3

variant was not available. Finally, the absence of long-term rhythm monitoring prior to the arrhythmic events limits assessment of arrhythmia burden over time.

Abbreviations

ATTR-CM
Transthyretin cardiac amyloidosis
AL
Light-chain amyloidosis
CTNNA3
Catenin alpha-3
CMR
Cardiac magnetic resonance imaging
ECG
Electrocardiography
ICD
Implantable cardioverter-defibrillator
LGE
Late gadolinium enhancement
LV
Left ventricle
LVEF
Left ventricular ejection fraction
NSVT
Non-sustained ventricular tachycardia
NYHA
New York Heart Association
PYP
Pyrophosphate
RV
Right ventricle
VF
Ventricular fibrillation
VT
Ventricular tachycardia.

Declarations

Ethics approval and consent to participate

This case report was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of Eskisehir City Hospital (Approval No: ESH/BAEK 2026/361; Date: 07.05.2026). Formal consent to participate was not required for this single case report per institutional policy; however, written informed consent for publication was obtained from the patient's next of kin, as described below.

Consent for publication

Written informed consent for the publication of clinical details and any identifying images was obtained from the patient's next of kin prior to submission, as the patient was deceased at the time of manuscript preparation. A copy of the consent form is available to the Editor-in-Chief on request.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Halit Emre Yalvaç (H.E.Y.) conceived the study, managed the patient, interpreted the clinical findings, and wrote the main manuscript text. Hazal Dağhan (H.D.) and Muhammet Burak Dağhan (M.B.D.) contributed to data collection, literature review, and manuscript revision. All authors reviewed and approved the final manuscript.

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Not applicable.

Data Availability

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

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Tables

Table 1. Echocardiographic Findings

Parameter	Value
Left ventricular ejection fraction (LVEF)	60%
Interventricular septum thickness	20 mm
Posterior wall thickness	18 mm
Left ventricular end-diastolic diameter (LVEDD)	40 mm
Mitral E wave velocity	79 cm/s
Septal e' velocity	3.9 cm/s
Lateral e' velocity	5.5 cm/s
E/e' ratio	24
Diastolic function	Grade III
Left atrial volume index (LAVI)	38 mL/m²
Mitral valve	Thickened, moderate regurgitation
Aortic valve	Thickened, mild regurgitation
Pericardial effusion	~5 mm

Table 2. Laboratory Findings at Presentation

Parameter	Value
High-sensitivity troponin I	317.4 ng/L
B-type natriuretic peptide (BNP)	466.2 ng/L
Creatinine	1.13 mg/dL
Hemoglobin	11.9 g/dL
Aspartate aminotransferase (AST)	49 U/L
Gamma-glutamyl transferase (GGT)	111 U/L
Lactate dehydrogenase (LDH)	344 U/L
Total protein	61.9 g/L
Potassium	3.1 mmol/L
Beta-2 microglobulin	5.88 mg/L
Free lambda light chain	33.7 mg/L
Free kappa light chain	21.5 mg/L
Kappa/lambda ratio	~0.64
Serum immunofixation	No abnormal monoclonal band detected
Urine immunofixation	No abnormal monoclonal band detected

Table 3. Comprehensive Red Flags for Cardiac Amyloidosis with Case-Specific Findings

Category	Red Flag	Present
Clinical features	Progressive dyspnea, orthopnea, peripheral edema	**Yes**
	Intolerance to antihypertensive therapy (hypotension)	**Yes**
	Unexplained fatigue and exercise intolerance	**No**
	History of carpal tunnel syndrome	**No**
	Peripheral neuropathy	**No**
	Orthostatic hypotension / autonomic dysfunction	**Yes**
Electrocardiography	Low QRS voltage in limb leads	**Yes**
	Pseudo-infarction pattern	**Yes**
	Atrial fibrillation or conduction abnormalities	**Yes**
	Discrepancy between LV hypertrophy and ECG voltage	**Yes**
Echocardiography	Increased left ventricular wall thickness	**Yes**
	Small left ventricular cavity	**Yes**
	Grade III diastolic dysfunction (restrictive filling)	**Yes**
	Biatrial enlargement	**Yes**
	Valvular thickening	**Yes**
	Pericardial effusion	**Yes**
	Granular sparkling myocardial appearance	**Yes**
	Apical sparing pattern on strain imaging	**No**
Biomarkers	Elevated BNP or NT-proBNP levels	**Yes**
	Elevated troponin levels	**Yes**
Advanced imaging	Grade 2–3 myocardial uptake on bone scintigraphy	**Yes**
	Late gadolinium enhancement on cardiac MRI	**No**
Laboratory / hematology	Absence of monoclonal protein (to exclude AL amyloidosis)	**Yes**

*Findings observed in the present case are highlighted in bold.

