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Heart failure

Cardiogenic shock in a woman with a mitochondrial cardiomyopathy: a case report

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Background Mitochondrial cardiomyopathy (MCM) is an alteration in cardiac structure and function caused by gene mutations or deletions affecting components of the mitochondrial respiratory chain. We report a case of MCM presenting as cardiogenic shock, ultimately requiring left ventricular assist device (LVAD) placement.

Case summary A 35-year-old woman with chronic weakness and non-ischaemic cardiomyopathy, on home dobutamine, was referred to our institution for heart transplantation evaluation. She was admitted to the hospital for suspected cardiogenic shock after laboratory tests revealed a lactate level of 5.4 mmol/L (ref: 0.5–2.2 mmol/L). Her hospital course was complicated by persistently undulating lactate levels (0.2–8.6 mmol/L) that increased with exertion and did not correlate with mixed venous oxygen saturation measurements obtained from a pulmonary artery catheter. Electrodiagnostic testing demonstrated a proximal appendicular and axial myopathy. A left deltoid muscle biopsy was performed that demonstrated evidence of a mitochondrial disease on light and electron microscopy. Muscle genetic testing revealed two large-scale mitochondrial deoxyribonucleic acid sequence deletions, confirming the diagnosis of MCM. She subsequently underwent LVAD placement, which was complicated by significant right ventricular failure requiring early mechanical support. She was ultimately discharged home with chronic inotropic support.

Discussion Mitochondrial cardiomyopathy in adults is a diagnostic and therapeutic challenge. Prompt diagnosis should be made in patients with unknown causes of heart failure via skeletal muscle histopathology guided by electrodiagnostic studies, and targeted genetic testing in affected tissue. Outcomes in adult MCM patients who receive an LVAD are unknown and warrant further investigation.

Keywords Mitochondrial cardiomyopathy • Mitochondrial DNA disease • Advanced heart failure • Mechanical circulatory support device • Case report

ESC Curriculum 6.1 Symptoms and signs of heart failure • 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy

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Learning points

- Mitochondrial cardiomyopathy (MCM) is a rare cause of heart failure and should be suspected in young patients with signs of neuromuscular disease.
- Clinically affected muscle histopathology and targeted genetic testing are necessary to accurately diagnose MCM and may identify large-scale mitochondrial DNA deletions.
- Outcomes following left ventricular assist device placement or cardiac transplantation in adults with MCM and end-stage heart failure are unknown, warranting further investigation.

Primary specialties involved other than cardiology

Neuromuscular medicine, genetics, ophthalmology, endocrinology, anatomic pathology.

Introduction

Mitochondrial disease encompasses a group of disorders caused by genetic defects affecting the mitochondrial respiratory chain, resulting in dysfunctional cellular oxidative phosphorylation. These genetic defects arise from mutations in either nuclear deoxyribonucleic acid (DNA) or mitochondrial DNA (mtDNA).[1] Clinically, mitochondrial disease can affect every organ system, but has a particular propensity to affect organ systems with high energy requirements including the heart, brain, skeletal muscle, and eye. A serious clinical manifestation of mitochondrial disease includes mitochondrial cardiomyopathy (MCM), which is defined as an alteration in cardiac muscle structure and function caused by genetic defects of the mitochondrial respiratory chain, in the absence of other causes of heart failure.[2]

Timeline

Date	Significant event
1 January 2017	Heart failure diagnosis A TTE revealed an EF of 10–15%. GDMT was initiated.
22 February 2018	1 year follow-up A repeat TTE showed an EF of 50%. GDMT was discontinued shortly thereafter due to hyperkalaemia and hypotension. Her EF continued to decline in a stepwise fashion over the next 3 years.
16–26 February 2021	Pre-referral testing A LHC and RHC confirmed the presence of a non-ischaemic cardiomyopathy with a measured cardiac index of 2.1 L/min/m^2. CPET revealed a peak oxygen consumption of <10 mL/kg/min, indicating need for transplantation.
17 May 2021	Home inotrope therapy was initiated.
23 June 2021–7 July 2021	Patient was referred to our institution for cardiac transplantation evaluation. Transplant clinic visit and initial hospital admission. Patient admitted to the hospital for suspected cardiogenic shock after laboratory data reviewed in clinic. Genetic testing of leucocyte DNA and mtDNA were performed. EDX studies were obtained.
31 August 2021–29 October 2021	Second hospital admission. A left deltoid skeletal muscle biopsy was obtained. Histopathology and genetic testing diagnosed a MCM. The patient underwent LVAD placement complicated by RV dysfunction requiring mechanical support and prolonged inotropic support.
1 November 2021–present	Patient discharged home after LVAD placement. She had multiple hospitalizations for volume overload and RV dysfunction and was initiated on chronic inotropic support by April 2022. She is undergoing consideration for cardiac transplantation.

