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Long-Term Cardiac Remodeling During Migalastat Therapy in a Heterozygote Woman With Fabry Disease (N224S): A 9-Year Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 40-year-old
Final Diagnosis: Cardiomyopathy • Fabry disease
Symptoms: Chest pain • diaphoresis • dyspnea • exercise intolerance
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare disease

Background: Fabry disease (FD) is a rare X-linked lysosomal disorder in which long-term cardiac outcomes, particularly in heterozygous females, remain incompletely defined. The N224S α-galactosidase A gene (*GLA*) variant is recognized as pathogenic, yet its cardiac phenotype and response to prolonged migalastat therapy are not well characterized. Although clinical trials and observational studies have reported variable cardiac responses to migalastat, real-world longitudinal data beyond 5 years remain limited. Understanding long-term structural and functional changes is especially important in patients with pre-existing cardiac involvement, where distinguishing favorable remodeling from fibrosis-related progression can be challenging.

Case Report: We describe a 9-year follow-up of a 71-year-old heterozygous woman with FD due to the N224S mutation treated with migalastat. Serial transthoracic echocardiography demonstrated a sustained reduction in left ventricular mass index (LVMI) over long-term therapy. Left ventricular systolic function remained preserved throughout follow-up, and there was no evidence of progressive structural deterioration. Available Doppler-derived diastolic indices, including a gradual decline in early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e'), suggested improving left ventricular filling pressures over time. Although LVMI showed minor year-to-year variability, these changes were consistent with expected technical or physiological variation and did not alter the clear long-term downward trend.

Conclusions: This case provides real-world evidence of favorable long-term cardiac remodeling during migalastat therapy in a heterozygous woman with the N224S variant. The sustained reduction in LVMI, preserved systolic function, and improving diastolic indices together indicate a durable cardiac response and extend the limited longitudinal data available for variant-specific outcomes in FD.

Keywords: Cardiomyopathy, Hypertrophic, Familial • Hypertrophy, Left Ventricular • Fabry Disease

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/952758

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Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the α-galactosidase A gene (*GLA*) gene, leading to deficient α-galactosidase A activity and progressive glycosphingolipid accumulation in multiple organs, particularly the heart. It affects approximately 1: 22 000 to 1: 40 000 males. Cardiac involvement—including left ventricular hypertrophy (LVH), conduction abnormalities, and heart failure—is a major determinant of morbidity and mortality. The *GLA* c.671A>G (p.Asn224Ser; N224S) missense variant is recognized as pathogenic, with markedly reduced in vivo and in vitro α-galactosidase A levels, yet its cardiac phenotype remains poorly characterized. Few reports have described LVH in individuals with this mutation, and long-term clinical trajectories, particularly in heterozygous females, are largely unknown [1].

Migalastat, an oral pharmacological chaperone, is approved since 2016 for amenable variants and has shown variable short term effects on LVH regression [2,3]. However, real world data beyond 5 years are scarce, and sustained cardiac improvement in older heterozygous women has not been well documented [3].

We present a 9-year longitudinal case of a 71-year-old heterozygous woman with FD due to the N224S variant, demonstrating favorable long term changes in left ventricular structure and preserved cardiac function during migalastat therapy.

Case Report

A woman in her 70s with FD—reflecting a heterozygous phenotype influenced by X-chromosome inactivation—was diagnosed in 1995 by genetic testing, identifying a heterozygous N224S missense mutation (c.671A>G), following evaluation of her son with classic FD on enzyme replacement therapy (ERT). She had recurrent emergency presentations with central chest pain at rest, occasionally with dyspnea and diaphoresis. Exercise tolerance was 400 to 500 m on flat ground. She remained independent in activities of daily living, with mild orthopnea and no paroxysmal nocturnal dyspnea.

Comorbidities included atrial fibrillation, hypertension, hyperlipidaemia, and type 2 diabetes mellitus. An implantable cardioverter-defibrillator (ICD) (Boston Scientific D177) was inserted for non-sustained ventricular tachycardia in the setting of LVH. Medications included candesartan 16 mg once a day, atenolol 50 mg twice a day, rivaroxaban 20 mg once a day, metformin 1 g twice a day, frusemide 40 mg once a day, ezetimibe 10 mg once a day, perindopril 5 mg once a day, and migalastat 123 mg a day, commenced in 2016. She remained on long-term diuretics and a 1.5-L fluid restriction for prior pericardial effusion. There was no family history of premature coronary disease or LVH phenocopies.

