ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–6
https://doi.org/10.1093/ehjcr/ytad132

GRAND ROUND
Heart failure

A mitochondrial cytopathy presenting with persistent troponin elevation: case report

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Received 1 August 2022; first decision 26 October 2022; accepted 22 March 2023; online publish-ahead-of-print 17 April 2023

Background Mitochondrial diseases represent an important potential cause of cardiomyopathy and should be considered in patients presenting with multisystem manifestations. Timely diagnosis of a mitochondrial disorder is needed as it can have reproductive implications for the offspring of the proband.

Case Summary We describe a case of undifferentiated rising and persistent troponin elevation in a 70-year-old female with only mild heart failure symptoms and signs. An eventual diagnosis of a mitochondrial cytopathy was made after genetic testing, striated muscle, and endomyocardial biopsy. Multidisciplinary involvement was vital in securing the ultimate diagnosis and is a key lesson from this case. On follow up, with institution of heart failure therapy including cardiac resynchronisation device therapy there was improvement in exercise tolerance and symptoms.

Discussion For discussion is the investigation of undifferentiated cardiomyopathies and consideration of mitochondrial disorders as an important diagnosis to exclude prior to diagnosis as an idiopathic cardiomyopathy.

Keywords Mitochondrial cytopathy • Cardiovascular magnetic resonance imaging • Troponin • Case report

ESC Curriculum 6.5 Cardiomyopathy • 2.1 Imaging modalities • 6.1 Symptoms and signs of heart failure

Learning Points

- To recognise the phenotypic spectrum of mitochondrial cytopathies, including cardiovascular involvement.
- To consider a broad range of differential diagnoses, including mitochondrial cytopathies, in patients presenting with 'idiopathic' or unexplained cardiomyopathy, as well as systemic, extracardiac manifestations.
- Making a mitochondrial cytopathy diagnosis has important management and reproductive implications for patients and their families.

Primary specialties involved other than cardiology

Clinical genetics, Rheumatology, Neurology and Pathology.

Introduction

The presentation of a mitochondrial cytopathy with persistent troponinaemia is unusual and important to recognise as an underlying diagnosis for patients with 'idiopathic' or unexplained cardiomyopathy.

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Handling Editor: Maya S Safarova
Peer-reviewers: Andriana Anagnostopoulou; Deborah Cosmi; Jagjit Khosla
Compliance Editor: Sara Monosilio
Supplementary Material Editor: Abdyullah Abdullah

Timely diagnosis of a mitochondrial disorder is important due to its management and reproductive implications to the offspring of the proband who may be asymptomatic carriers of significant mitochondrial DNA (mtDNA) mutations.[1] Here, we describe a patient with persistent troponin elevation and heart failure that underwent assessment for cardiac myositis leading to a final diagnosis of a mitochondrial cytopathy after multidisciplinary review, discussion, and investigation.

Timeline

5 years prior to current presentation	Episode of myocarditis Non-obstructive coronary arteries Troponin peak at 236 mg/dL Late gadolinium enhancement on CMR
Over 3 years prior to current presentation	Relapsing and remitting mild heart failure signs and symptoms
Day 1	Worsening dyspnoea, new chest pain and presyncope Non obstructive coronary arteries Late gadolinium enhancement on CMR Troponin 204
Day 3	Progressive troponin rise to 600 Methylprednisolone pulse therapy
Day 10	Progressive troponin rise to 1380 Second methylprednisolone pulse therapy
Day 14	Progressive troponin rise to 1800 No change in symptomology or signs of heart failure Discharge home after
By 2 weeks post-discharge	Genetic testing positive for m.3243A>G

