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Case Report Article

Unrecognized Fabry Disease in a Transplanted Patient: The Cost of a Delayed Diagnosis

Izadora Raduan Brigo[1]*, José Victor da Nóbrega Borges[1], Murillo Oliveira Antunes[1,2], Thais Baptista Teixeira[1], Ana Paula de Morais Rodrigues Barros[1], Juliana Alzira Gonzales Oliveira Leguizamon[1], Viviani Tiemi Hotta[1], Vagner Madrini Junior[1], Vinicius Machado Correia[1], Fábio Fernandes[1]

[1]Heart Institute (InCor), Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo, Brazil.
[2]São Francisco University (USF), Bragança Paulista, Brazil.

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***Corresponding author:** Izadora Raduan Brigo, Enéas Carvalho de Aguiar Avenue, 44 - Cerqueira César, São Paulo - SP, 05403-900, Brazil.

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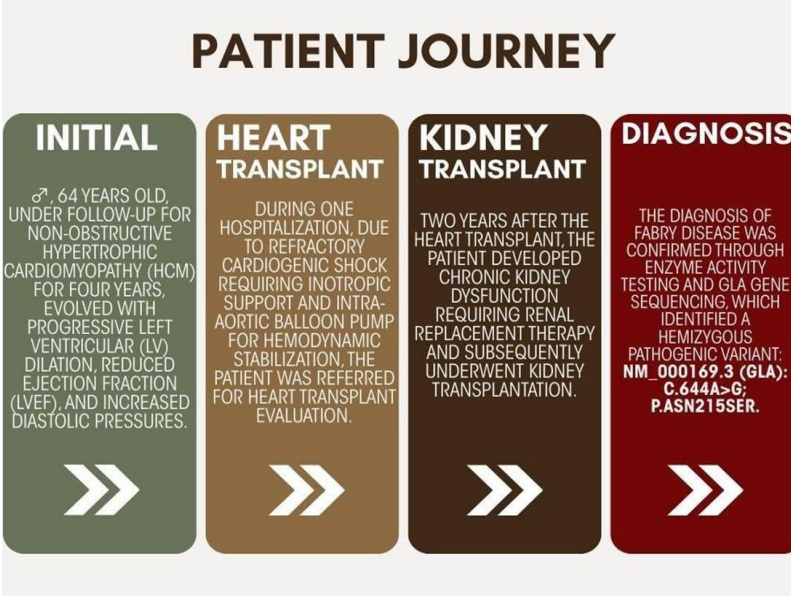
Abstract:

Background: Fabry disease is an X-linked lysosomal storage disorder caused by α-galactosidase A deficiency, leading to globotriaosylceramide accumulation in multiple tissues. Cardiac involvement is common and may mimic hypertrophic cardiomyopathy (HCM), especially in late-onset forms.
Case Summary: We present a 64-year-old man initially diagnosed with non-obstructive HCM, who progressed to severe systolic dysfunction requiring heart transplantation. Within a year, he developed end-stage renal disease, also requiring kidney transplantation. This atypical course prompted further evaluation.
Discussion: The patient's clinical evolution raised suspicion of a phenocopy. Genetic testing revealed the p.(Asn215Ser) pathogenic variant in the GLA gene, confirming late-onset Fabry disease. In such cases, cardiac or renal manifestations may appear in isolation, delaying diagnosis. Studies suggest up to 3% of HCM cases may actually represent undiagnosed Fabry disease.
Conclusion: This case underscores the importance of early genetic testing in cardiomyopathies with atypical progression. Prompt diagnosis allows for disease-specific therapy, potentially modifying the clinical course.



