CJC Open 7 (2025) 137–140

Case Report

Unveiling Mitochondrial Cardiomyopathy: The Crucial Role of Multiparametric Cardiac Magnetic Resonance

Rita dos Reis Santos, MD,[a] Joana Certo Pereira, MD,[a] Pedro Lopes, MD,[a] Pedro Freitas, MD,[a] Marisa Trabulo, MD,[a] and João Abecasis, MD, PhD[a,b]

[a] *Cardiology Department, Hospital de Santa Cruz, Centro Hospitalar de Lisboa Ocidental, Carnaxide, Portugal*

[b] *Nova Medical School, Lisbon, Portugal*

We report the clinical case of a 39-year-old Caucasian man with a complex medical history, including a previous renal transplant and a confirmed m.3243A>G mutation associated with mitochondrial retinal dystrophy and hearing loss. The patient was admitted with acute heart failure. Diagnostic tests revealed significant biventricular hypertrophy and reduced left ventricular ejection fraction (LVEF), with no coronary artery disease. Cardiac magnetic resonance (CMR) imaging identified abnormal myocardial tissue characteristics, including reduced native T1 values, elevated T2 values, and extensive late gadolinium enhancement (LGE). These findings, combined with his mitochondrial disease history, led to a diagnosis of mitochondrial cardiomyopathy.

Novel Teaching Points

- Mitochondrial cardiomyopathy, a rare cause of adult-onset heart failure, should be suspected when multiple organs or tissues are affected. Genetic testing is an essential tool for confirming the diagnosis.
- LVH is a common feature of mitochondrial cardiomyopathy, and this differential diagnosis should be considered, particularly in the presence of extracardiac manifestations.
- CMR imaging offers valuable insights for diagnosing and understanding the rare clinical entity of mitochondrial cardiomyopathy.
- A multisequence CMR study provides detailed myocardial tissue characterization, supplying essential information to support differential diagnosis.

The patient was admitted to the emergency department because of new-onset acute heart failure. He had a past medical history of hypertension, long-standing type 1 diabetes mellitus, and a renal transplant performed 5 years earlier because of hereditary focal segmental glomerulosclerosis (with no previous report of kidney storage disease on kidney biopsy). Previous genetic investigation at endocrinology was positive for m.3243A>G mutation in the MT-TL1 gene, encoding for mitochondrial tRNALeu, and associated with mitochondrial retinal dystrophy and bilateral sensorineural hearing loss. There was no significant family history of cardiac disease or sudden cardiac death. The patient reported chronic daily use of immunosuppressive medications, including tacrolimus, mycophenolate mofetil, prednisolone, carvedilol, and insulin for ongoing management.

At presentation, initial investigation was notable for slight anemia, mildly elevated troponin and a N-terminal pro-B-type natriuretic peptide (proBNP) level of 2700 pg/mL. A 12-lead electrocardiogram (ECG) showed sinus rhythm with left ventricular hypertrophy (LVH) voltage criteria.

The transthoracic echocardiogram showed biventricular hypertrophy with a maximum septal-wall thickness of 17 mm (Fig. 1). Both ventricles had systolic dysfunction with a severely reduced LVEF caused by diffuse hypokinesia (LVEF of 30%; global longitudinal strain of −9.5%).

Cardiac computed tomography angiography revealed a coronary calcium score of 0, with normal coronary arteries. Additional investigation through 1.5T CMR confirmed severe concentric LVH, predominantly affecting the mid-interventricular septum (18 mm). The left ventricle was moderately dilated, with a significantly reduced LVEF (29%). In addition, the right ventricle was of normal size but exhibited a moderately impaired ejection fraction of 31%, attributed to diffuse hypokinesia.

Native T1 mapping revealed significant signal heterogeneity, characterized by globally reduced native T1 values (mean 939 ± 67 ms, for reference values of 972 to 1070 ms)

Received for publication October 12, 2024. Accepted November 8, 2024.

Corresponding author: Dr Rita dos Reis Santos, Cardiology Department, Hospital de Santa Cruz, Centro Hospitalar de Lisboa Ocidental, 2790-134 Carnaxide, Portugal. Tel.: (+351) 210 433 134.

