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Case Report

Clinical Benefit of the Transthyretin Stabiliser Tafamidis in Hereditary Transthyretin Amyloid Cardiomyopathy: A Case Report

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Abstract

Aims/Background: This case report aims to illustrate the critical importance of a standardized diagnostic approach and genotype-specific therapy in hereditary transthyretin amyloid cardiomyopathy (ATTR-CM). It highlights the clinical challenge of diagnosing ATTR-CM amidst complex comorbidities and addresses the evidence gap regarding the long-term efficacy of tafamidis for the rare and aggressive p.Val40Ile (protein-level substitution of valine to isoleucine at codon 40) mutation. **Case Presentation**: A 72-year-old East Asian man with multiple comorbidities presented with refractory heart failure. Key clinical clues included the classic "red flag" of electrocardiogram (ECG)-echocardiogram discordance (low voltage with ventricular hypertrophy). Genetic testing identified the pathogenic p.Val40Ile transthyretin (*TTR*) mutation. **Results**: The diagnosis was confirmed non-invasively via cardiac magnetic resonance (CMR) and technetium-99m pyrophosphate scintigraphy. Following the initiation of tafamidis, the patient's symptoms significantly improved. Over a two-year follow-up period, he sustained clinical stability with a marked reduction in heart failure-related hospitalizations. **Conclusion**: This report provides detailed case-based evidence supporting the long-term efficacy of tafamidis in stabilizing disease and improving prognosis for patients with ATTR-CM harboring the p.Val40Ile mutation. It underscores the value of timely diagnosis, genetic subtyping, and access to targeted therapy in altering the clinical course of this aggressive genotype.

Keywords: amyloid; cardiomyopathy; mutation; prognosis; case report

1. Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative cardiomyopathy caused by the myocardial deposition of misfolded transthyretin (TTR) protein, ultimately leading to progressive heart failure [1]. ATTR-CM is a significant yet under-recognized cause of heart failure, particularly in older adults, and diagnosis is frequently delayed because of nonspecific symptoms mimicking common conditions. Recent advances in non-invasive diagnostics, specifically bone scintigraphy, have greatly improved detection, enabling accurate diagnosis without the need for biopsy [2]. In parallel, disease-modifying therapies such as the transthyretin stabiliser tafamidis have emerged [3], demonstrating survival and morbidity benefits in clinical trials and transforming the management landscape [4]. However, prognosis and treatment response can be highly mutation-specific. The p.Val40Ile (protein-level substitution of valine to isoleucine at codon 40) mutation is a rare *TTR* variant, previously characterized by high penetrance and a severe cardiac phenotype, primarily in a Caucasian cohort [5]. While the TTR stabiliser tafamidis improves outcomes in broad ATTR-CM trials, its efficacy in altering the natural history of specific, aggressive mutations such as p.Val40Ile requires real-world validation. We present a case that bridges this gap in evidence, demonstrating how early diagnosis and tafamidis therapy substantially improved the long-term outcome of a patient with this genotype.

2. Case Report

A 72-year-old man was referred to the Department of General Practice for a three-month history of bilateral lower limb edema. The patient's initial symptoms included exertional chest tightness and dyspnea, as well as episodes of paroxysmal nocturnal dyspnea (PND). His medical history was significant for atrial fibrillation, hypertension, type 2 diabetes, schistosomiasis-induced liver disease, and refractory heart failure that was suboptimally responsive to guideline-directed medical therapy including sacubitril/valsartan (Novartis, TNTF1, Beijing, China), bisoprolol (Yueyang Xinhua Da Pharmaceutical Co., Ltd., 20231205, Yueyang, China), and diuretics (furosemide, Tianjin Lisheng Pharmaceutical Co., Ltd., 2306037, Tianjin, China; spironolactone, Hangzhou Minsheng Pharmaceutical Co., Ltd., T23K038, Hangzhou, China). A coronary angiogram performed two years prior for elevated troponin had shown no significant stenosis. The patient's parents were deceased with unknown medical histories. His daughter and grandson were reportedly in good health.

