Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

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Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Pinheiro L, de Castro M, Cordeiro F, et al. **How to escape from sudden death: a challenging case of a rare cardiomyopathy with an unexpected twist**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3526

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How to escape from sudden death:
a challenging case of a rare cardiomyopathy with an unexpected twist

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Contributions: LP, write the manuscript; MC, performed data extraction; FC, FF, VS, OA, AL, contributed to manuscript revision and critical reviews. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no conflicts of interest.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient included in this study.

Patient consent for publication: the patient gave his written consent to use his personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all data underlying the findings are fully available.

Funding: none.

Acknowledgments: the authors thank their colleagues from the Cardiology Department who provided insight and expertise that greatly assisted the article elaboration.

Abstract

A 59-year-old man presented with recurrent syncope and was found to have bifascicular block and severe concentric left ventricular hypertrophy. A permanent double-chamber pacemaker was implanted. Initial investigations revealed elevated transferrin saturation and homozygosity for the *HFE* gene p.C282Y variant, indicating hereditary hemochromatosis. However, cardiac magnetic resonance imaging showed inferolateral intramyocardial late gadolinium enhancement (LGE) without evidence of iron deposition, raising suspicion for Fabry disease (FD). This was confirmed by low α-galactosidase A activity and detection of the pathogenic *GLA* p.F113L variant. Multisystemic evaluation revealed additional FD manifestations, and enzyme replacement therapy was initiated, later switched to oral migalastat.

The patient subsequently developed left ventricular systolic dysfunction and apical thrombus, attributed to high ventricular pacing burden, and was scheduled for cardiac resynchronization therapy (CRT) device implantation. Before the upgrade, he suffered a cardiac arrest due to ventricular fibrillation, associated with coronary artery stenosis, requiring CRT-D implantation. Despite device therapy and amiodarone initiation, recurrent ventricular tachycardias (VTs) persisted, leading to percutaneous coronary intervention and electrical stability.

This case highlights the diagnostic complexity of overlapping cardiac diseases, the significance of inferolateral LGE and conduction abnormalities in suspecting FD, and the crucial role of family screening. The p.F113L variant is associated with late-onset, cardiac-predominant FD, where bradyarrhythmias are more prognostically relevant, but concurrent pathologies like coronary artery disease must be considered in VT presentations.

Key words: left ventricular hypertrophy, Fabry disease, ventricular tachycardia.

Case Report

A 59-year-old man, previous smoker, was admitted in the emergency room for recurrent syncopes. He had no family history of cardiac disease or sudden death. Electrocardiogram showed sinus rhythm, bifascicular block and LVH. Transthoracic echocardiogram (TTE) revealed severe concentric symmetric LVH and normal left ventricle ejection fraction (LVEF) (Figure 1). Laboratory analysis was unremarkable except for high transferrin saturation (98%). One day after admission the patient suffered another syncope due to advanced atrioventricular block followed by ventricular asystole and a permanent double-chamber pacemaker was implanted. Genetic testing of *HFE* gene revealed the pathogenic variant p.C282Y in homozygosity, establishing the diagnosis of hemochromatosis.

MRI confirmed severe LVH and revealed an extensive intramyocardial LGE in the inferolateral wall, raising suspicion of FD (Figure 2). No evident iron deposition was observed. Enzymatic activity of α-galactosidase A was reduced (0.01 nmol/h/spot) and the *GLA* gene test revealed the pathogenic variant p.F113L, confirming the diagnosis of FD.

Multisystemic evaluation showed sensorineural deafness at 4000 and 8000 Hz, cornea verticillata and discreet bilateral brain white matter lesions in brain MRI, all signs of the systemic impact of FD [1].

Patient started enzyme replacement therapy with agalsidase beta 1 mg/Kg every other week with favorable clinical evolution. Four years later, treatment was switched to migalastat due to patient preference for an oral drug. TTE showed reduced LVEF (45%) and LV apical thrombus, which resolved under warfarin. Stress echocardiogram was negative for ischemia. High ventricular pacing (approximately 100%) was deemed as the cause of left ventricle systolic dysfunction and patient accepted upgrade to a CRT device.

However, before upgrade, the patient suffered cardiorespiratory arrest by ventricular fibrillation (VF), leading to a car accident, being resuscitated after 2 shocks. On the emergency room, TTE showed a lower LVEF (40%) and resurging of LV apical thrombus (Figure 3). No significant troponin elevation, renal, electrolyte or thyroid abnormalities were detected. Pacemaker interrogation revealed VT that degenerated in VF. On the intensive care unit, patient had recurrence of VT and intravenous amiodarone was started. Coronary angiography revealed stenosis of distal circumflex artery (90%). Pacemaker was upgraded to CRT-D and patient was discharged with betablocker.

At 1-month follow up, the thrombus had disappeared, LVEF had recovered, but CRT-D remote monitoring revealed multiple VTs treated with anti-tachycardia pacing. Oral amiodarone was started, weighting risk/benefit in a FD patient [2].

During myocardial perfusion scintigraphy the patient suffered multiple shocks due to monomorphic VTs, being readmitted to hospital. Percutaneous coronary intervention of the distal circumflex artery was performed and amiodarone dose was increased. Since then, the patient maintained clinical and electrical stability. Family screening enabled FD diagnosis of 24 and treatment of 9 relatives.