TTE, transthoracic echocardiogram; EF, ejection fraction; GDMT, guideline directed medical therapy; CPET, cardiopulmonary exercise test; LHC, left heart catheterization ; RHC, right heart catheterization; DNA, deoxyribonucleic acid; mtDNA, mitochondrial DNA; EDX, electrodiagnostic; MCM, mitochondrial cardiomyopathy; RV, right ventricular; LVAD, left ventricular assist device.

Case presentation

A 35-year-old woman with a history of hypothyroidism and heart failure with a reduced left ventricular ejection fraction (LVEF) was referred to our institution for transplant evaluation. Four years prior, a transthoracic echocardiogram (TTE) demonstrated an LVEF of 10–15%. She was started on medical therapy with lisinopril and metoprolol succinate, and her LVEF improved to 50% after 1 year of therapy. However, she was unable to tolerate medical therapy due to recurrent hypotension and hyperkalaemia, and serial TTEs revealed a stepwise decline in her LVEF over the next 3 years. Four months prior to her referral, she underwent cardiopulmonary exercise testing with cycle ergometry, as well as left and right heart catheterizations. The results of these tests are included in *Table 1*. Ultimately, her fatigue and dyspnoea progressed, and she was started on a home dobutamine infusion at 5 μg/kg/min. She was subsequently diagnosed with American Heart

Table 1 Results of pre-referral cardiac transplantation evaluation

Test	Value or result
Cardiopulmonary exercise testing	
Peak heart rate (beats/min)	96
Peak O_2 consumption (L/kg/min)	6
Respiratory exchange ratio	1.12
Left heart catheterization	
LMCA	No CAD
LAD	No CAD
LCx	No CAD
RCA	No CAD
Right heart catheterization	
Right atrial pressure (mmHg)	13
Right ventricular pressure (mmHg)	50/1
Pulmonary artery pressure (mmHg)	51/20
Mean pulmonary artery pressure (mmHg)	30
PCWP (mmHg)	20
Cardiac output (L/min)	3.2
Cardiac index (L/min/m^2)	2.1
Systemic vascular resistance (dynes s cm^{-5})	1833
Pulmonary vascular resistance (dynes s cm^{-5})	258
Pulmonary artery pulsatility index	2.38

Cardiopulmonary exercise testing, a left heart catheterization, and a right heart catheterization were obtained. The patient notably has a peak O_2 consumption < 10 L/kg/min on cardiopulmonary exercise testing, meeting criteria for cardiac transplantation. Right and left heart catheterization revealed a reduced cardiac index and no evidence of coronary atherosclerosis.
LMCA, left main coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; PCWP, pulmonary capillary wedge pressure; CAD, coronary artery disease.

Association Stage D heart failure with New York Heart Association Class IV symptoms and was referred to our institution for cardiac transplantation evaluation.

At her first heart failure clinic visit, a complete history and physical was performed. Her symptoms and functional status had not improved while on home inotrope therapy, and she was dependent on her mother for care. Her home medications included levothyroxine, torsemide, and ivabradine, all of which were initiated prior to dobutamine. Her family history was only notable for heart failure in her paternal grandfather and grandmother. Her temperature was 36.5°C, blood pressure, 113/79 mmHg; heart rate, 106 b.p.m.; respiratory rate, 20 r.p.m.; and pulse oximetry, 99% on room air. On physical examination, she was jaundiced, and her internal jugular vein pulsation was measured at 10 cm H_2O. An electrocardiogram demonstrated sinus tachycardia with evidence of biatrial enlargement (*Figure 1*). *Table 2* shows laboratory data at the clinic visit. Notably, her lactate was elevated to 5.4 mmol/L.

She was admitted to the hospital's advanced heart failure service for an expedited transplantation evaluation and for suspected cardiogenic shock. On admission, a right brachial peripherally inserted central catheter (PICC) venous sample showed an elevated lactate level of 5.8 mmol/L and a mixed venous oxygen saturation of 53%. Milrinone 0.2 μg/kg/min was initiated, in addition to dobutamine 5 μg/kg/min. A TTE revealed an LVEF of 20–25%, moderate to severe mitral regurgitation (MR), severe left ventricular (LV) dilation, and a right ventricular (RV) systolic pressure of 40–50 mmHg. In addition, a right heart catheterization was performed, and the following measurements were obtained: right atrial pressure, 7 mmHg; pulmonary wedge pressure, 20 mmHg; Fick cardiac index, 2.1 L/min/m^2; and systemic vascular resistance, 1919 dynes s cm^{-5}. She subsequently underwent cardiovascular magnetic resonance imaging with gadolinium contrast. Imaging revealed severe LV systolic dysfunction, severe MR, and late gadolinium enhancement of the septal, inferior, and inferolateral walls in a midwall and subepicardial pattern (*Figure 2* and Supplementary material online, *VideoS1*). Follow-up labs were notable for a thiamine level of 7 nmol/L (ref: 8–30 nmol/L), for which thiamine supplementation was initiated. Based on her clinical history, thiamine deficiency was not believed to be the cause of her heart failure, though it may have contributed to a more progressive disease course.