Case Presentation

A 70-year-old woman of Chilean origin was admitted for investigation of recurrent troponin-positive chest pain and new peripheral oedema. There had been a presentation five years prior with chest pain, troponin-T elevation to 236 mg/dL at peak, non-obstructive coronary anatomy on invasive angiography, reduced ejection fraction at 40% and lateral mid-wall late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging (CMR), with corresponding tissue oedema and inflammation by T1- and T2-tissue-weighted imaging. The diagnosis of undifferentiated myocarditis was made. Medical background included type 2 diabetes mellitus, diagnosed 15 years previously, managed with metformin and empagliflozin, and bilateral sensorineural hearing impairment of moderate severity, onset age 50 years. There was no family history of deafness, diabetes, seizures, or stroke. There were no other systemic or neurological signs or symptoms at the time of this presentation. From this initial presentation, the symptoms of heart failure resolved, the troponin normalised, and the patient was lost to follow up, having been commenced on heart failure therapy with perindopril 2.5 mg daily, bisoprolol 2.5 mg daily, and frusemide 40 mg daily.

The patient represented five years later with dyspnoea on minimal exertion, pre-syncope, angina, and reported several episodes of remitting and relapsing dyspnoea and ankle oedema over the preceding three years. Systems review was relevant for a reduced level of mobility of gradual onset over the preceding months. The cardiovascular examination was unremarkable apart from a degree of bipedal oedema. Electrocardiogram (ECG) showed sinus rhythm with broadened QRS complex in a typical left-bundle-branch-block pattern, with a QRS duration of 130 ms. Severe acute respiratory syndrome coronavirus 2 by reverse transcription polymerase chain reaction testing was negative. Initial echocardiogram showed mild concentric hypertrophy with moderate global impairment of systolic function, without valvulopathy. Global longitudinal strain was reduced -10.5%. With non-obstructive coronary disease on repeat invasive angiography, the patient proceeded to CMR, corroborating moderate impairment of left-ventricular (LV) systolic function and normal right-ventricular systolic function, with an LV ejection fraction of 40%. There were multiple areas of increased oedema on T2-weighted imaging and scar, with LGE uptake in the basal inferolateral wall and septum in a mid-wall pattern (*Figure 1*). Right heart catheterisation performed after effective diuresis demonstrated a pulmonary capillary wedge pressure of 14 mmHg, mean pulmonary artery pressure of 18 mmHg, right atrial pressure of 13 mmHg, a transpulmonary gradient 6 mmHg and systemic vascular resistance of 3.5 Wood units. The measured cardiac output was complicated by the fact that the patient went into complete heart block with haemodynamic collapse just prior to measurement with further right heart catheterisation assessment not pursued. The calculated cardiac output was 1.3 L/min with a cardiac index of 0.9 L/min/m^2. The high degree atrio-ventricular block did not recur and did not require further treatment. Serum lactate undertaken at the time of right heart catheterisation was found to be elevated at 4.0 mg/dL. Repeat lactate levels subsequently showed fluctuations between 2 and 4 mg/dL (normal range <2 mg/dL). Troponin-T was 1380 mg/dL at day 10 of admission, *n* terminal pro-brain natriuretic peptide was 3160 ng/L (normal range <200 ng/L) and creatine kinase was normal. Serum creatinine was 90 mmol/L (normal range <100 mmol/L) and there were no concomitant fluctuations in renal function through the admission.

Given the leading differential of inflammatory myocarditis, and the lack of viral prodrome or raised inflammatory markers to suggest a viral or bacterial aetiology, two courses of 1500 mg pulsed methylprednisolone in divided doses over days 3–5 and days 10–11 were administered. Despite this, a progressive rise in troponin-T was observed to 1380 mg/dL by day 10 and 1800 mg/dL by day 14 (*Figure 2*). A technetium-99 m pyrophosphate amyloid scan was negative for transthyretin cardiac amyloidosis, a combined positron emission tomography and computed tomography scan excluded cardiac sarcoidosis, whilst serum and urine protein electrophoresis excluded light chain amyloidosis. An endomyocardial biopsy showed non-specific myopathic changes of variable myocyte atrophy, hypertrophy, and minimal interstitial fibrosis.

In summary, the patient manifested troponin elevations with active myocardial injury and moderate LV functional impairment without a clear cause, and treatment with high-dose pulsed steroids for presumed myocarditis did not suppress myocardial injury. Throughout the admission, the patient remained hemodynamically stable with clinically mild heart failure.