Figures

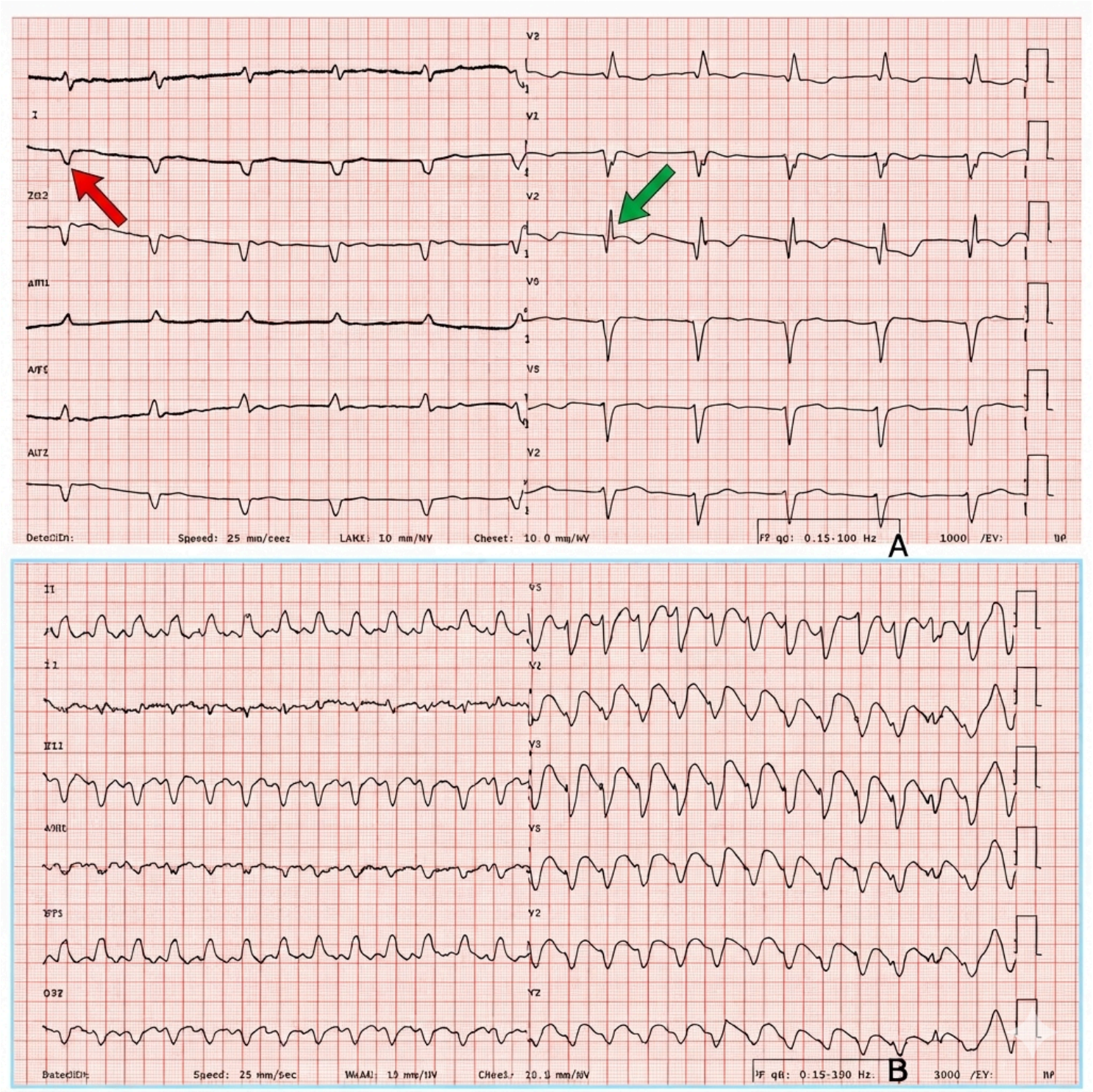


Figure 1

Electrocardiographic features of the dual cardiomyopathy phenotype

(A) Baseline 12-lead electrocardiogram demonstrating atrial fibrillation with slow ventricular response, low QRS voltage in limb leads (red arrow), and a pseudo-infarction pattern in the precordial leads (green arrow), consistent with cardiac amyloidosis.