The patient demonstrated undulating lactate levels (range: 0.2–8.6 mmol/L) while hospitalized. Her lactate levels increased after periods of exertion, and often did not correlate with mixed venous oxygen saturation measurements. The findings of non-ischaemic heart failure, chronic weakness, and elevated lactate levels after exertion were suggestive of mitochondrial disease. This was supported by a serum pyruvate level of 1.68 mg/dL (ref: 0.3–1.5 mg/dL) and lactate-to-pyruvate ratio of 31:1 (normal <20:1). A multidisciplinary team, including genetics, neurology, endocrinology, and ophthalmology, was assembled to further evaluate the patient.

Genetic testing of peripheral blood leucocyte DNA and mtDNA content was unrevealing and included variants for ~1800 mtDNA genes, 188 nuclear-encoded genes associated with mitochondrial dysfunction, and 168 genes responsible for inherited cardiomyopathies and arrhythmias. Electrodiagnostic (EDX) studies demonstrated a mild non-irritable proximal appendicular and axial myopathy. Ophthalmologic evaluation revealed a >90% limitation in lateral gaze deviation in both eyes. Direct ophthalmoscopy did not reveal pigmentary retinopathy.

At the time of discharge, she was transitioned to milrinone for home inotrope therapy. Her cardiac transplantation evaluation was deferred pending further evaluation by a neuromuscular specialist. Shortly after discharge, the patient was seen in the neuromuscular disease clinic, and testing for transthyretin amyloid, adrenal insufficiency, paraproteinemia, and autoimmunity as causes of her muscular weakness and non-ischaemic cardiomyopathy were all negative. Guided by the EDX study results, she was scheduled for a skeletal muscle biopsy to further characterize her disease.

Unfortunately, the patient was readmitted to the hospital for cardiogenic shock with a lactate above the detectable limit of 20 mmol/L, pulmonary oedema, and hypoxaemic respiratory failure prior to the scheduled muscle biopsy. A repeat TTE demonstrated severe LV dilation, an LVEF of 20%, severe MR, and mildly reduced RV function. The TTE included the following RV measurements: tricuspid annular plane systolic excursion, 15 mm; RV annular systolic velocity, 7.1 cm/s; RV basal diameter, 3.30 cm; and RV to LV size ratio, 0.69. She was emergently placed on veno-arterial extracorporeal membrane oxygenation. LV unloading was achieved by percutaneous placement of a transeptal left atrial drain cannula via the femoral vein. Given her deteriorating clinical status, an expedited left deltoid muscle biopsy was obtained. Key light and electron microscopy histopathological features are shown in *Figure 3*. Next generation sequencing of mtDNA obtained from the frozen muscle biopsy specimen revealed two pathogenic overlapping mtDNA sequence deletions, diagnostic of primary mitochondrial disease. Based on her clinical presentation, she was diagnosed with MCM.

The interventional cardiology and cardiothoracic surgery teams evaluated the patient and elected to pursue early LVAD placement rather than transcatheter mitral valve edge-to-edge repair. The patient subsequently underwent LVAD placement as a bridge to cardiac transplantation. A core LV excisional biopsy was obtained during device placement. Light microscopy findings are shown in *Figure 4*. After LVAD placement, her hospital course was complicated by RV failure.