E-mail: reissantos.rita@gmail.com

See page 140 for disclosure information.

https://doi.org/10.1016/j.cjco.2024.11.008

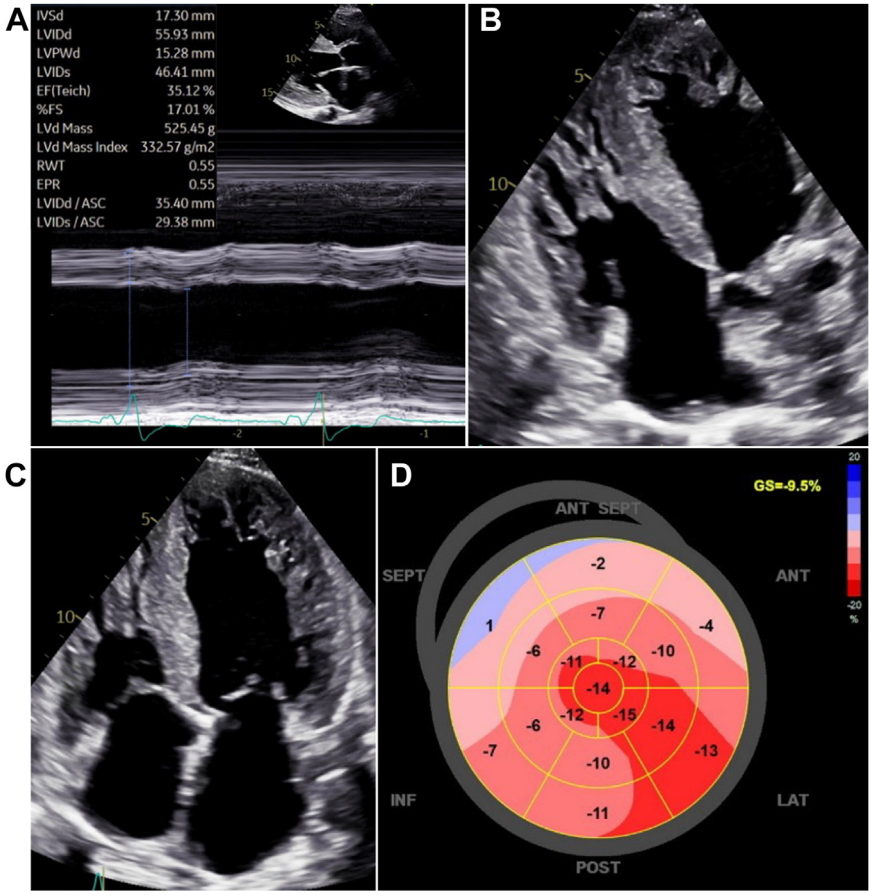

Figure 1. Transthoracic echocardiographic study. (**A**) M-mode measurement of the left ventricle shows a maximum thickness in the basal septum of 17 mm. (**B**) Hypertrophied right ventricle. (**C**) Hypertrophied and dilated left ventricle. (**D**) Bull's eye plot of global longitudinal strain.

(Fig. 2A). A trend toward normal T1 values (1000 ms) was observed in the basal and midinferior ventricular segments. Global T2 values were at the upper limit of normal (50 ± 6 ms, for reference values of 45 ± 3 ms). A more pronounced increase in T2 values (maximum of 58 ms) was observed in the basal and midanterior segments (Fig. 2A).

Additional tissue characterization revealed extensive patchy midwall LGE, which was not restricted to areas of pronounced hypertrophy (Fig. 2B). The extracellular volume was estimated at 38 ± 12%.

Given the patient's history of mitochondrial disease and the findings from multiparametric CMR imaging, a diagnosis of mitochondrial cardiomyopathy was established.

In-hospital clinical outcome was favourable, with symptomatic improvement under progressively increased tolerated doses of guideline-directed medical therapy for heart failure.

Mitochondrial cardiomyopathy is a cardiac disorder characterized by structural and functional abnormalities of the myocardium, mainly caused by mitochondrial respiratory chain defects.[1] Although rare in adults, it accounts for approximately 20% to 40% of heart failure cases in children with mitochondrial diseases.[2] The m.3243A>G variant in the mitochondrial tRNALeu gene is one of the most common mutations, being associated with diverse syndromes, exhibiting considerable variability in cardiac manifestations. This mutation leads to hypertrophic cardiomyopathy in approximately 18% of affected individuals.[3] Indeed, hypertrophic cardiomyopathy is the most prevalent phenotype of mitochondrial cardiomyopathy, observed in more than 50% of patients with mitochondrial-related cardiac conditions. However, it may also manifest as dilated, restrictive, excessive trabeculation or histiocytoid cardiomyopathy.[3] Myocardial involvement and heart failure may be the first and sole manifestation of the disease, albeit more common concomitant multisystemic disease affection.[1,2] As a recommendation, all patients with known or suspected mitochondrial diseases should undergo screening for the presence of cardiomyopathy.[4]