The patient was noted to have a reduced level of mobility, with a wide-based gait and reduced proximal limb girdle strength (Medical Research Council grade 4/5), but did not have other features of frailty or sensory neurological findings. Given the constellation of unexplained cardiomyopathy and proximal limb weakness, consideration was then given to a generalised myopathic process. Neurological assessment was undertaken. Electromyography supported a myopathic process, without the characteristic features of myotonia, and no neuropathy was found on nerve conduction studies. Magnetic resonance imaging (MRI) brain demonstrated marked periventricular deep white matter and white matter subcortical and supratentorial T2/FLAIR hyperintensities. Basal ganglia calcification and global cerebral, brain stem and cerebellar volume loss were noted. MRI of the thighs showed bilateral symmetric muscle oedema and diffuse wasting. Genetic testing was negative for myotonic dystrophy types 1 and 2.

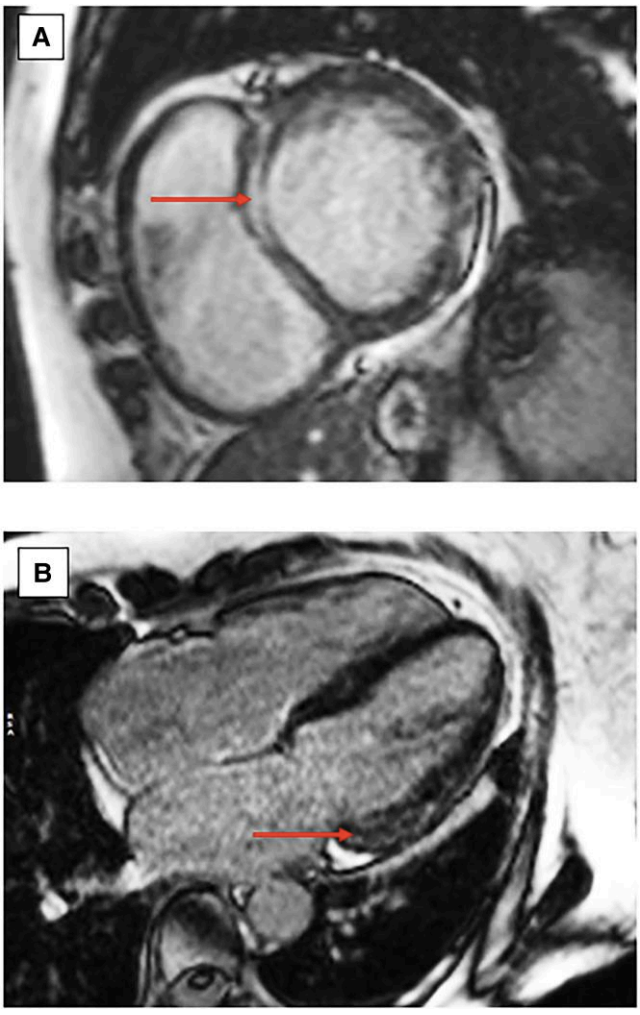

Figure 1 Representative axial (*A*) and long axis (*B*) cardiovascular magnetic resonance imaging demonstrating septal (*A*) and basolateral (*B*) late gadolinium enhancement (arrow).

Given the patient was of Chilean descent, the possibility of a Chagas cardiomyopathy due to *Trypanasoma cruzi* was considered. Chagas cardiomyopathy is characterised by segmental wall motion and CMR abnormalities typically involve the apical and inferolateral walls, with predilection for apical aneurysm formation and thrombus, probably secondary to microvascular disturbance and chronic myocarditis.[2,3] In contrast to these findings, our patient had relative apical sparing in terms of wall motion, and fibrosis involved the basolateral wall and basal septum. Eventually, negative *T. cruzi* serology excluded Chagas cardiomyopathy.