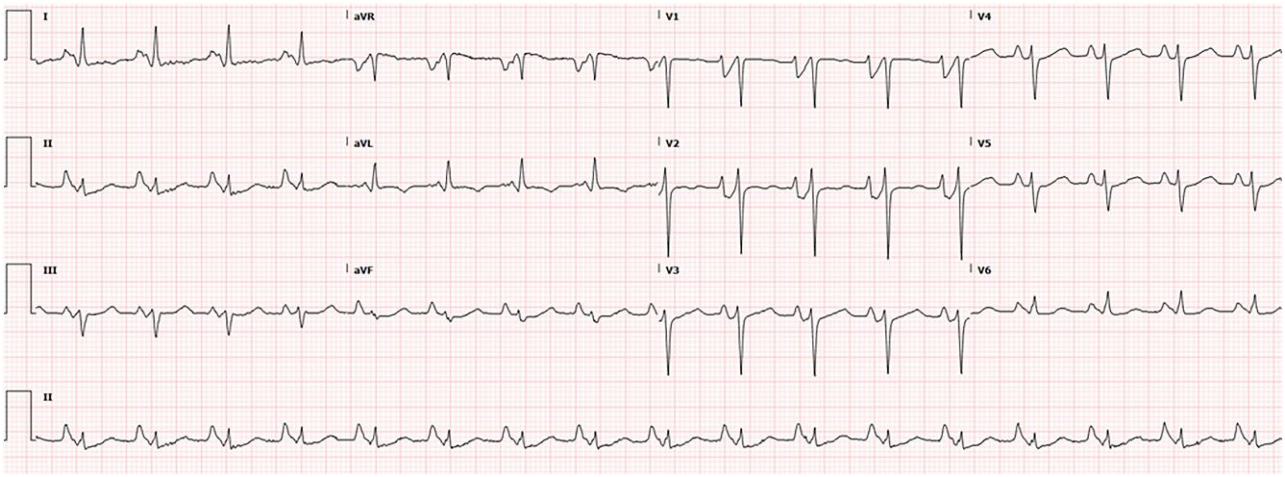

Figure 1 Admission electrocardiogram. The patient was in sinus tachycardia with a heart rate = 102 beats/min. A large *P* wave (>2.5 mm) is present in Lead II, indicating right atrial enlargement. A large negative *P* wave is present in Lead V1 (>1 mm deep and >1 mm wide), indicating left atrial enlargement.

Table 2 Laboratory testing obtained during the initial transplant clinic visit for a 35-year-old female with a non-ischaemic cardiomyopathy

Variable	Value	Reference range
Sodium (mmol/L)	138	135–145
Potassium (mmol/L)	5.1	3.1–5.1
Chloride (mmol/L)	93	97–108
Bicarbonate (mmol/L)	26	22–28
Anion gap (mmol/L)	19	4.0–16.0
BUN (mg/dL)	32	5–22
Creatinine (mg/dL)	1.3	0.4–1.2
Albumin (g/dL)	4.2	3.7–5.5
Total bilirubin (mg/dL)	5.8	0.3–1.4
AST (IU/L)	96	12–39
ALT (IU/L)	56	7–52
BNP (pg/mL)	1800	0–100
Lactate (mmol/L)	5.4	0.5–2.2

BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNP, B-type natriuretic peptide.

A ProtekDuo dual lumen catheter (LivaNova, London) was inserted through the right internal jugular vein into the pulmonary artery, through which blood was pumped from the right atrium into the pulmonary artery. Furthermore, she developed acute renal failure requiring continuous renal replacement therapy. The ProtekDuo catheter was removed after RV recovery and a tunneled subclavian venous catheter was placed for short-term haemodialysis. The patient's renal function recovered before discharge, and the subclavian catheter was removed. Her estimated glomerular filtration rate at discharge was 20 mL/min/1.73 m^2. She received carnitine, arginine, creatinine, and coenzyme Q10, as well as nutritional supplementation during her hospitalization and upon discharge. Following discharge, the patient has been hospitalized multiple times for volume overload and RV dysfunction. She has been on chronic inotropic support since April 2022, initially with milrinone and more recently with dobutamine. She follows regularly with neuromuscular and advanced heart failure specialists for her MCM, medical comorbidities, and LVAD management.

Discussion

We present a case of a young woman with a MCM, confirmed by histopathology and genetic testing, who developed cardiogenic shock and received an LVAD and dietary supplements commonly used to treat primary mitochondrial disorders. The prevalence of MCM is unknown. However, it should be no greater than the prevalence of mitochondrial disease, estimated to be as high as 1 in 5000 births.[3] Previous data on MCM epidemiology and natural history have been limited to paediatric populations in small, retrospective studies due to the early age at diagnosis and rarity of adult-onset MCM. In three previous studies, MCM occurred in 17–40% of paediatric patients diagnosed with mitochondrial disease.[4–6] Of note, multiple studies have confirmed lower overall survival rates in mitochondrial disease with cardiac manifestations, compared with those without cardiac manifestations.[5–7]

Mitochondrial diseases are maternally inherited, progressive disorders with heterogenous presentations varying from isolated disorders of a single organ system to multisystemic disease. This clinical heterogeneity is explained by heteroplasmy, defined as the existence of two or more distinct mitochondrial genomes (mutant and wild type) within the same tissue.[7] As the proportion of mutant to wild-type genomes in each mitochondrion increases, the probability of disease manifesting in that tissue also increases. A complete description of each extra-cardiac finding is beyond the scope of this case report and has been summarized elsewhere.[8] Mitochondrial cardiomyopathy cardiovascular manifestations vary from clinically asymptomatic cases to those with symptoms of frank heart failure.[9] The structural and arrhythmic phenotypes of MCM are diverse. In one study examining the morphologic characteristics of MCM, 58% of paediatric patients had hypertrophic cardiomyopathy, 29% had dilated cardiomyopathy, and 13% had LV non-compaction. Only 11% of the MCM patients exhibited cardiac arrythmias, with ventricular tachycardia being the most frequently observed arrhythmia.[5]