A recent examination revealed the following: BP 122/92 mm Hg, HR 74 bpm, SpO_2 97%, RR 18/min, and temperature 36.7 °C. Her chest was clear, with dual heart sounds and no murmurs or heart failure signs. ECG showed AF with LVH (**Figure 1**). Laboratory test results showed high-sensitivity troponin I 1857 ng/L, B-type natriuretic peptide 202 ng/L, creatinine 89 µmol/L, and estimated glomerular filtration rate 57 mL/min/1.73 m^2. A chest X-ray (**Figure 2**) was unremarkable. ICD interrogation was normal with no recent therapies.

High-sensitivity troponins remained moderately elevated with stable serial trends over 12 months. Heterophile antibody screen was negative, and renal function remained stable. The last cardiac magnetic resonance (CMR) imaging in 2013 showed asymmetric septal hypertrophy with increased left ventricle mass (83 g/m^2), and subtle plexiform enhancement in the basal septum and basal inferolateral segments.

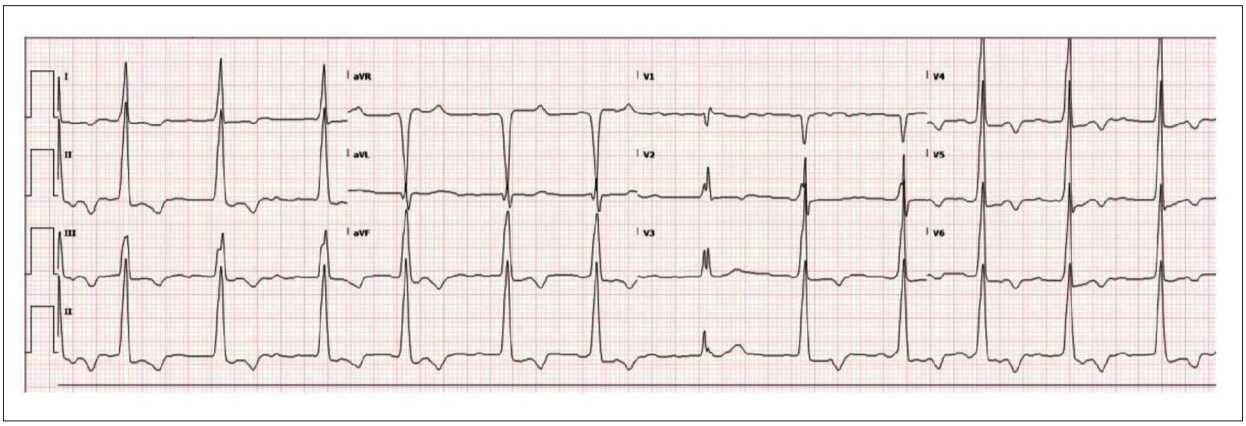

Figure 1. ECG – atrial fibrillation with left ventricular hypertrophy (voltage criteria).

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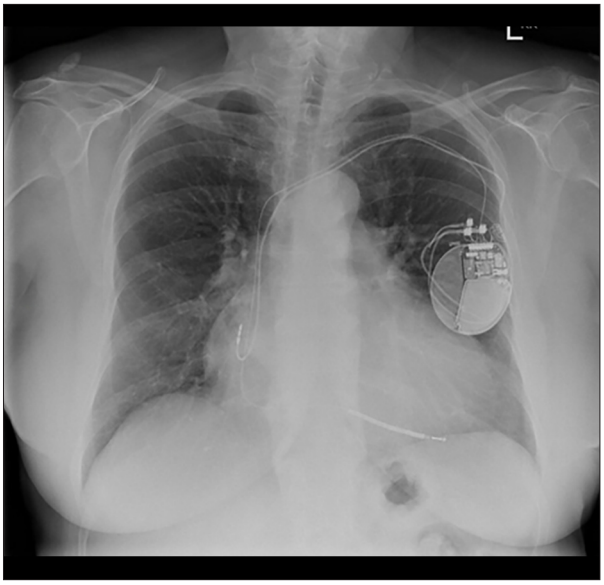

Figure 2. Chest X-ray – no cardiomegaly, intact implantable cardioverter-defibrillator leads, no pleural effusion.