His vital signs were as follows: temperature 36.8 °C, pulse 79 beats per minute, respiratory rate 20 breaths per

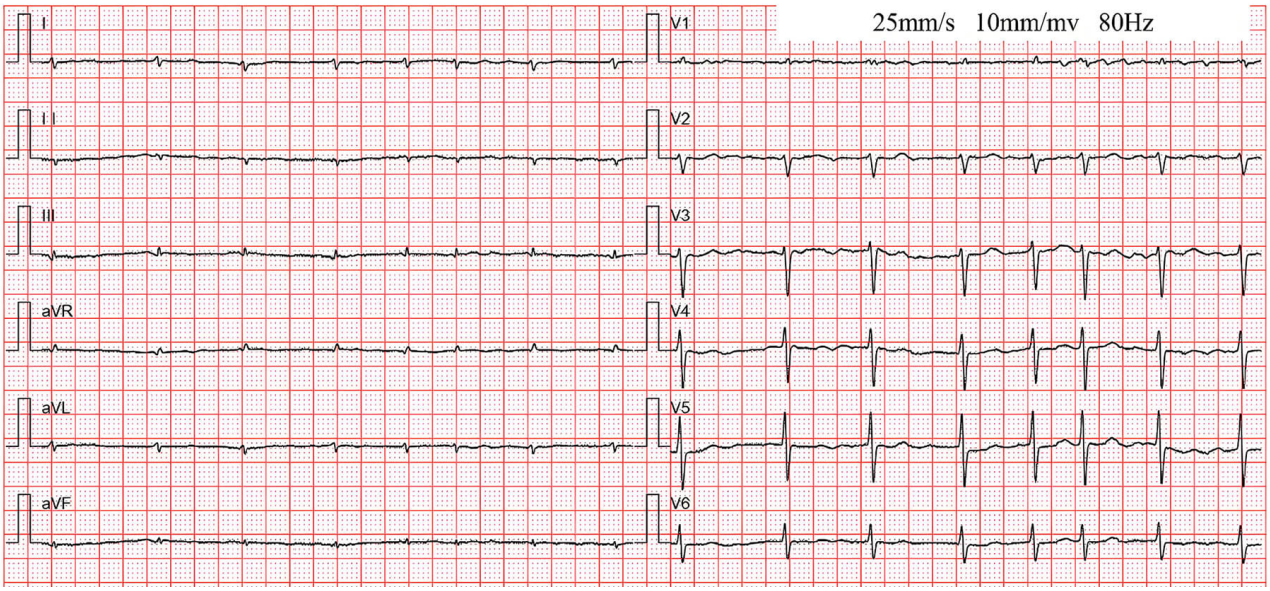

Fig. 1. Electrocardiogram (ECG). ECG demonstrated atrial fibrillation with low voltage in the limb leads. aVR, augmented Vector Right; aVL, augmented Vector Left; aVF, augmented Vector Foot.