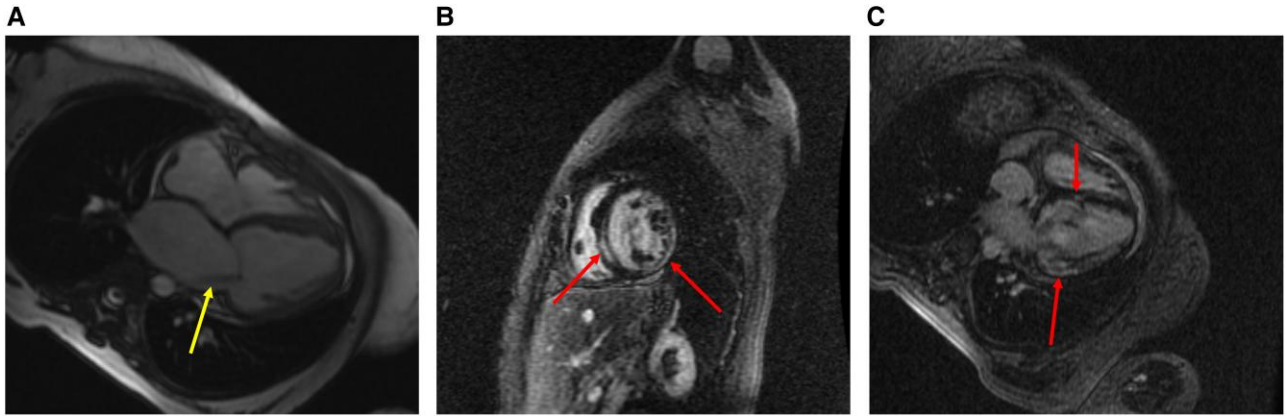

Figure 2 Cardiac magnetic resonance imaging of a 35-year-old female patient who presented with suspected cardiogenic shock. (*A*) Cine images demonstrated a dilated left ventricle (left ventricular end-diastolic dimension = 56 mm) with severe systolic dysfunction and severe secondary MR (yellow arrow indicates MR jet through the mitral orifice). (*B*) Inversion recovery images in short axis view at mid-ventricle level and (*C*) modified 4 chamber view demonstrating late gadolinium enhancement (red arrows) of the septal, inferior, and inferolateral walls in a midwall and subepicardial pattern, consistent with a non-ischaemic cardiomyopathy. The left ventricular walls in the septal, inferior, and inferolateral distributions are thinned.