The constellation of cardiomyopathy, skeletal myopathy, extensive white matter changes, basal ganglia calcification, diabetes, sensorineural hearing impairment, and elevated serum lactate prompted consideration of a mitochondrial cytopathy. With autoimmune serological testing being positive for anti-polymyositis and scleroderma proteins, the differential diagnosis included autoimmune skeletal and cardiac myositis. A left quadriceps muscle biopsy was stained with a panel of routine, histochemical, and immunohistological stains. The muscle contained numerous angular atrophic esterase-positive (denervated) myofibers, a few scattered COX-deficient myofibers with a disorganised mitochondrial pattern, but fewer than 1% of COX-negative myofibers overall (*Figure 3*). These mitochondrial changes are within normal limits for this age.[4] Of note, muscle histopathology can be normal in genetically proven mitochondrial cytopathies, which should, therefore, not be excluded based on a negative striated muscle biopsy alone, particularly if denervated myofibers are present.[5,6] The large number of denervated myofibers present suggest this mitochondrial mutation caused an intramuscular neuropathy rather than a clinical striated muscle myopathy.

Genetic testing of 125 genes associated with myopathy, including 88 nuclear genes and 37 mitochondrial genes, demonstrated a pathogenic mutation in the mitochondrial genome, *MT-TL1* m.3243A>G, at a heteroplasmic level of 18% in buccal cells and 64% mutational load in the striated muscle cells, confirming the diagnosis of a mitochondrial cytopathy.

Discussion

Mitochondrial disorders are a group of genetic conditions that occur secondary to a mutation that affects the mitochondrial respiratory chain function.[1,5,6] Depending on the locus of the pathogenic mutation, they can exhibit either a Mendelian inheritance, when the nuclear genome is implicated or mitochondrial inheritance, when the

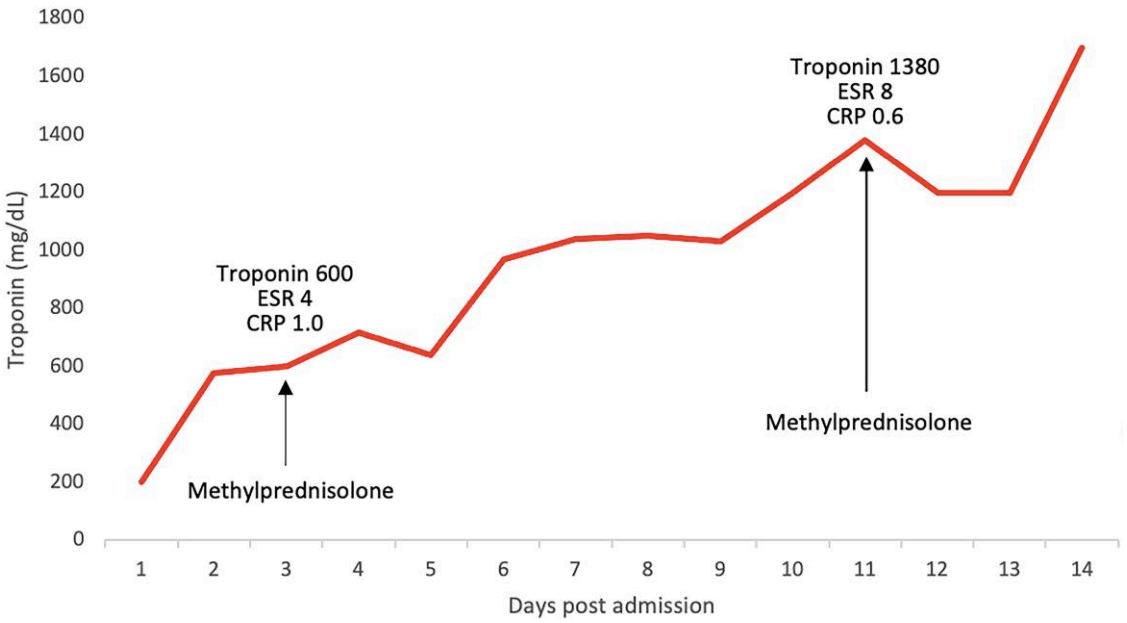

Figure 2 Troponin-T levels during hospital admission. *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate.