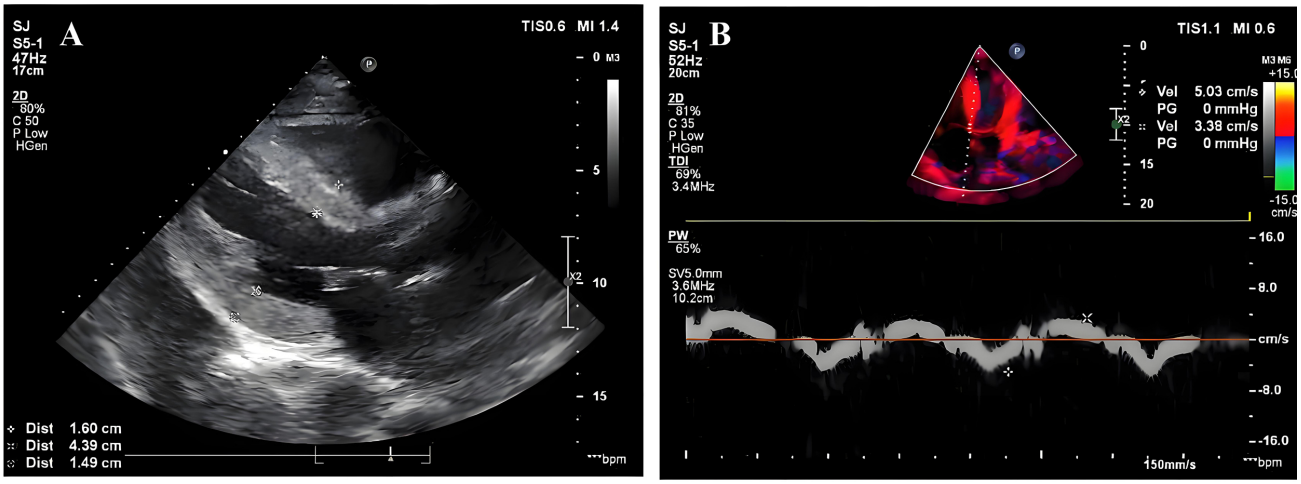

Fig. 2. Echocardiography. (A) Parasternal long-axis view demonstrating a thickened interventricular septum (16 mm) with a granular sparkling appearance, a characteristic echocardiographic feature of amyloid cardiomyopathy. (B) Pulsed-wave tissue Doppler imaging at the lateral mitral annulus showing reduced e' (5 cm/s) and s' (3 cm/s) velocities.

minute, and blood pressure 101/77 mmHg. His anthropometric measurements were as follows: Height 1.75 m, weight 74 kg, and body mass index 24.16 kg/m^2. Physical examination revealed an irregular pulse, elevated jugular venous pressure, bibasilar pulmonary crackles, hepatomegaly, and bilateral symmetric pitting edema.

3. Diagnostic Workup

Initial evaluation: A 12-lead electrocardiogram (ECG) revealed atrial fibrillation with low voltage in the limb leads (Fig. 1). Echocardiography revealed left ventricular (LV) hypertrophy (interventricular septal thickness of 16 mm), biatrial enlargement, and a reduced left ventricular ejection fraction (LVEF) of 39% (Fig. 2). Cardiac biomarkers were markedly elevated: N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I were 10,057 pg/mL (normal range $<$116 pg/mL) and 404.5 pg/mL (normal range $<$15.6 pg/mL), respectively.

Diagnostic clues and further investigation: The discordance between low ECG voltage and significant LV hypertrophy on echocardiography ("voltage-mass discordance"), coupled with persistently elevated troponin in the absence of coronary artery disease, raised a strong suspicion of an infiltrative cardiomyopathy. Cardiac magnetic resonance (CMR) imaging revealed severely impaired LV systolic function (ejection fraction 17.5%) with global hy-

