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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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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.

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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 left ventricular hypertrophy (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.

Magnetic resonance imaging (MRI) confirmed severe LVH and revealed an extensive intramyocardial late gadolinium enhancement (LGE) in the inferolateral wall, raising suspicion of Fabry disease (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].

The patient started enzyme replacement therapy with agalsidase β 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 left ventricle (LV) apical thrombus, which resolved under warfarin. The stress echocardiogram was negative for ischemia. High ventricular pacing (approximately 100%) was deemed as the cause of left ventricle systolic dysfunction, and the patient accepted an upgrade to a cardiac resynchronization therapy (CRT) device.

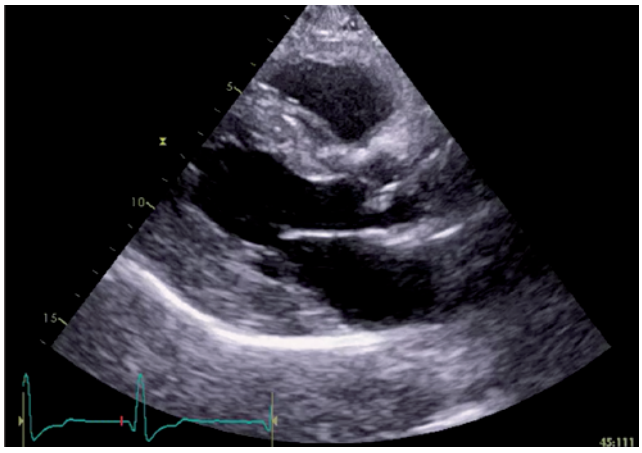


Figure 1. Parasternal long-axis view at first hospital admission.

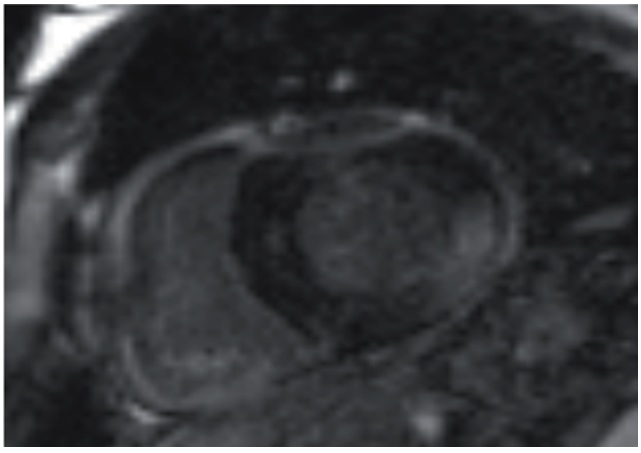


Figure 2. Cardiac magnetic resonance imaging showing late gadolinium enhancement in the inferolateral wall.

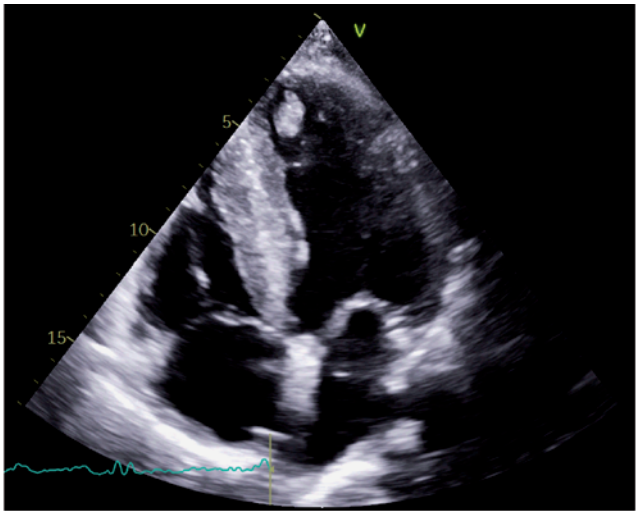


Figure 3. Four-chamber view with an apical left ventricle thrombus.

However, before the upgrade, the patient suffered cardiorespiratory arrest by ventricular fibrillation (VF), leading to a car accident, and was resuscitated after 2 shocks. In 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 ventricular tachycardia (VT) that degenerated in VF. On the intensive care unit, the patient had a recurrence of VT, and intravenous amiodarone was started. Coronary angiography revealed stenosis of the distal circumflex artery (90%). The pacemaker was upgraded to CRT-D, and the patient was discharged with a β-blocker.

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

During myocardial perfusion scintigraphy, the patient suffered multiple shocks due to monomorphic VTs and was readmitted to hospital. Percutaneous coronary intervention of the distal circumflex artery was performed, and the amiodarone dose was increased. Since then, the patient has 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 leads 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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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.

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