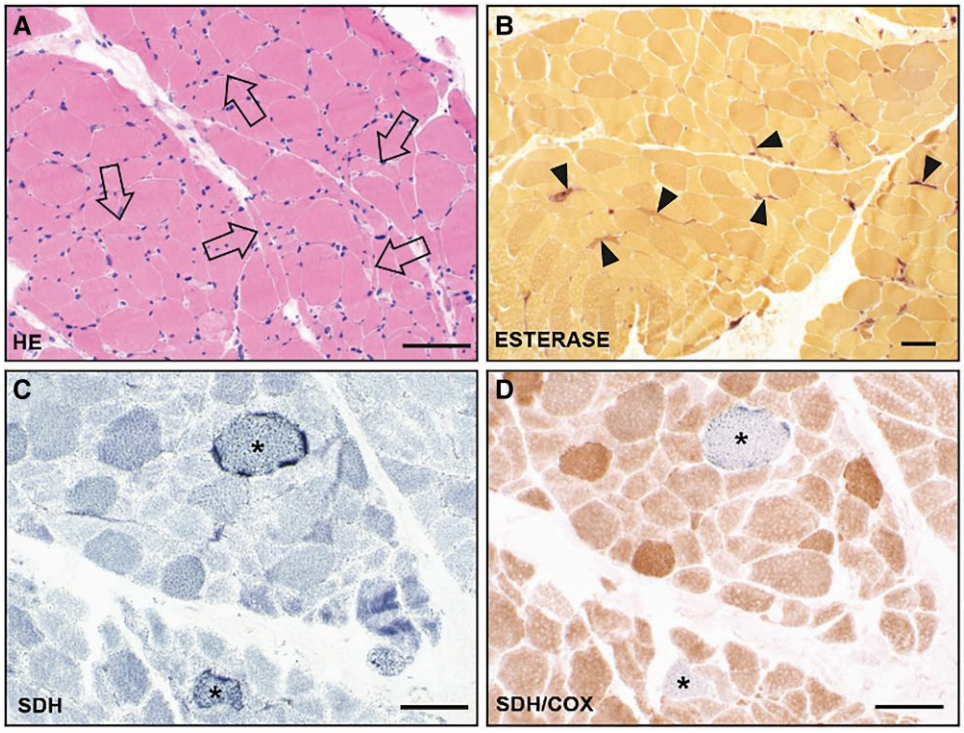

Figure 3 Histopathology of striated (left thigh) muscle biopsy. *(A)* Hematoxylin and eosin (HE) staining shows numerous angular atrophic myofibres (e.g. arrows). *(B)* Non-specific esterase histochemistry shows dark staining of angular atrophic myofibres (arrowheads) indicating the presence of denervated myofibres. *(C)* Succinate dehydrogenase (SDH) histochemistry shows two myofibres with sub-sarcolemmal accumulation of mitochondria (as seen in 'ragged-red' myofibres). *(D)* Combined cytochrome *c* oxidase (COX) histochemistry and SDH (asterisk) shows the same two myofibres are COX-deficient.

mitochondrial genome is implicated. In mitochondrial inheritance, disorders are passed down to offspring from their affected mothers only, via egg cells that carry mutant mitochondria. Mitochondrial heteroplasmy is due to random segregation of mtDNA at cell division; the varied mutational load can be present in different cells and tissues, generating varying severity of end-organ dysfunction, even within the same individual.[1] When the level of mutant mtDNA exceeds a threshold for a particular tissue, cell dysfunction ensues and symptoms manifest.[1] Consistent with this, our patient exhibited 64% heteroplasmic level of mutant mtDNA in her muscle biopsy sample, thus accounting for her neuromuscular symptoms.