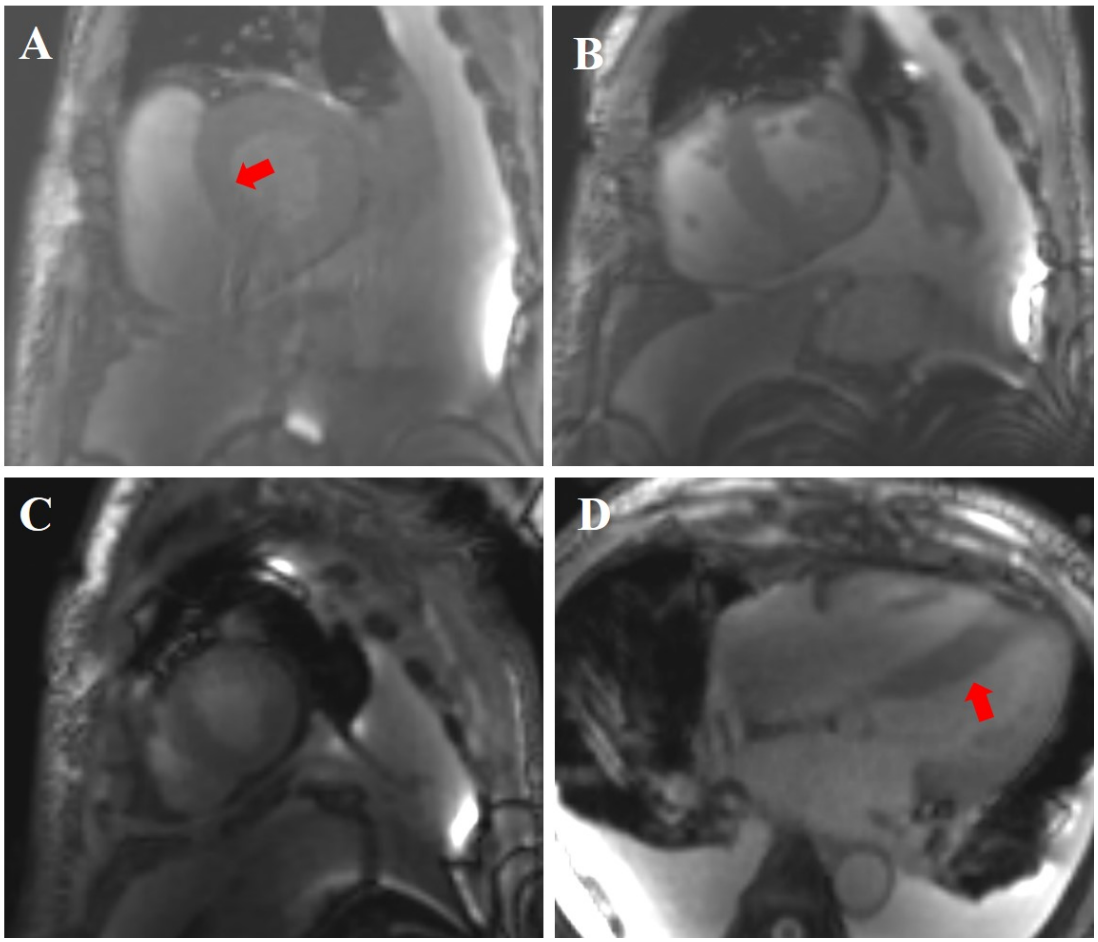

Fig. 3. Cardiac magnetic resonance (CMR). Cine CMR images in basal short-axis (A), mid-short-axis (B), apical short-axis (C), and 4-chamber (D) views, demonstrating an increase in left ventricular wall thickness at 16.4 mm (red arrows).