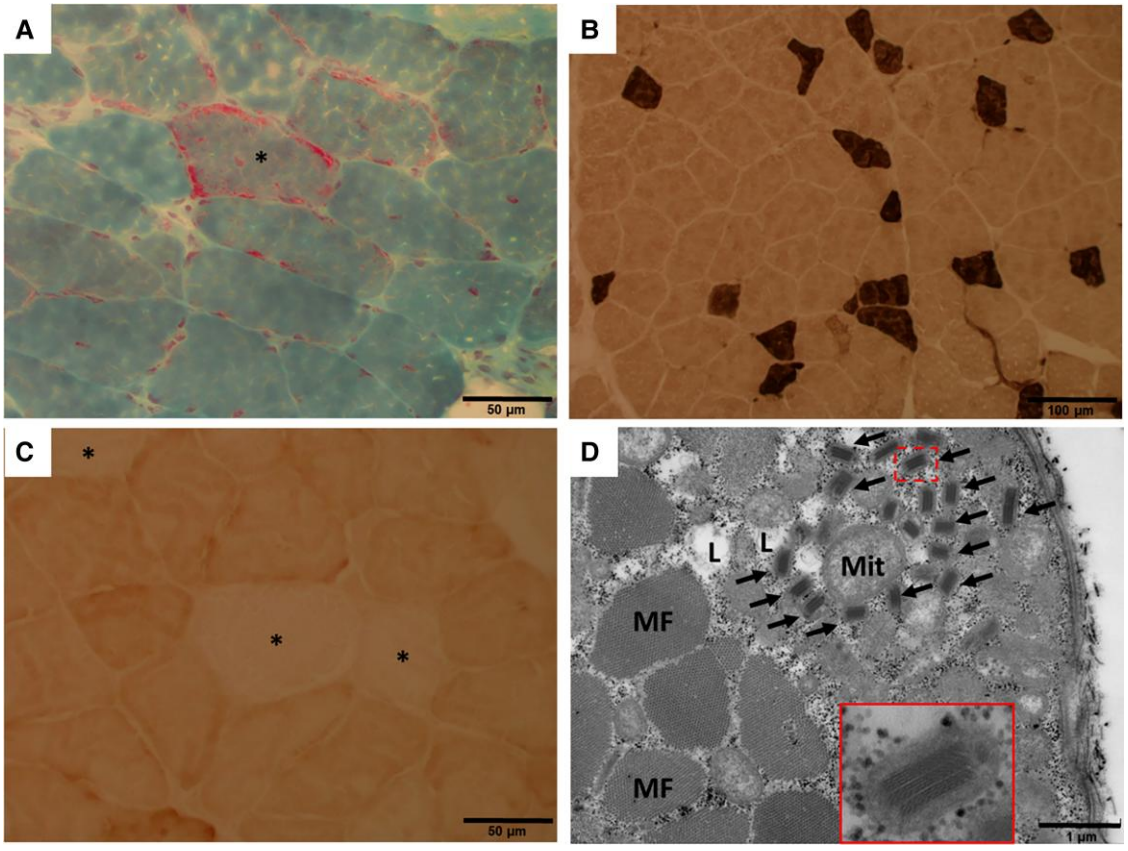

Figure 3 Left deltoid muscle biopsy histopathology. (*A*) Ragged red fibers with an altered myofibrillar network consisting of increased positive subsarcolemmal staining (asterisk, Modified Gomori Trichrome Stain). (*B*) Type 1 myofiber predominance (tan) with Type 2 specific myofiber atrophy (brown) (Alkaline ATPase 10.2 Stain). (*C*) Myofibers with cytochrome oxidase (COX) stain absent (asterisk, COX stain). (*D*) Subsarcolemmal mitochondria accumulation with paracrystalline inclusions (PCIs, arrow), swollen mitochondria (Mit), and lipid droplets (L) between myofibrils (MF, electron microscopy original magnification ×13 000). Rectangular inset with higher magnification highlighting PCIs.

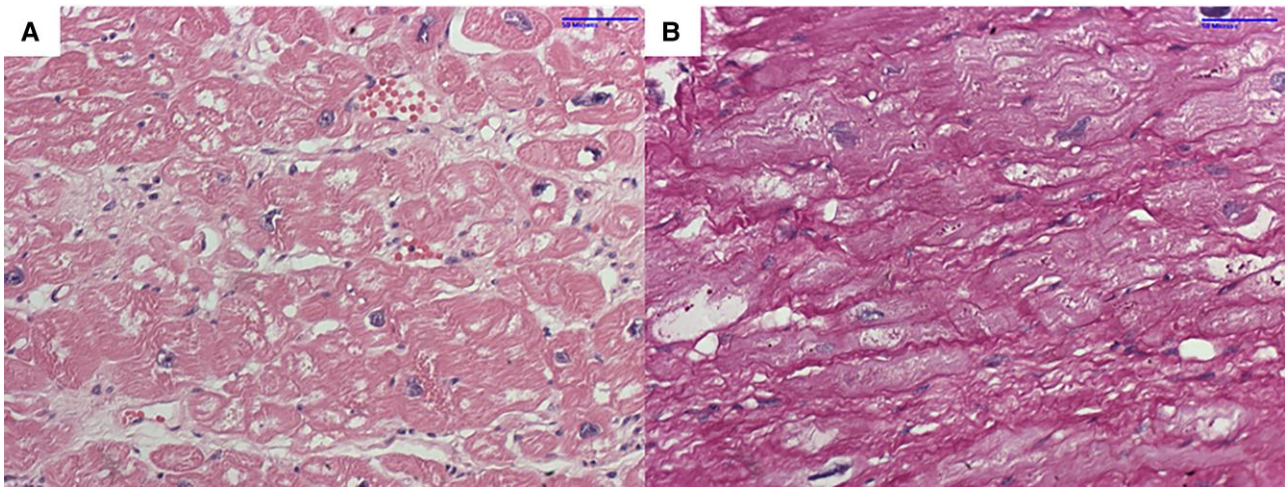

Figure 4 Left ventricular excisional core biopsy histopathology following LVAD placement. (*A*) Hematoxylin and Eosin stained, formalin-fixed paraformaldehyde-embedded section demonstrates dense fibrosis, myocyte hypertrophy, myofibrillar loss. (*B*) Periodic-Acid-Schiff-stained section showing blue, positively stained vacuoles indicative of glycogen accumulation. These features, in the appropriate clinical context, are suggestive of a mitochondrial cardiomyopathy. Blue scale bar = 50 μm.