(B) Non-sustained ventricular tachycardia episode recorded during monitoring, supporting the arrhythmogenic component associated with the CTNNA3 variant.

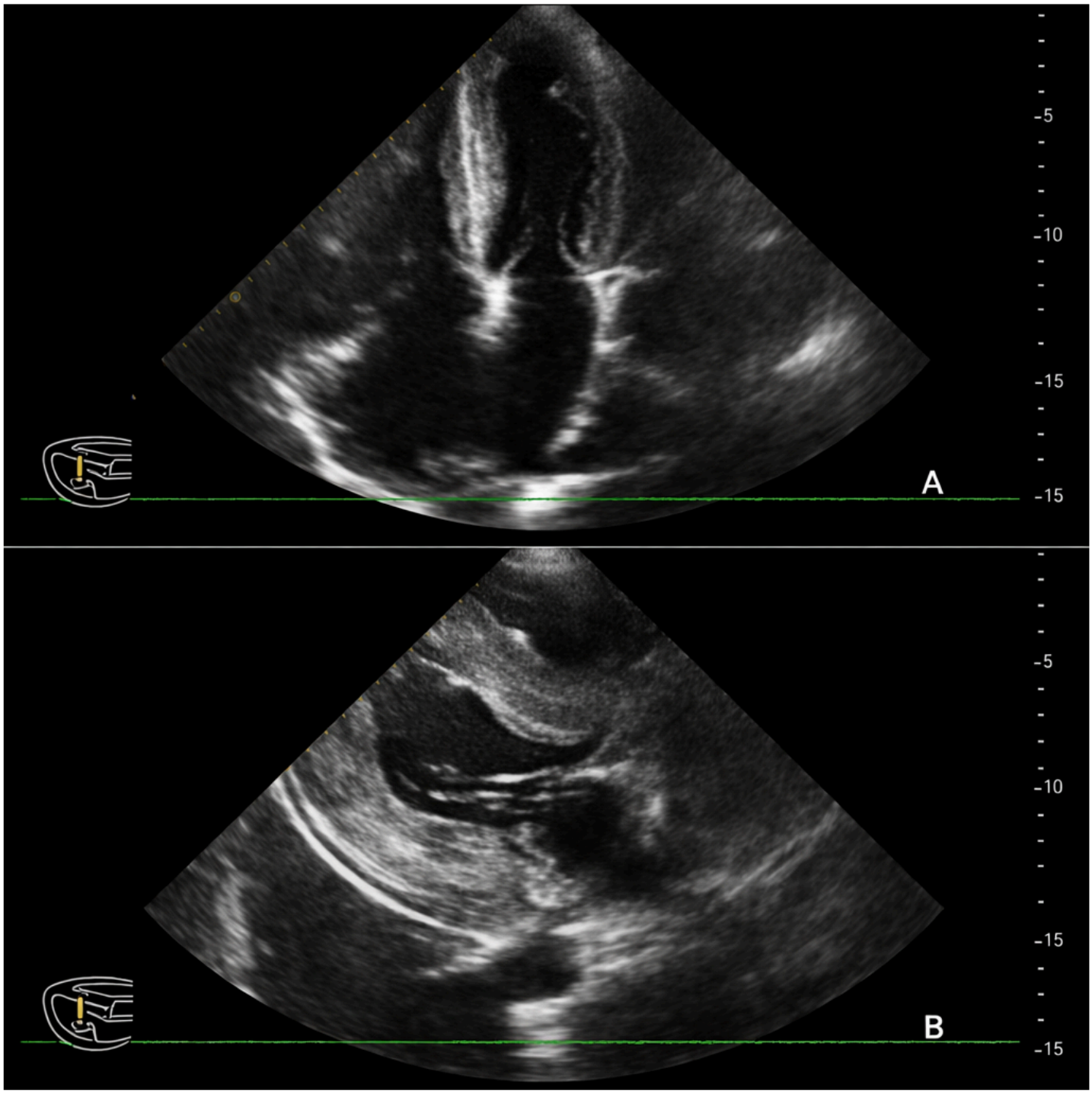


Figure 2

Transthoracic echocardiographic findings demonstrating features of dual cardiomyopathy.
(A) Apical four-chamber view showing biatrial dilatation, small left ventricular cavity, and a characteristic granular sparkling appearance of the myocardium, suggestive of cardiac amyloidosis.
(B) Parasternal long-axis view demonstrating asymmetric septal hypertrophy mimicking a hypertrophic phenotype, along with granular myocardial texture and a minimal pericardial effusion.