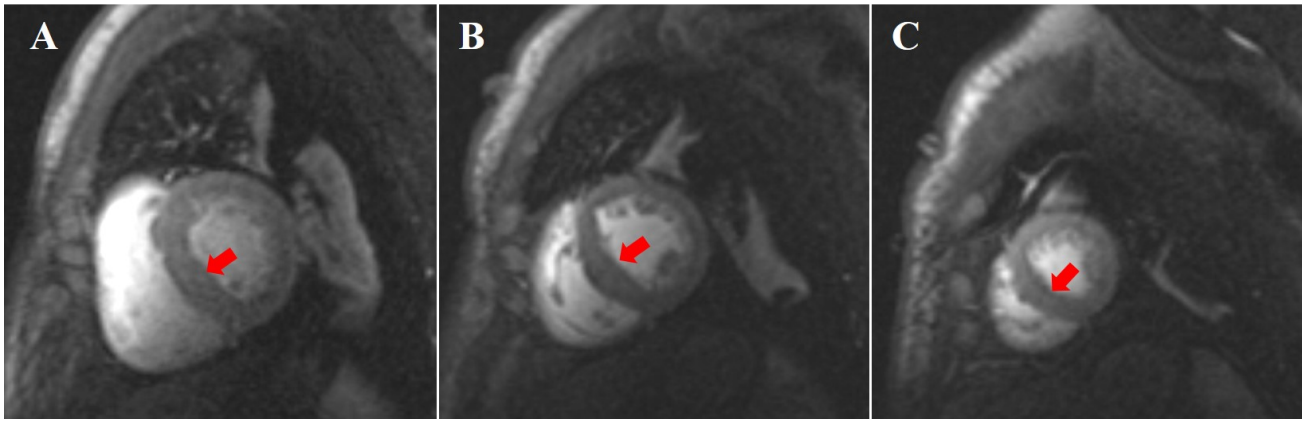

Fig. 4. First-pass perfusion CMR. First-pass perfusion CMR images in basal short-axis (A), mid-short-axis (B), and apical short-axis (C) views, demonstrating preserved myocardial perfusion without defects; red arrows indicate homogeneous myocardial enhancement (no perfusion defect).

pokinesia and significant diastolic dysfunction. Asymmetric LV hypertrophy was observed, predominantly involving the mid to basal segments, with maximal wall thickness in the interventricular septum (16.4 mm at the basal segment) (Fig. 3). First-pass perfusion imaging revealed preserved myocardial perfusion without defects (Fig. 4). Late gadolinium enhancement (LGE) imaging demonstrated extensive subendocardial and mid-myocardial enhancement extending from the basal segments (Fig. 5A) to the apex (Fig. 5C), exhibiting patchy and circumferential