The most recent TTE showed a small LV with EF 60% and concentric wall thickening from base to apex, without systolic anterior motion of mitral valve (SAM), mid-cavity, or left ventricle outflow tract (LVOT) obstruction. Right ventricle (RV) size was normal, with RV systolic pressure 21 mm Hg. A small circumferential pericardial effusion was present without tamponade. No significant valvular disease was seen. Overall, serial left ventricular mass index (LVMI) over 9 years (**Table 1**) demonstrated an overall decline, accompanied by a reduction in available ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e') measurements in later years. A line plot of LVMI over time shows an overall downward trend, with the regression line demonstrating a significant negative decline (slope -6.52 g/m^2 per year, 95% CI -11.3 to -1.7, $P = 0.015$) (**Figure 3**). Given the single-patient design, this analysis is descriptive and intended mainly to illustrate longitudinal trajectory. Representative TTE images are shown in **Figure 4**, with 2021 omitted due to COVID-19–related risk. Routine coronary angiography showed normal coronaries, unchanged from 9 years prior.

During an episode of chest pain, she was treated as acute coronary syndrome with dual antiplatelet therapy for elevated high-sensitivity troponin I; the chronic elevation was later attributed to stable FD-related microvascular ischemia. LVH was initially attributed to hypertension but was excluded given good adherence and sustained systolic BP ~ 125 mm Hg on clinic and home monitoring. Aortic stenosis was excluded, with serial TTEs showing stable mild aortic sclerosis. Alternative LVH phenocopies were considered. Cardiac amyloidosis was unlikely due to absence of typical echocardiographic features (elevated RV pressure, apical sparing, biventricular hypertrophy, valve thickening; sensitivity 93%, specificity 82%) [4]. Hypertrophic cardiomyopathy was excluded due to lack of asymmetric hypertrophy, SAM, syncope, or family history. Prior CMR showed no features of either condition. The concentric LVH was therefore attributed to FD.

Table 1. Serial left ventricular mass index (LVMI) and transthoracic echocardiographic parameters over 9 years, including available ratio of early mitral inflow velocity to early diastolic tissue velocity (E/e') measurements.

Year	Ejection fraction	Left ventricular mass index (LVMI) (g/m^2)	Body surface srea (m^2)	Left ventricular end-diastolic diameter (LVEDD) (mm)	Interventricular septal end-diastole (IVSd) thickness (mm)	Posterior wall thickness at end-diastole (PWd) thickness (mm)	Ratio of early mitral inflow velocity to early diastolic tissue velocity (E/e')*
2016	71%	176.20	1.90	36.3	19.9	20.4	24.5
2017	73%	136.88	1.95	33.1	19.4	17.7	25.4
2018	67%	145.98	1.99	36.9	18.8	17.9	–
2019	71%	155.10	1.99	33.7	21.4	19.1	–
2020	65%	163.35	2.00	38.2	19.6	18.7	28.2
2022	66%	145.45	1.90	40.0	18.1	15.3	–
2023	65%	131.30	1.90	38.6	17.3	15.0	17.5
2024	55%	146.65	1.76	43.0	15.0	15.0	15.4
2025	60%	97.30	1.84	38.7	14.8	10.8	–

* E/e' available for selected timepoints only.

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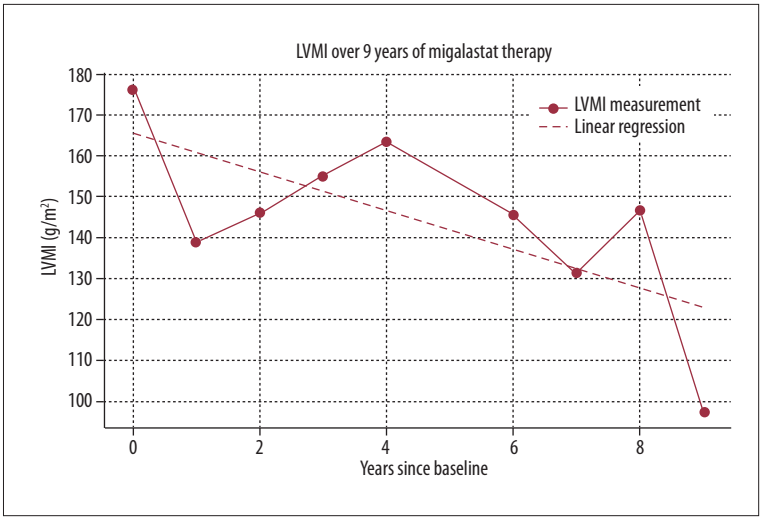