The diagnosis of mitochondrial disease involves a comprehensive approach that includes clinical assessment, biochemical testing, histopathology, mitochondrial-function assessment, and molecular genetic analysis. Mitochondrial cardiomyopathy is confirmed when other potential causes of heart disease, such as coronary artery disease, valvular disease, congenital heart defects, or other forms of cardiomyopathy, have been systematically excluded.[2,3]

At present, there are no definitive therapies available for mitochondrial disorders. Analogous to classic sarcomeric hypertrophic cardiomyopathy, mitochondrial cardiomyopathy is also characterized by LVH. In this setting, CMR tissue characterization—particularly reduced T1 mapping—plays a critical role in the differential diagnosis, and this may have

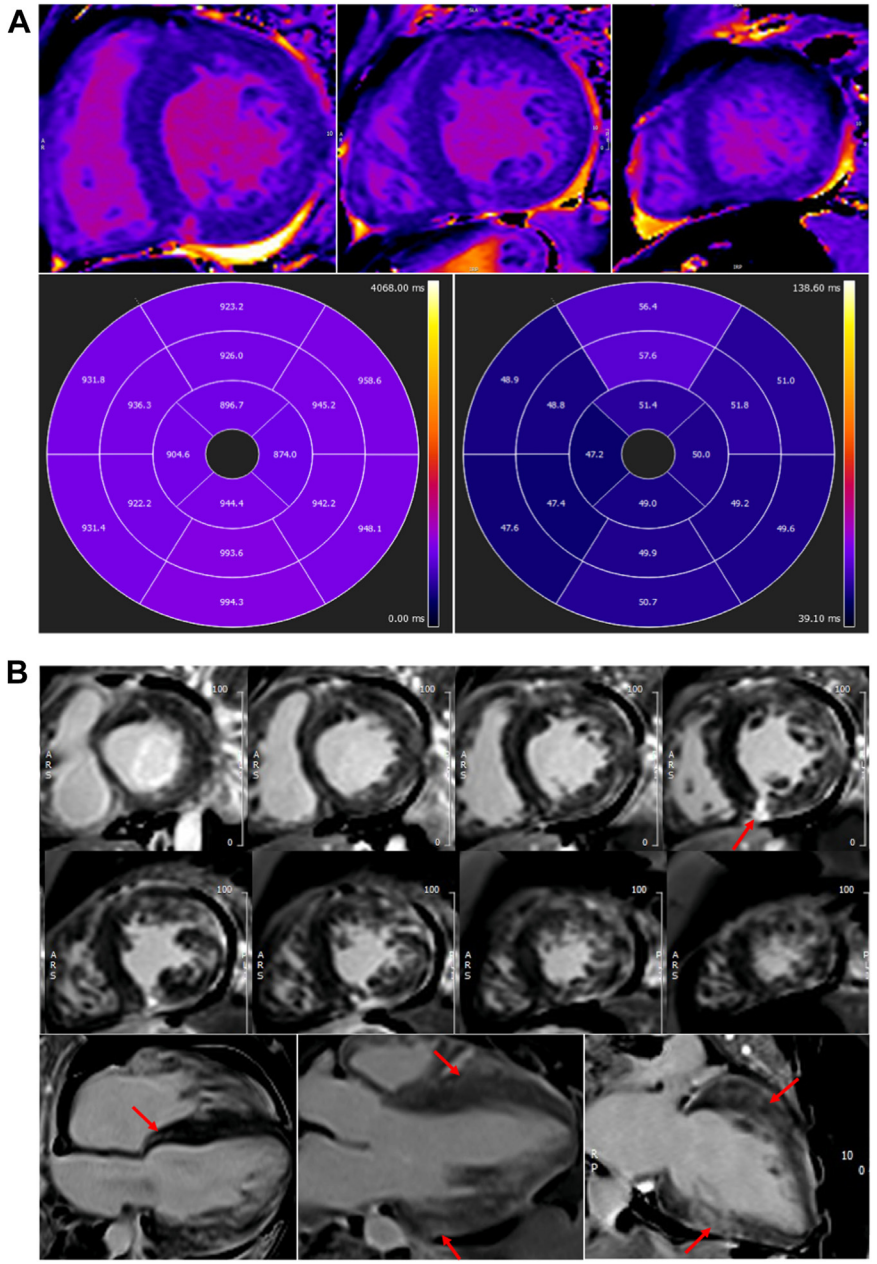

Figure 2. Tissue characterization at CMR study (*Siemens* 1.5T). (**A**) Native T1 mapping (MOLLI) showing globally reduced native T1 values 939 ± 67 ms (**upper images and top inferior left**); Native T2 mapping (*FLASH*) with global T2 values in the upper limit of normality (**top inferior right**). (**B**) Delayed enhancement sequence with extensive irregular midmural LGE, linear in the basal segments of the interventricular septum, and several midmyocardial scattered foci in multiple segments (**arrow**). CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