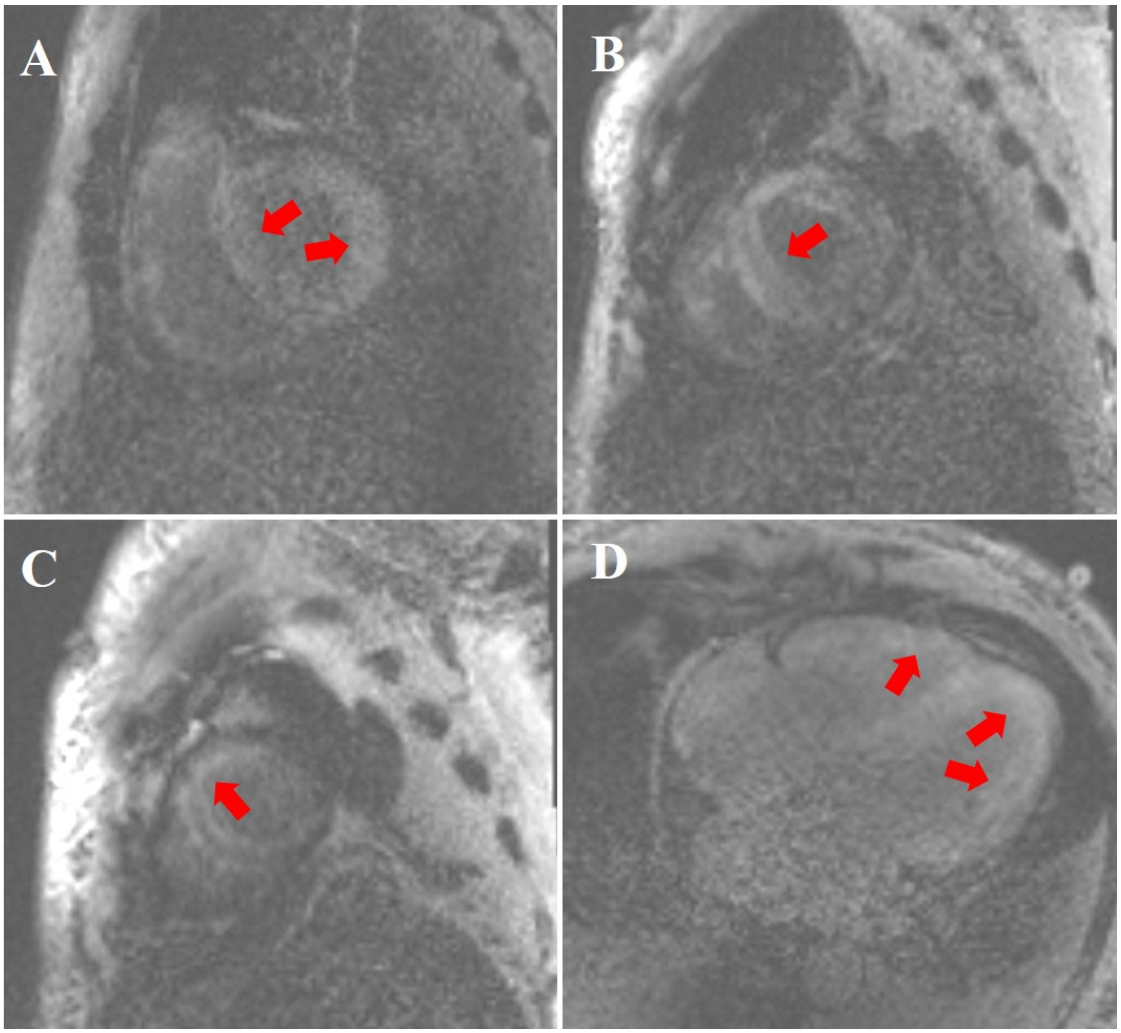

Fig. 5. Late gadolinium enhancement (LGE) CMR. LGE CMR images in basal short-axis (A), mid-short-axis (B), apical short-axis (C), and 4-chamber (D) views, demonstrating diffuse subendocardial (red arrows) and mid-myocardial LGE.

patterns with areas of transmural involvement (Fig. 5A–C). Additionally, linear enhancement was noted in the walls of both the atria and right ventricle (Fig. 5D). Serum and urine immunofixation electrophoresis were negative for monoclonal protein. Serum free light chain assay revealed a minimally elevated κ chain level (25.43 mg/L), with a normal λ chain level (20.41 mg/L) and a normal κ/λ ratio (1.246). Technetium-99m pyrophosphate scintigraphy (General Electric Healthcare, single-photon emission computed tomography/computed tomography [SPECT/CT] discovery 670) demonstrated intense myocardial radiotracer uptake (Perugini Grade 3, heart-to-contralateral lung [H/CL] ratio = 1.76), confirming the diagnosis of ATTR-CM non-invasively.

Genetic analysis: Genetic testing identified a pathogenic heterozygous mutation in the *TTR* gene (c.118G>A [a guanine-to-adenine substitution at nucleotide position 118 of the coding DNA sequence], p.Val40Ile) (Fig. 6), establishing a definitive diagnosis of hereditary ATTR-CM. This specific variant is associated with a high-penetrance, predominantly cardiac phenotype and carries a risk of rapid progression to end-stage heart failure [5], underscoring the urgency of initiating disease-modifying therapy. His daughter and grandson refused to undergo the *TTR* gene test due to psychological stress.

4. Management and Outcome

Following the diagnosis, the patient was started on the TTR stabiliser tafamidis (Vyndamax, 61 mg; Pfizer, 6300765CA, New York, NY, USA) once daily. An important aspect of the therapeutic intervention involved navigating access to this targeted treatment. Tafamidis is the first and only disease-modifying drug approved for the treatment of ATTR-CM in China. Prior to insurance coverage, the monthly cost exceeded 10,000 RMB (1 RMB = 0.140 USD). Through a combination of national health insurance reimbursement and rare disease medical assistance, the out-of-pocket cost was significantly reduced to approximately 3000 RMB per month. Nonetheless, this remains a considerable and sustained economic pressure for an average