Keywords: Fabry Disease; Hypertrophic Cardiomyopathy; Heart Transplantation; Renal Dysfunction; Differential Diagnosis

Introduction:

Abbreviations:

Fabry Disease (FD)
α-galactosidase A (AGAL)
Hypertrophic Cardiomyopathy (HCM) Transthoracic Echocardiography (TTE) Left Ventricle (LV)
Left Ventricular Ejection Fraction (LVEF) B-type Natriuretic Peptide (BNP)
Creatinine (Cr)
Reference Value (RV)
Left Ventricular Hypertrophy (LVH) Ischemic Stroke (IS)
Transient Ischemic Attack (TIA)
Cardiac Magnetic Resonance Imaging (CMR) Enzyme Replacement Therapy (ERT) Glomerular Filtration Rate (GFR)

Case Description History of Presentation

A 64-year-old man presented with a one-year history of progressive exertional dyspnea, orthopnea, and recurrent lower limb edema. Initial transthoracic echocardiography revealed asymmetric septal hypertrophy, preserved LVEF, and no significant left ventricular outflow tract obstruction. Based on these findings, a diagnosis of non-obstructive HCM was established, and outpatient follow-up was initiated.

Medical History

Over the subsequent four years, the patient exhibited progressive clinical deterioration, requiring multiple hospitalizations for heart failure decompensation. Imaging demonstrated progressive ventricular dilation, decreased LVEF, and elevated diastolic filling pressures, consistent with transition to the dilated phase of HCM. Concurrently, moderate renal dysfunction (creatinine 1.78 mg/dL; estimated GFR <45 mL/min/1.73 m²) and increased cardiac biomarkers (BNP 165 pg/mL; RV <100 pg/mL) were noted.

During one admission, the patient developed refractory cardiogenic shock requiring inotropic support and intra-aortic balloon pump placement for hemodynamic stabilization. Due to clinical refractoriness, heart transplantation was performed with good functional recovery, and the patient remained in NYHA functional class I.

Twelve months after heart transplantation, he developed progressive renal dysfunction, culminating in end-stage renal disease requiring kidney transplantation. The atypical course—initial HCM diagnosis progressing to severe systolic dysfunction and renal failure—prompted genetic testing, which revealed a homozygous pathogenic variant NM_000169.3 (GLA): c.644 A>G; p.(Asn215Ser), confirming a diagnosis of late-onset Fabry disease.

Differential diagnosis:

The unusual clinical evolution, with transition from hypertrophic to dilated phenotype and significant renal impairment, raised suspicion of a systemic underlying etiology. Differential diagnoses included sarcomeric HCM progression, infiltrative cardiomyopathies such as cardiac amyloidosis, and storage diseases—especially Fabry disease.

Investigations and Management:

Initial histopathological analysis of the explanted heart revealed symmetric hypertrophy, myocardial fiber disarray, marked vacuolization of cardiomyocytes, microvascular changes, and extensive fibrosis of the LV—initially suggesting HCM. Electron microscopy was not performed at that time.

Following heart transplantation, the patient developed progressive renal failure requiring kidney transplantation. Given the atypical presentation—initial LVH evolving to systolic dysfunction and renal failure—genetic testing was performed, confirming a homozygous pathogenic variant in GLA [NM_000169.3 (GLA): c.644A>G; p.(Asn215Ser)], consistent with Fabry disease. Upon genetic confirmation, initial histopathology slides were reviewed for diagnostic reassessment.

Discussion:

Fabry disease (FD) is a rare, X-linked lysosomal storage disorder caused by mutations in the GLA gene, which encodes α-galactosidase A (AGAL)1,2. Enzymatic deficiency leads to progressive accumulation of globotriaosylceramide (Gb3) in various tissues—including endothelial cells, cardiomyocytes, fibroblasts, and vascular smooth muscle cells3,6.

Although considered a rare disease, recent studies have revealed a substantially higher prevalence when late-onset variants are included, with estimates as high as 1 in 5,732 individuals2. Phenotypic severity correlates with residual AGAL activity. The classic phenotype is associated with nearly complete absence of enzymatic activity (<1%) and manifests early with multiorgan involvement, particularly in males. In contrast, late-onset variants, such as p.N215S, preserve some enzymatic function and typically involve isolated cardiac manifestations. In heterozygous females, random X-inactivation (lyonization) results in variable expressivity, ranging from asymptomatic to severe phenotypes6.