significant therapeutic implications. Notably, unlike classic sarcomeric hypertrophic cardiomyopathy, targeted therapies for mitochondrial cardiomyopathy are still lacking. Treatment strategies are largely symptomatic and do not affect progression of metabolic disease. Solid organ transplantation is generally regarded as a relative contraindication, given the multiorgan involvement. Nevertheless, heart transplantation may be considered when in the presence of predominant myocardial involvement with mild and stable extracardiac affection.[4]

In the presented case, CMR tissue characterization revealed reduced native myocardial T1 values within a hypertrophic phenotype. The major cardiac differential diagnoses, in this case, are hypertrophic cardiomyopathy (HCM), Anderson-Fabry disease, and tacrolimus-induced HCM. Classical sarcomeric hypertrophic cardiomyopathy is associated with diffuse fibrosis and elevated native T1 values, with predominant LGE distribution at more thickened myocardial segments. Both reduced native T1 mapping values and LGE favours an alternative diagnosis. As mitochondrial diseases involve changing the use of the substrates for myocardial energy provision, the fatty acid metabolic shift may explain potential intracellular fat accumulation, lowering myocardial

T1 values.[5,6] Considering the LGE pattern and low T1 values, Fabry disease was also considered a differential diagnosis. However, the patient's kidney biopsy revealed no evidence of storage disease, and there was a previous diagnosis of mitochondrial disease. Furthermore, guideline-directed medical therapy during the follow-up improved LVEF, a less common finding when in the presence of glycogen storage diseases. In addition, given the patient's history of transplantation and use of tacrolimus, the hypothesis of tacrolimus-induced HCM was considered. However, tacrolimus-induced HCM may not consistently show reductions in T1 mapping and often presents with normal T2 mapping. In contrast, mitochondrial cardiomyopathy may exhibit localized edema or inflammation caused by mitochondrial stress. Another key differentiator is the LGE pattern—mitochondrial cardiomyopathy—typically displays patchy or focal fibrosis associated with metabolic dysfunction, whereas tacrolimus-induced HCM often shows fibrosis patterns indicative of cellular hypertrophy or interstitial fibrosis.

This case is noteworthy for illustrating the application of multiparametric CMR imaging in achieving a specific diagnosis by providing comprehensive tissue characterization, which offers insights beyond conventional imaging techniques and aids in distinguishing between different underlying pathologies. Beyond the current clinical screening protocols involving a 12-lead ECG and transthoracic echocardiography (TTE) for individuals with pathogenic mitochondrial DNA mutations, it may be advisable to recommend CMR for all patients presenting with LVH identified on either ECG or TTE. Also, CMR should be considered for those who exhibit new-onset left ventricular systolic dysfunction.

Ethics Statement

This case report has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient.

Funding Sources

No funding was provided for this article.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Meyers DE, Basha HI, Koenig MK. Mitochondrial cardiomyopathy: pathophysiology, diagnosis, and management. Tex Heart Inst J 2013;40:385-94.

2. Holmgren D, Wåhlander H, Eriksson BO, et al. Cardiomyopathy in children with mitochondrial disease: clinical course and cardiological findings. Eur Heart J 2003;24:280-8.

3. Brunel-Guitton C, Levtova A, Sasarman F. Mitochondrial diseases and cardiomyopathies. Can J Cardiol 2015;31:1360-76.

4. Pankuweit S, Richter A. Mitochondrial disorders with cardiac dysfunction: an under-reported aetiology with phenotypic heterogeneity. Eur Heart J 2015;36:2894-7.

5. Wajner M, Amaral AU. Mitochondrial dysfunction in fatty acid oxidation disorders: insights from human and animal studies. Biosci Rep 2015;36:e00281.

6. Palecek T, Tesarova M, Kuchynka P, et al. Hypertrophic cardiomyopathy due to the mitochondrial DNA mutation m.3303C>T diagnosed in an adult male. Int Heart J 2012;53:383-7.