Figure 3. Longitudinal change in left ventricular mass index (LVMI) (g/m^2) over 9 years of migalastat therapy, demonstrating a sustained reduction in LVMI with minor interim fluctuations. Exploratory linear regression showed significant downtrend over time (Slope -6.52 g/m^2 per year, 95% CI -11.3 to -1.7, $P = 0.015$).

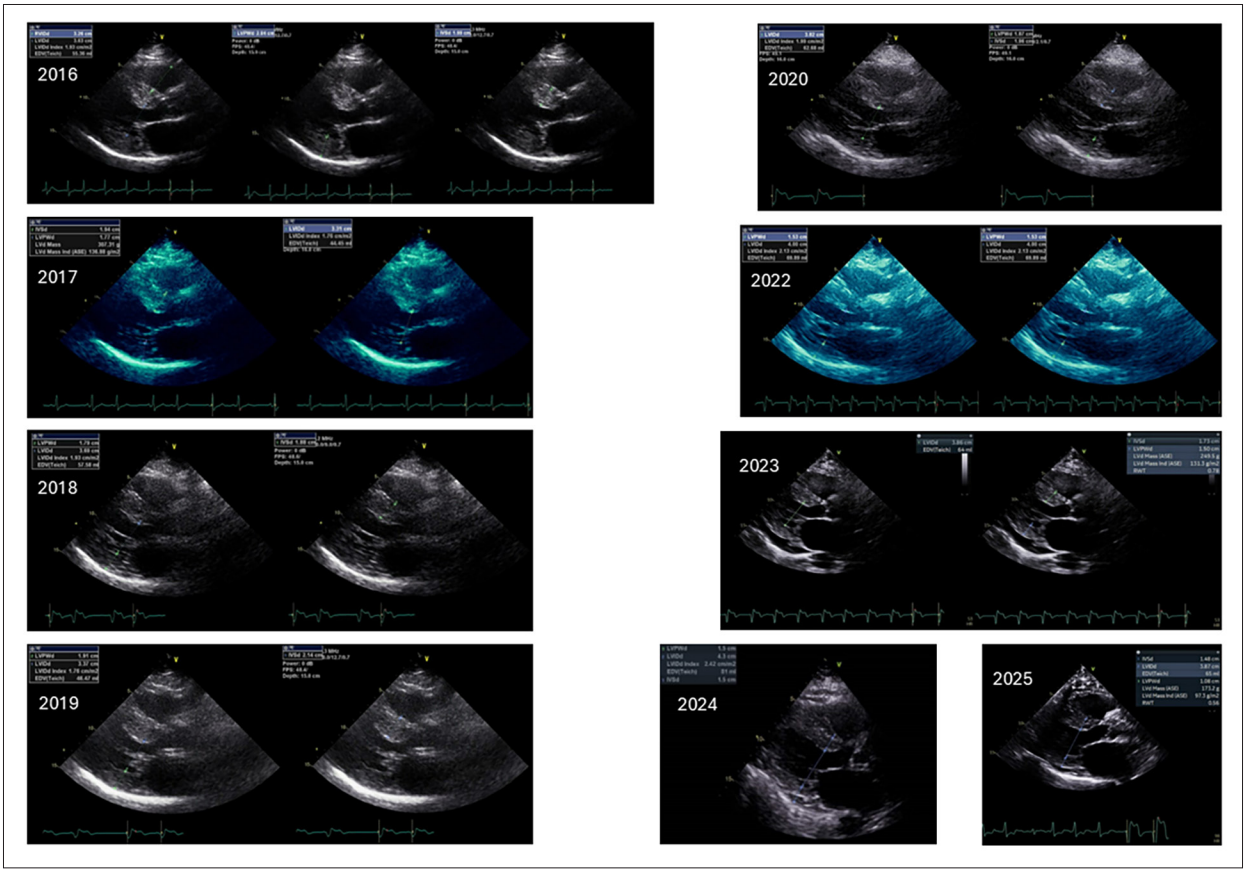

Figure 4. Pictures of transthoracic echocardiograms over the last 9 years. Year 2021 was missed due to it not being done at the height of the Covid-19 pandemic.