Clinical presentations and symptom severity can vary depending on the mutant mtDNA heteroplasmic level within each tissue/organ and between different family member, which can range from being asymptomatic, to having oligo-system manifestations, or to multi-system severe disease involving endocrine, musculoskeletal, neurological, and cardiovascular systems.[6] Our patient carried the most common mutation associated with mitochondrial disease, *MT-TL1* m.3243A>G, which manifests a wide range of clinical phenotypes, including mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), maternally inherited diabetes and deafness, as well as (less commonly) myoclonic epilepsy with ragged red fibre, Leigh syndrome, and Kearns–Sayre syndrome[6]

Cardiac manifestations of mitochondrial cytopathies include both structural arrhythmogenic abnormalities and tendencies towards atherosclerosis.[7] Abnormal ECGs and echocardiograms are found in up to 35% and 30% of patients respectively, occurring more commonly in patients with MELAS than other conditions.[7] LV hypertrophy is the most common abnormality, being present in up to 50% of patients with MELAS.[7] When LV systolic impairment occurs it typically presents with diffuse rather than focal abnormalities.[8] Elevated troponin levels in mitochondrial disorders are not consistently described in the literature, being present in between 1% and 13% of patients recruited for cardiac characterisation.[8–10] Cardiac MRI abnormalities are found in up to 50% of patients with mitochondrial cytopathy, with non-ischaemic LGE being most common.[11] Among these, patients with MELAS tend towards concentric hypertrophy relative to other mitochondrial diseases, with more diffuse at times patchy LGE, rather than showing a predilection for specific focal areas.[11] It is postulated that this represents replacement fibrosis secondary to dysfunction in the respiratory chain due to inherited mitochondrial abnormalities.[11] CMR may have advantages over standard echocardiography in patients with mitochondrial cytopathies by identifying these areas of fibrosis. This would allow earlier identification of patients at risk of cardiomyopathy or malignant arrhythmia.

The striking troponin elevation seen in our patient has to our knowledge not been described before in the literature among people with *MT-TL1* m.3243A>G, while the echocardiographic and CMR findings are in keeping with those described with this mutation.

Follow-up

In view of the diagnosis with a mitochondrial cytopathy, the patient's metformin was ceased, and she was commenced on Coenzyme Q10 supplementation alongside heart failure therapies, including the sodium-glucose cotransporter 2 inhibitor, empagliflozin. Her mobility and heart failure symptoms have improved and her cardiac function remains stable on echocardiography. Given the unchanged echocardiography findings, possibilities for the sub-clinical improvement in symptoms may be secondary to up-titrated heart failure therapies, more consistent preservation of euvolaemia or improved substrate for mitochondrial function with supplementation, which has been demonstrated to improve exercise capacity.[12] Interval improvement in symptoms between this presentation and that from 5 years previous may be attributed to commencement of heart failure therapies. This initial improvement may have masked ongoing subclinical disease. Further troponin-T evaluation was not performed after initial presentation due to unclear clinical utility.

The patient has two adult children, both of whom would be at risk of having inherited the *MT-TL1* m.3243A>G mutation from her with variable degrees of heteroplasmy.[6]

Predictive genetic testing was taken up by her 31-year-old daughter, who was pregnant at the time with her first child, to assist with her reproductive decision making. The daughter's testing showed a 0% mutational load in her urine sample, and she proceeded with her pregnancy (without prenatal testing) to successfully deliver a healthy baby.

Conclusion

The recurrent elevations of troponin seen in our patient have to our knowledge not been previously described in patients with *MT-TL1* m.3243A>G mutations. A poor response to steroid therapy and unexplained cardiomyopathy, together with systemic extra-cardiac manifestations, should prompt consideration of a mitochondrial cytopathy as an underlying diagnosis. Confirming a genetic mitochondrial diagnosis has important management and reproductive implications for patients and their families.

Lead author biography

Anish is been a physician trainee at St Vincent's Hospital in Sydney, Australia, with a strong interest in multimodal cardiac imaging and heart failure.

Supplementary material

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

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 consent has been obtained prior to submission of the article enclosed in accordance with COPE guidelines.

Funding: The authors have no funding to disclose.

Conflict of interest: None declared.

Data availability

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

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