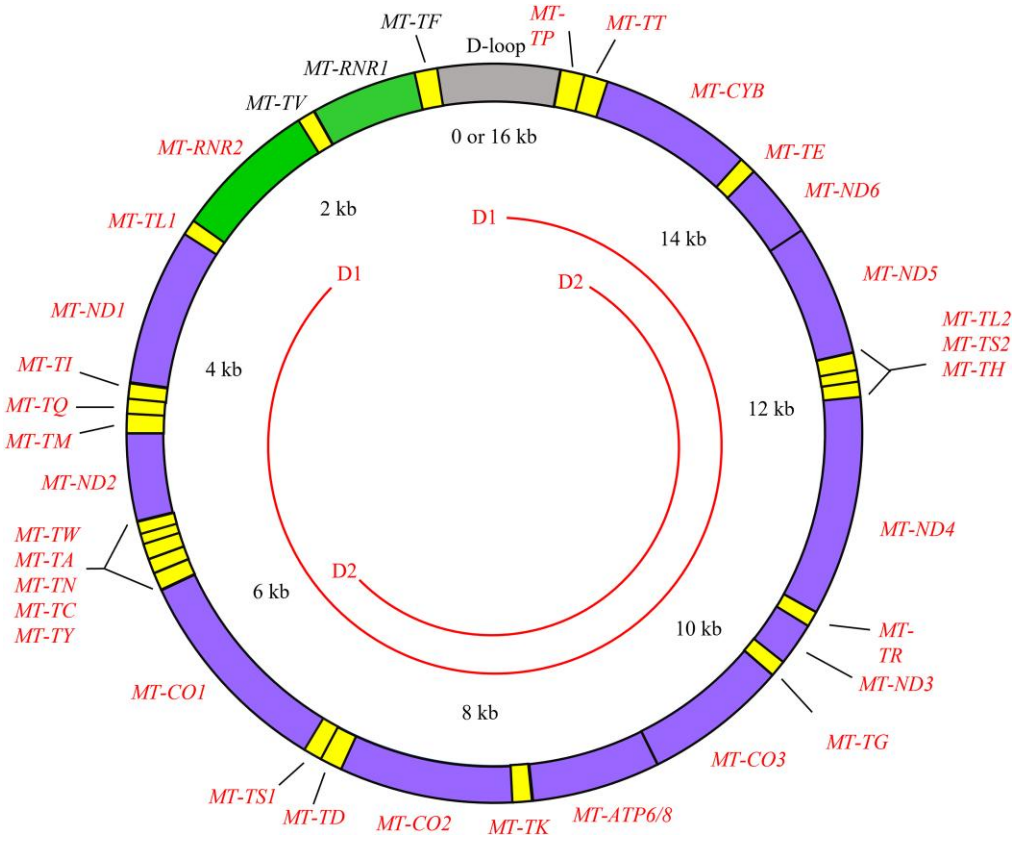

Figure 5 Mitochondrial DNA deletions. The human mitochondrial genome is circular and encompasses a total 16 569 base pairs which code for 22 transfer ribonucleic acids (RNAs) (yellow), 2 ribosomal RNAs (green), and 13 polypeptides involved in the mitochondrial respiratory chain (purple; one polypeptide is encoded within *MT-RNR2* and two polypeptides are encoded in *MT-ATP6/8*). The patient has mtDNA deletions denoted as 'D1' (m.2819_16072del13254) and 'D2' (m.6342_14004del7663). The length of each associated red arc approximates the span of the deletions in kilobases (kb). Italicized genes in red are affected by these deletions.

The diagnosis of mitochondrial disease has traditionally relied on a diagnostic framework proposed by Walker *et al.*, which estimates the likelihood of mitochondrial disease using clinical, histologic, biochemical, and genetic criteria.[8,10] Alternatively, if a specific mitochondrial disease is suggested by the clinical and family history, proceeding with genetic testing of peripheral blood leucocyte nuclear DNA or mtDNA is reasonable to obtain a diagnosis. However, these tests lack sensitivity, and a negative result cannot rule out mitochondrial disease. Thus, clinically affected tissue analysis histologically and by genetic testing is often necessary to establish a diagnosis of mitochondrial disease. On light microscopy, typical features include the presence of >2% ragged red muscle fibers, cytochrome oxidase-negative myofibers, and Type II specific myofiber atrophy.[10] Electron microscopy can reveal subsarcolemmal mitochondria accumulation with or without paracystalline inclusions.[11] With advances in genetic testing, biopsy specimens can undergo comprehensive analysis using next generation sequencing. This has allowed for rapid and accurate detection of point mutations and large-scale deletions within the entire mitochondrial genome, aiding significantly in diagnosis.[1,12] Next generation sequencing of a skeletal muscle biopsy specimen in our case revealed two overlapping 7 and 13 kb mtDNA sequence deletions, consistent with a multiple mtDNA deletion syndrome (*Figure 5*).

Multiple mtDNA deletion syndromes typically result from gene mutations in nuclear DNA, with the *POLG*, *PEO1*, and *ANT1* genes commonly affected, encoding polypeptides responsible for mtDNA biogenesis (replication).[1] Unique to this case, genetic testing did not reveal these mutations or other nuclear DNA mutations involved in mtDNA biogenesis. However, the genetic test used in this case only detects 95% of the known nuclear gene variants responsible for mitochondrial disease. There are classically three clinical phenotypes described in the mtDNA deletion syndrome spectrum (*Table 3*).[12] Our patient's clinical features overlap with the phenotypic spectrum of chronic progressive external ophthalmoplegia and Kearns–Sayre syndrome. However, our patient lacks onset of symptoms before age 20, pigmentary retinopathy, and cardiac conduction defects characteristic of Kearns–Sayre syndrome. On the other hand, she has additional findings not typically seen in chronic progressive external ophthalmoplegia, including a dilated cardiomyopathy and exertional lactic acidosis. Importantly, the discordance between lactate and mixed venous oxygen saturation measurements following exertion were most reflective of myopathic changes rather than end organ hypoperfusion due to myocardial dysfunction. These findings highlight the heterogeneity of mitochondrial disease. Close follow-up is needed to monitor for additional clinical features, including ocular and conduction abnormalities.