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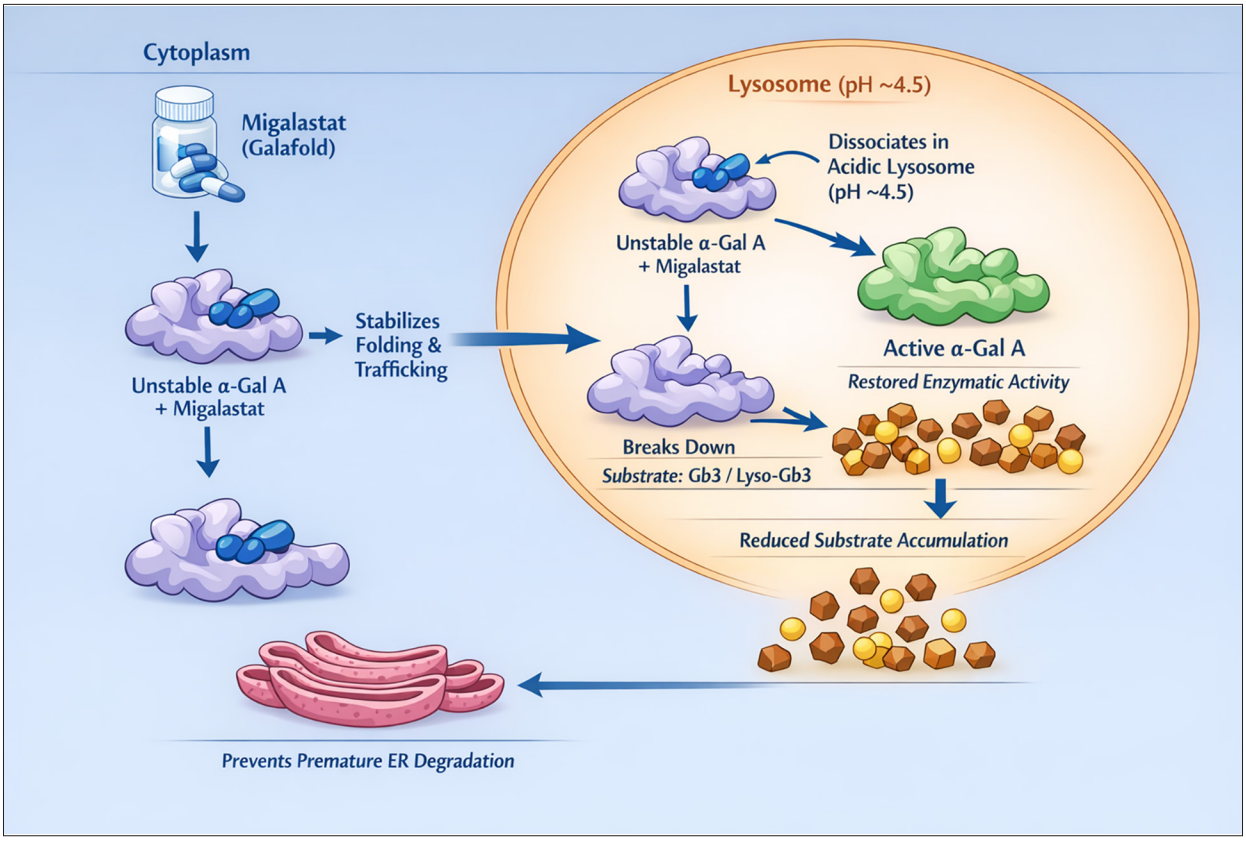

Figure 5. Mechanism of action of migalastat (Galafold). Migalastat binds unstable α-galactosidase A (α-Gal A) in the cytoplasm, preventing premature endoplasmic reticulum (ER)-associated degradation through stabilizing folding and lysosomal trafficking. In the acidic lysosome, it dissociates, restoring enzymatic activity to degrade accumulated glycosphingolipids, globotriaosylceramide (Gb3) and lyso-Gb3, thereby reducing substrate accumulation in Fabry disease.