Late-onset variants typically present between the 4th and 7th decades of life, most commonly with LVH, early myocardial fibrosis, arrhythmias, cryptogenic ischemic strokes or TIAs (especially in the posterior circulation), and silent progression to proteinuria and advanced renal dysfunction6,7. In our case, the predominant features were LVH and renal dysfunction, consistent with the late-onset cardiac variant.

Diagnostically, LVH in FD may mimic sarcomeric HCM or infiltrative cardiomyopathies, such as PRKAG2 variants, mitochondrial cardiomyopathies, amyloidosis, and hydroxychloroquine-induced toxicity8. In this case, the initial diagnosis of HCM masked the underlying etiology. Nonetheless, several cardiovascular features may suggest FD.

Electrocardiographic abnormalities may precede structural changes and include short PR interval, LVH, bradycardia, and T-wave abnormalities predominantly in the inferior leads. TTE may show concentric LVH and reduced global longitudinal strain, especially in the basal inferolateral segment. Cardiac magnetic resonance (CMR) with T1/T2 mapping has revolutionized FD diagnosis. Typical findings include reduced native T1 (reflecting lipid storage), basal inferolateral late gadolinium enhancement, and elevated T2 in inflammatory phases—indicating chronic edema8,10.

Laboratory diagnosis begins with AGAL activity measurement in plasma or leukocytes, with<1% levels being diagnostic in males. Genetic sequencing of the GLA gene is essential, especially in females. Plasma and urinary lyso-GL-3 levels and, in selected cases, tissue biopsies help confirm diagnosis and monitor therapy7,10.

Enzyme replacement therapy (ERT) with agalsidase alfa or beta, approved since 2001, has shown benefits in reducing clinical events and improving survival—even in advanced disease stages. Although it does not reverse established myocardial fibrosis, ERT improves symptoms, stabilizes disease progression, and enhances quality of life, reinforcing the importance of early diagnosis and

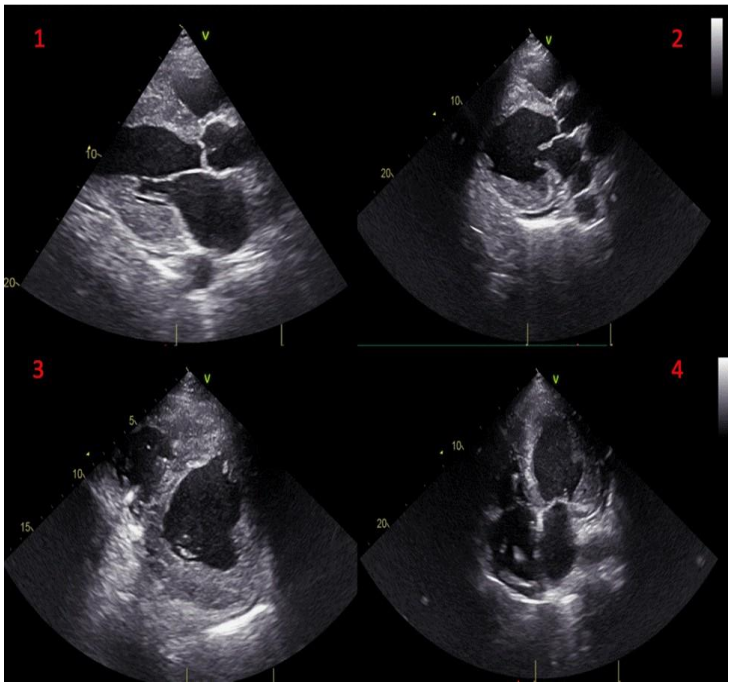
treatment. Migalastat, an oral pharmacologic chaperone, has shown efficacy in amenable variants with preserved renal function.