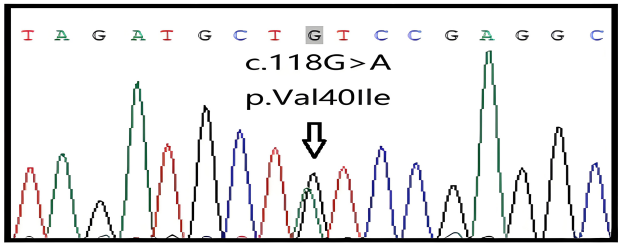

Fig. 6. Genetic testing. Genetic testing identified a heterozygous c.118G>A mutation in exon 2 of the transthyretin (*TTR*) gene, resulting in a p.Val40Ile amino acid substitution. This variant is annotated as Pathogenic in the ClinVar database (https://www.clinicalgenome.org/data-sharing/clinvar/). p.Val40Ile, protein-level substitution of valine to isoleucine at codon 40; c.118G>A, a guanine-to-adenine substitution at nucleotide position 118 of the coding DNA sequence.

family, highlighting a real-world challenge in the long-term management of rare diseases. His diuretic regimen was concurrently optimized to include furosemide (20 mg, Tianjin Lisheng Pharmaceutical Co., Ltd., 2306037, Tianjin, China) and spironolactone (20 mg, Hangzhou Minsheng Pharmaceutical Co., Ltd., T23K038, Hangzhou, China) administered twice daily.

The clinical response was pronounced. The patient's symptoms improved within a few weeks. No further episodes of PND were reported, and physical examination findings showed a reduction in bilateral lower limb edema and pulmonary crackles. During a subsequent two-year follow-up with regular monthly outpatient visits, the patient remained clinically stable for the most part. The patient demonstrated good adherence to tafamidis, as assessed through consistent monthly outpatient follow-up visits for prescription refills and self-reported daily intake. The medication was well-tolerated throughout the follow-up period, with no notable adverse or unanticipated events reported. He was hospitalized twice for acute heart failure exacerbations triggered by upper respiratory tract infections (on 22 September 2024 and 11 December 2025). During these acute episodes, his NT-proBNP level was elevated to approximately 9000 pg/mL, and echocardiography indicated an LVEF of 38–40%, which was comparable to his pre-tafamidis baseline levels. Notably, according to retrospective history provided by the patient and his family, the patient required hospitalization for heart failure three to four times per year before starting tafamidis. After commencing tafamidis therapy, the frequency of heart failure-related hospitalizations decreased significantly and his cardiac function remained relatively stable with no significant deterioration. This marked reduction in hospitalization frequency, coupled with sustained cardiac function, demonstrates tangible mitigation of disease progression and concomitant improvement in the patient's quality of life.

This case report was prepared in accordance with the case report (CARE) guidelines [6]. The completed CARE checklist is provided as **Supplementary Material**.

5. Discussion

ATTR-CM is a progressive and fatal infiltrative disease, with genotype significantly influencing phenotypic expression and prognosis. The p.Val40Ile mutation, first characterized in the German "Wagshurst study", is known to cause late-onset, high-penetrance cardiac amyloidosis with rapid progression and a predominantly cardiac phenotype [5]. However, real-world evidence on the long-term efficacy of genotype-specific therapy for this aggressive mutation remains limited, particularly in East Asian populations. This case provides crucial longitudinal data addressing this gap.

Several key points emerge from this case. First, it validates the diagnostic value of a systematic, non-invasive workflow integrating multimodality imaging and genetic testing [7]. The presence of classic "red flags"—including discordantly low QRS voltage relative to left ventricular wall thickness, and diffuse subendocardial late gadolinium enhancement with preserved first-pass perfusion on CMR—prompted targeted evaluation leading to genetic confirmation. This diagnostic precision was not merely academic but directly enabled access to disease-modifying therapy. Second, this report provides genotype-specific evidence for tafamidis efficacy. Although the ATTR-ACT trial established tafamidis as an effective treatment for ATTR-CM overall [4,8], its specific impact on patients carrying the p.Val40Ile mutation remained unclear. Our findings demonstrate that tafamidis produced sustained clinical stability over two years in this genetic context, with marked improvement in functional capacity and marked reduction in heart failure hospitalizations. This confirms that the benefits observed in large trials are directly applicable to this aggressive mutation and can be successfully extended to an East Asian population.