Discussion

Migalastat (Galafold) is an oral pharmacological chaperone that stabilizes amenable mutant α-galactosidase A. **Figure 5** shows a schematic mechanism of action. Migalastat is ineffective in non-amenable mutations. The GLP-HEK assay identifies 367 amenable and 711 non-amenable variants and underpins a clinically validated amenability tool [3,5,6]. Current recommendations support initiating migalastat after confirmed FD diagnosis and mutation amenability, following shared decision-making regardless of LVH. Treatment switching is recommended only with progression in cardiac, renal, or cerebrovascular disease [5].

Evidence from randomized trials and observational cohorts, including FACETS, ATTRACT, FAMOUS, and MAIORA, demonstrates that migalastat can reduce or stabilize LVH in amenable FD, but these studies are limited to 12 to 24 months of follow-up [7-10]. This case report extends the existing literature by providing a 9-year longitudinal trajectory in a heterozygous woman with the amenable N224S mutation, a variant with limited phenotype and treatment response data. Longer term imaging studies, such as the CMR based cohort by Gatterer et al, report follow up of approximately 3 to 5 years and predominantly describe stabilization rather than regression of cardiac parameters [11]. In contrast, our patient demonstrated sustained LVMI reduction with preserved systolic function and a gradual improvement in diastolic indices. An exploratory linear regression supported the overall downward trajectory in LVMI over time, although the mechanism underlying this change cannot be definitively established. The combination of prolonged follow up, variant specific detail, and dense serial echocardiographic measurements offers novel real world insight into long term cardiac response to migalastat.

Over 9 years, the patient demonstrated a significant reduction in LVMI despite relative plateauing between 2018 and 2024, followed by a further decline to 97.30 g/m^2 in 2025. This pattern may reflect variability inherent to two-dimensional TTE but may also represent underlying pathophysiological processes. Notably, increased LVMI and myocardial fibrosis despite migalastat therapy have been reported in a small cohort by Gatterer et al, possibly related to persistent glycosphingolipid-driven inflammation [11]. Similar findings have been described in a

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subset of male patients receiving ERT by Cabrera et al, highlighting the heterogeneity of disease progression in FD [12].

A key consideration in interpreting the observed reduction in wall thickness is whether it reflects true regression of hypertrophy or a decrease in myocardial matrix—specifically, replacement of hypertrophied myocytes by fibrotic extracellular matrix. In FD, progressive matrix expansion and interstitial fibrosis can coexist with or replace hypertrophy and, in advanced stages, can result in apparent wall thinning despite ongoing pathological remodeling [13]. CMR, particularly with late gadolinium enhancement and T1 mapping, can help to distinguish these processes, but such data were not available in this case. However, the pattern observed—a sustained reduction in LVMI, stable LV cavity size without progressive dilatation, a gradual decline in E/e', and preserved systolic function—is not typical of matrix-driven wall thinning or advanced fibrotic remodeling, which generally increase diastolic stiffness. While the underlying mechanism cannot be definitively established, these findings are more consistent with favorable remodeling and possible regression of hypertrophy during long-term migalastat therapy.

Conclusions

This case illustrates sustained cardiac benefit during long-term migalastat therapy in a woman heterozygote with an amenable FD mutation. Over 9 years, LVMI declined, systolic function remained preserved, and comorbidities were well controlled. Minor fluctuations in LVMI likely reflected technical or physiological variation and did not alter the overall downward trajectory. Improvements in available diastolic indices further suggest favorable changes in left ventricular filling pressures over time. Collectively, these findings indicate a durable long-term cardiac response to migalastat and contribute real-world evidence to the limited longitudinal data available in FD.

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We would like to thank all the staff and clinicians involved in the care of the patient throughout the years.

Availability of Data and Materials

The information used and/or discussed during the current study are available from the corresponding author on request.

Ethics Approval and Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal. This case report was conducted and written in accordance with the Townsville Hospital and Health Service Human Research Ethics Committee EX/2024/QTHS/107255. No institutional approval was required for the publishing of this case report.

Institution Where Work Was Done

Mackay Base Hospital, Mackay, Queensland, Australia.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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