Discussion

Initially, the clinical picture of severe concentric LVH, conduction disease, and high transferrin saturation suggested cardiac involvement secondary to iron overload [3]. However, cardiac magnetic resonance imaging did not suggest myocardial iron deposition, which is a hallmark of hemochromatosis-related cardiomyopathy. Instead, the presence of extensive inferolateral LGE lead to the diagnosis of FD through enzymatic and genetic testing. This case underscores the importance of a comprehensive approach to unexplained LVH, especially when associated with conduction abnormalities and LGE on cardiac MRI. While sarcomeric hypertrophic cardiomyopathy remains a common cause of LVH, infiltrative and storage disorders such as FD must be considered in the differential diagnosis [4]. The p.F113L mutation identified in the *GLA* gene is a known pathogenic variant associated with the late-onset, cardiac-predominant phenotype of FD, in which bradysrhythmias carry a higher prognostic impact than tachydysrhythmias [1]. So clinical presentation with VT should raise suspicion of concomitant factors, such as coronary artery disease (CAD). Finally, this case illustrates the importance of cascade screening in inherited metabolic cardiomyopathies. Family screening led to the diagnosis and early treatment of nine relatives, underscoring the genetic implications and preventive potential of early identification in FD.

Conclusions

LVH with conduction disease and inferolateral LGE should prompt evaluation for FD, especially in the absence of typical features of sarcomeric hypertrophic cardiomyopathy. Coexisting pathologies, such as CAD, can influence disease presentation and progression. Family screening is essential to early diagnosis and treatment of relatives in inherited metabolic disorders.

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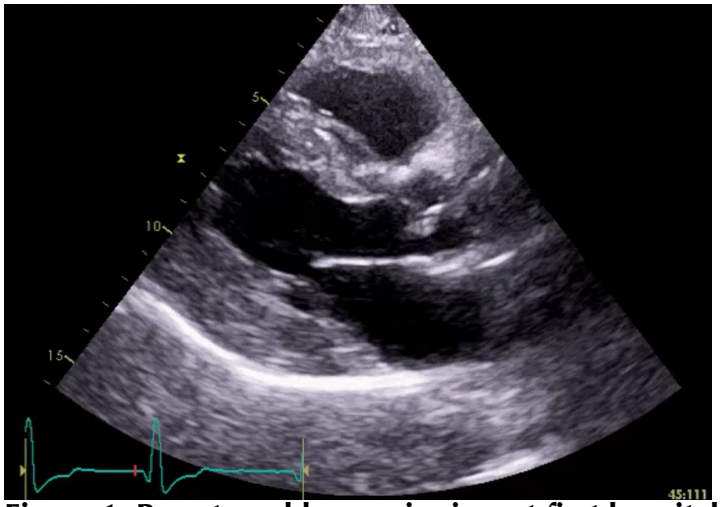

Figure 1. Parasternal long-axis view at first hospital admission.

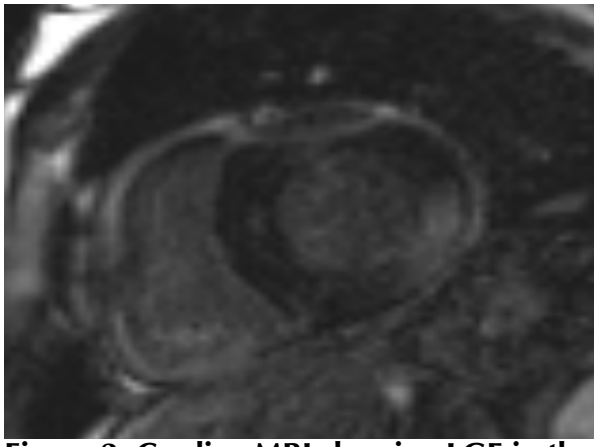
Figure 2. Cardiac MRI showing LGE in the inferolateral wall.

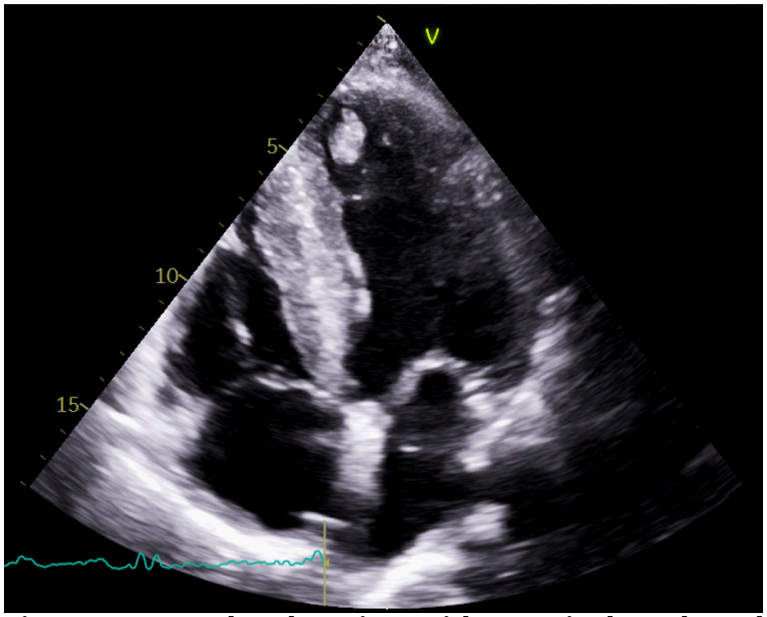

Figure 3. Four-chamber view with an apical LV thrombus.