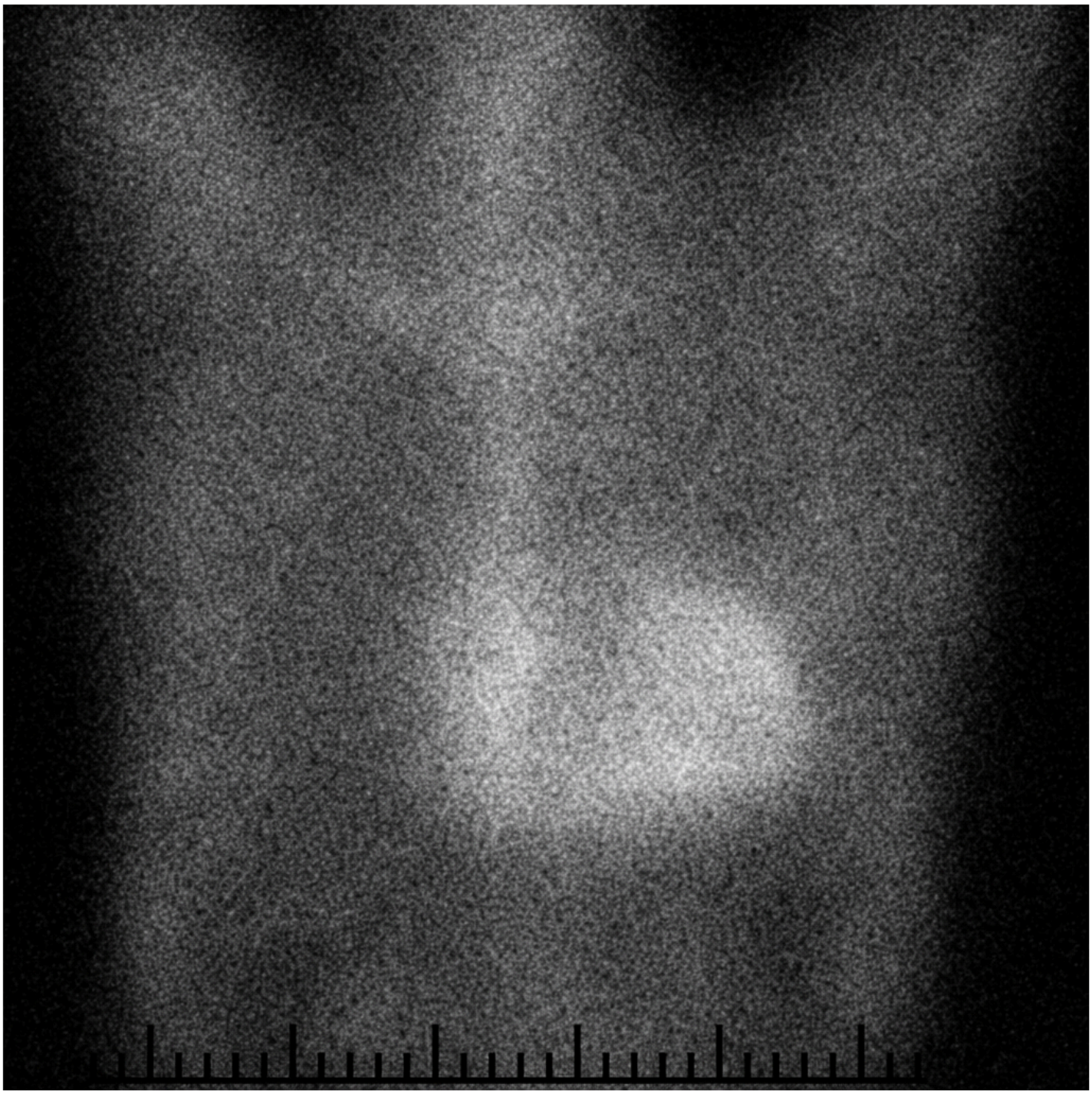


Figure 3

99mTc-pyrophosphate (PYP) scintigraphy confirming transthyretin cardiac amyloidosis.
Planar scintigraphy demonstrates intense myocardial tracer uptake greater than adjacent rib uptake, corresponding to Grade 3 myocardial involvement and strongly supporting the diagnosis of transthyretin cardiac amyloidosis.