The discrepancy between echocardiography-derived LVEF (39%) and CMR-derived LVEF (17.5%) in this patient warrants explanation and offers insights into the pathophysiological mechanisms underlying cardiac amyloidosis. This observed difference can be attributed to two main factors. First, technical and methodological differences between modalities play a role. CMR is considered the gold standard for LVEF assessment due to its superior endocardial border delineation, higher spatial resolution, and three-dimensional volumetric acquisition without geometric assumptions [9]. Echocardiography, particularly when using two-dimensional methods, may overestimate LVEF depending on image quality and geometric modeling. Second, and more importantly, cardiac amyloidosis is primarily a restrictive cardiomyopathy characterized by predominant diastolic dysfunction and myocardial infiltration. Recent studies have demonstrated that in patients with car-

diac amyloidosis, global circumferential and radial strain may be relatively preserved even when longitudinal strain is severely impaired, serving as a compensatory mechanism to maintain LVEF [10,11]. This phenomenon—preserved circumferential function despite significant subendocardial amyloid deposition—can lead to echocardiography overestimating systolic function, as conventional 2D LVEF calculation does not fully capture the extent of myocardial dysfunction. In contrast, CMR with late gadolinium enhancement directly visualizes the extent of amyloid infiltration and provides a more accurate assessment of true systolic function.

The principal strength of this report lies in the provision of detailed, longitudinal outcome data for an exceedingly rare genotype. The two-year follow-up under consistent tafamidis therapy offers robust real-world evidence of treatment efficacy in stabilizing cardiac function, a dimension often missing from large trials focused on broader populations. Furthermore, this case enriches the phenotypic database by corroborating the mutation's aggressive cardiac profile in an East Asian patient. However, these findings are inherently limited by the single-case study design, which precludes definitive causal conclusions or generalizability. The retrospective nature may also introduce recall bias in historical hospitalization frequency.

The patient's perspective powerfully illustrates the clinical significance of these findings. Before initiating tafamidis, the patient described feeling "like I was drowning every day", with severe leg swelling, orthopnea, and frequent hospitalizations despite conventional heart failure therapy. After treatment, he reported that "the heavy feeling in my chest slowly lightened", with reduced edema, improved sleep, and markedly fewer hospital admissions. While acknowledging that the disease is not cured, he expressed profound gratitude: "The constant fear of dying has lifted. I feel like I have my life back".

6. Conclusion

In conclusion, this report moves beyond describing a diagnosis to demonstrating a successful therapeutic intervention. It confirms that the p.Val40Ile mutation confers a severe cardiac phenotype that is susceptible to modification by tafamidis. The key clinical implication is that a high index of suspicion leading to precise genetic diagnosis is the critical first step in unlocking life-altering therapies. For patients with aggressive ATTR-CM genotypes such as p.Val40Ile, tafamidis represents a powerful tool for significantly improving long-term outcomes. Further studies with larger cohorts are warranted to confirm these findings and explore genotype-specific responses to emerging therapies.

Learning Points

• This case provides what we believe to be the first detailed report of sustained, real-world efficacy of tafamidis in an East Asian patient carrying the rare p.Val40Ile *TTR* mutation.

• It adds crucial genotype-specific outcome data to the medical literature, confirming that the survival and hospitalization benefits of tafamidis extend to this aggressive genetic variant.

• The report reinforces the high clinical suspicion required to diagnose ATTR-CM, exemplified by the recognition of "voltage-mass discordance" in a patient with treatment-resistant heart failure.

• It offers a practical, step-by-step demonstration of the modern non-invasive diagnostic pathway for ATTR-CM, which can be reliably implemented in clinical practice to avoid unnecessary biopsies.

• The observed significant reduction in hospitalization rate underscores the tangible impact of timely diagnosis and precision therapy on both disease progression and healthcare resource utilization.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Diagnosis and treatment of this case: XX, MCY and LD; CMR image processing and figure preparation: MCY; original draft preparation: XX and LD. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed written consent was obtained from the patient for publication of this case report.

Acknowledgment

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM58285.

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