Management of MCM is supportive. Given the heterogenous nature of mitochondrial disease, a multidisciplinary team including a geneticist, neuromuscular medicine specialist, and cardiologist is beneficial. This patient received multiple dietary supplements including thiamine, coenzyme Q10, L-carnitine, creatinine, and L-arginine. However, data on the beneficial effects of dietary supplementation on symptoms and functional status are marginal and show conflicting results.[13–16] Guideline directed medical therapy (GDMT) in MCM is generally considered reasonable, though no studies have examined the effect of treatment on outcomes in this population. Patients progressing to cardiogenic shock, as in this case, can be considered for either LVAD placement or cardiac transplantation. Given this patient's rapidly deteriorating clinical status, LVAD placement was initially pursued. However, long-term outcomes in MCM patients following LVAD placement have not been studied. Following LVAD placement, patients who are female, require circulatory support as a bridge to LVAD, and have a non-ischaemic cardiomyopathy are at high risk for RV failure.[17] Our patient shared these characteristics, placing her at high risk for requiring RV support. Unfortunately, she required early mechanical RV support during her second admission, and prolonged inotropic support for delayed RV failure 5 months following discharge. The delayed development of RV failure following her second admission may reflect the progressive nature of her mitochondrial disease. Furthermore, chronic renal insufficiency following LVAD placement prevented initiation of GDMT, further compounding the progressive nature of her cardiomyopathy.

Table 3 Phenotypic spectrum of mtDNA deletion syndromes (these classically are divided into Pearson's syndrome, chronic progressive external ophthalmoplegia, and Kearns–Sayre syndrome)

Syndrome	Clinical and laboratory findings	Mitochondrial DNA mutation
Pearson's syndrome	Onset in infancy with sideroblastic anaemia, exocrine pancreatic insufficiency, hepatopathy, nephropathy; children who survive the disease can go on to develop Kearns–Sayre Syndrome.	Single, large-scale mtDNA deletion
Chronic progressive external ophthalmoplegia	Ptosis, external ophthalmoplegia, severe proximal limb myopathy	Single or multiple mtDNA deletions
Kearns–Sayre syndrome	Onset before age 20, pigmentary retinopathy, ataxia, external ophthalmoplegia, and cardiac conduction defects.	Single, large-scale mtDNA deletion

Clinical features, laboratory findings, and associated genetic abnormalities are shown.

In contrast to LVADs, long-term outcomes following cardiac transplantation have demonstrated favorable results in paediatric populations. In a retrospective study examining outcomes in paediatric populations undergoing cardiac transplantation, survival was similar between patients with and without MCM over a median follow up of 4 years.[18] The authors noted that the MCM patients in this study had limited extracardiac manifestations, as those with significant comorbidities were excluded during the pre-transplant evaluation. While these results imply that MCM patients with limited extracardiac findings have favorable post-transplantation outcomes, our reported patient differs in a few important ways. First, she had medical contraindications to transplantation that require ongoing management, including severe chronic kidney disease and profound frailty related to severe muscular weakness. Second, she is an adult patient and her outcome following cardiac transplantation is challenging to extrapolate from studies evaluating paediatric populations. Ultimately, cardiac transplantation should be considered a reasonable option in age appropriate MCM patients with a well-defined mitochondrial disease, who are otherwise good candidates for transplantation.

In conclusion, MCMs should be considered early in the differential diagnosis for young patients with chronic weakness and structural heart disease or cardiac conduction defects. Undulating lactate levels that increase with exertion and decrease with rest should alert clinicians to mitochondrial disease. When concern for cardiogenic shock is high, biopsy of clinically affected tissues should be performed to prevent a delay in diagnosis and management. In patients with confirmed MCM,

LVAD placement is a reasonable approach, though long-term outcomes following implantation are unknown. It is also reasonable to consider cardiac transplantation with stage D heart failure, assuming no contraindications, as long-term outcomes after transplant may not differ significantly between those with and without MCMs. The long-term management of mitochondrial disease is complex, and consultation with a multidisciplinary team is helpful to optimize functional status, quality of life, and treatment of multisystemic comorbidities.

Lead author biography

Andrew Girard was born in Tampa, FL, USA, and grew up in Orlando, FL, USA. He received his undergraduate degree in Chemical Engineering at the University of Florida and studied medicine at the University of Central Florida College of Medicine. He is currently an internal medicine resident at the University of Alabama at Birmingham Medical Center, and he plans to pursue a career in cardiovascular medicine.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

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None

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

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 in line with COPE guidance.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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