Conclusions:

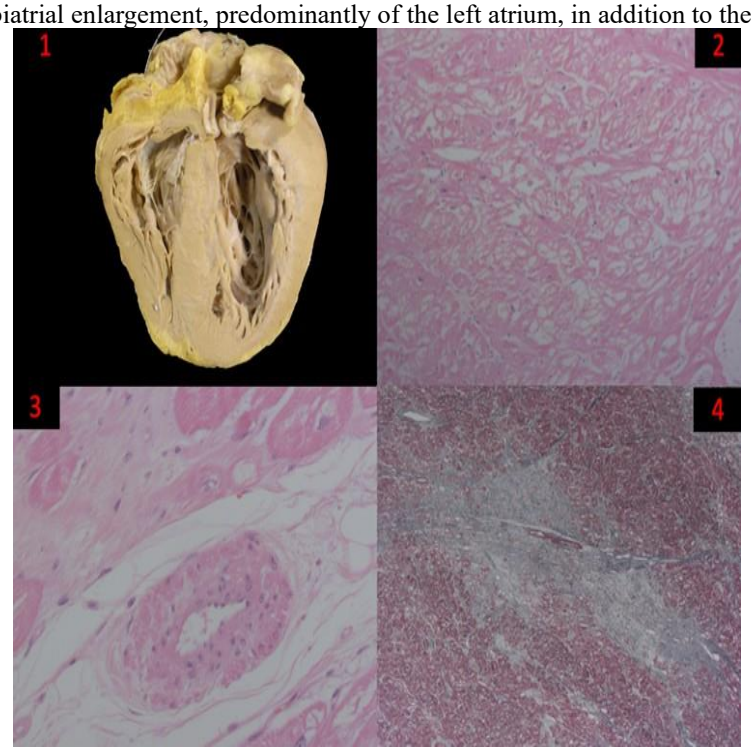
Delayed diagnosis of Fabry disease impairs timely treatment, which is essential to prevent irreversible complications and improve outcomes. ERT, available since 2001, has demonstrated clinical benefit in reducing adverse events, particularly in men over 40, even in advanced stages8. While it cannot reverse fibrosis, ERT helps stabilize or slow disease progression, improve quality of life, and reduce morbidity and mortality—highlighting the critical need for early intervention8,10.

Take Home Messages:

- Consider Fabry disease in the differential diagnosis of cardiomyopathies with atypical features and associated renal dysfunction, especially when LVH evolves into systolic dysfunction.
- Diagnostic delay is common in the late-onset form of Fabry disease, particularly when organ involvement is isolated, limiting the therapeutic benefit of disease-modifying therapies.



Echocardiographic Findings – Figures 1 and 2: Parasternal long-axis view showing marked hypertrophy of the interventricular septum and posterior wall, without evidence of left ventricular outflow tract obstruction. Figure 3: Parasternal short-axis view demonstrating significant left ventricular dilation and prominent wall thickening as previously described. Figure 4: Apical four-chamber view revealing biatrial enlargement, predominantly of the left atrium, in addition to the aforementioned findings.



Bibliography:

1. Zarate YA, Hopkin RJ. Fabry's disease. Lancet. 2008; 372:1427–35.
2. Gilchrist M, et al. Prevalence of Fabry disease-causing variants in the UK Biobank. J Med Genet. 2023;60(4):391-396.
3. Hwu WL, et al. Newborn screening for Fabry disease in Taiwan. Hum Mutat. 2009; 30:1397–405.
4. Eng CM, et al. Baseline characteristics in the Fabry Registry. J Inherit Metab Dis. 2007; 30:184–92.
5. Burlina AB, et al. Newborn screening in North East Italy. J Inherit Metab Dis. 2018; 41:209–19.
6. Ortiz A, et al. Fabry disease management recommendations. Mol Genet Metab. 2018; 123:416–27.
7. Mehta A, Hughes DA. Fabry Disease. In: GeneReviews® [Internet]. Seattle: University of Washington; Updated 2024.
8. Pieroni M, et al. Cardiac involvement in Fabry disease. J Am Coll Cardiol. 2021;77(7):922–36.
9. Nair V, et al. Lysosomal storage disorders and the heart. Cardiovasc Pathol. 2019; 39:12–24.
10. Linhart A, et al. Expert consensus on cardiovascular manifestations. Eur J Heart Fail. 2020; 22:1076–96.