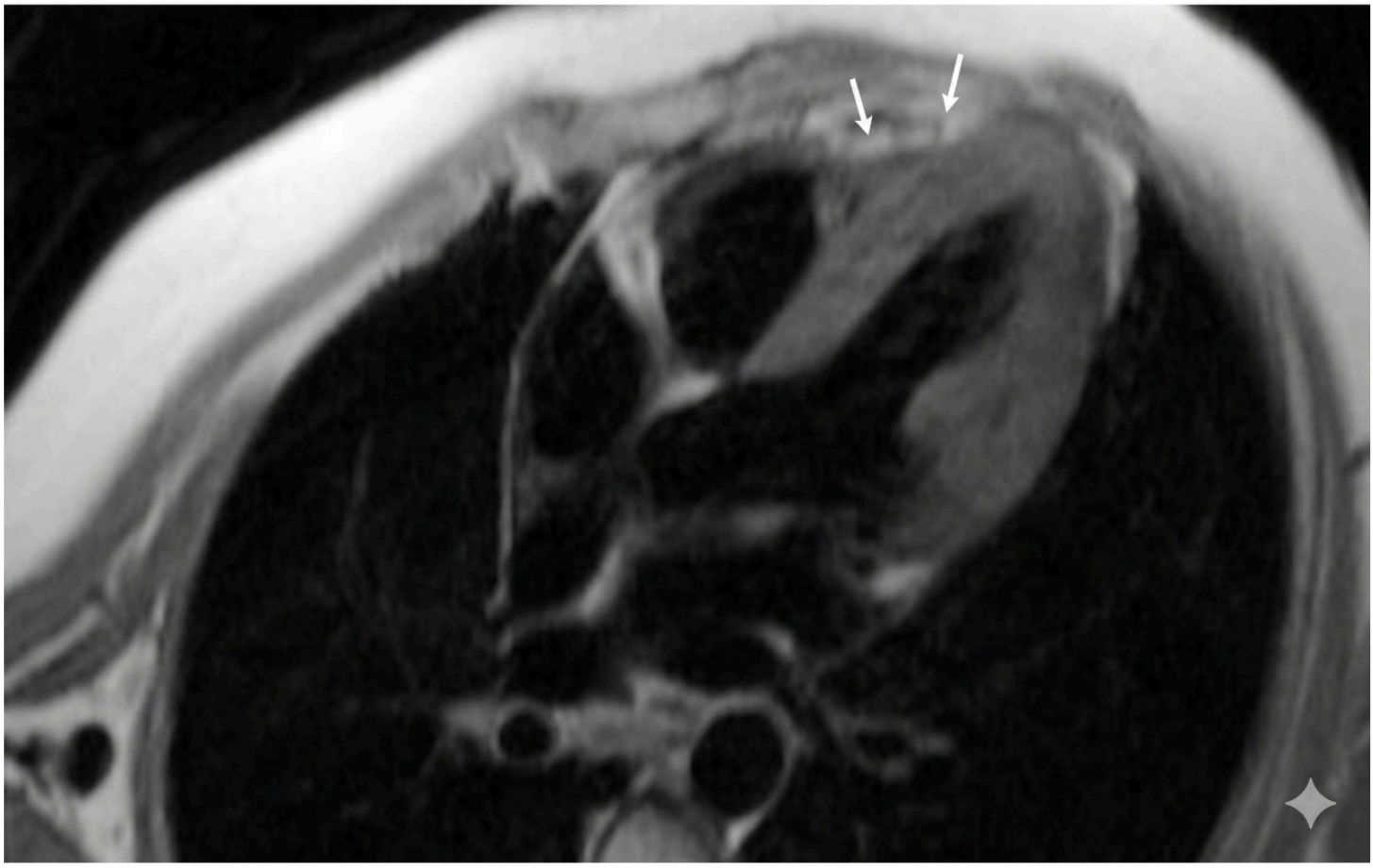


Figure 4

Cardiac magnetic resonance imaging findings suggesting arrhythmogenic involvement.

Cardiac magnetic resonance imaging demonstrating late gadolinium enhancement involving the right ventricular free wall (white arrows), suggestive of arrhythmogenic myocardial involvement. In addition, asymmetric septal hypertrophy and hypertrophic left ventricular morphology are observed, supporting a complex overlap phenotype involving infiltrative and arrhythmogenic cardiomyopathic features.

Supplementary Files

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