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CASE REPORT
Heart failure

Adult-onset MELAS syndrome in a 51-year-old woman without typical clinical manifestations: a case report

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Background Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is a multi-organ disorder resulting from mitochondrial DNA (mtDNA) mutations. We report a case of suspected MELAS syndrome that progressed to left ventricular dysfunction 24 years after an initial diagnosis of atrioventricular block (AVB).

Case summary A 51-year-old woman was referred to heart failure clinic because of dyspnoea on exertion and progressive cardiomegaly. She had a dual-chamber pacemaker implanted for 24 years because of a high-degree AVB. She was treated for diabetes mellitus for 23 years and used hearing aids for 12 years because of sensorineural hearing loss. Transthoracic echocardiography revealed reduced left ventricular ejection fraction (26%), with increased thickness and unusual texture of the myocardium. The absence of abnormal findings on serum and urine protein electrophoresis suggested that light-chain amyloidosis was unlikely. In addition, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy revealed no definite uptake in the myocardium. Endomyocardial biopsy revealed a hypertrophy of myocytes in haematoxylin-eosin staining, and electron microscopy revealed a disarrangement of mitochondrial cristae, which were suggestive of mitochondrial cardiomyopathy. A mtDNA test detected the m.3243A > G mutation in the *MT-TL1* gene. According to these findings, MELAS syndrome was the most probable diagnosis despite the absence of common symptoms such as stroke-like episodes or lactic acidosis.

Discussion The patient had progressed to heart failure with reduced ejection fraction 24 years after the first cardiac manifestation. An identification of the mutation in the *MT-TL1* gene, indicative of MELAS syndrome, enabled the diagnosis of MELAS syndrome without typical manifestations.

Keywords Heart failure with reduced ejection fraction • Atrioventricular block • MELAS syndrome • Mitochondrial disease • Cardiomyopathy • Case report

ESC Curriculum 6.2 Heart failure with reduced ejection fraction • 2.2 Echocardiography

Learning points

- The m.3243A > G mutation of the *MT-TL1* gene is an indicative finding of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome, but typical manifestations may not be established because of the nature of mitochondrial disease.
- Endomyocardial biopsy and genetic testing could be helpful for differential diagnosis of dilated cardiomyopathy of unknown aetiology.

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Introduction

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is a multi-organ disorder resulting from mitochondrial DNA (mtDNA) mutations.[1] In addition to the common manifestations embedded in the name, histologic findings or genetic testing could help diagnose MELAS syndrome. We report a case of an adult woman without the typical manifestations who was diagnosed with MELAS syndrome based on findings from endomyocardial biopsy (EMB) and genetic testing that were indicative of MELAS syndrome.

Timeline

Date	Age	Clinical events
5 June 1997	27	Permanent pacemaker implantation due to a high-degree atrioventricular block
5 May 1998	28	Right total thyroidectomy due to papillary thyroid cancer
1998	28	First diagnosis of diabetes mellitus
1 October 2009	39	First use of hearing aid due to sensorineural hearing loss
25 September 2019 to 21 September 2021	49	Treatment for non-tuberculous mycobacteria lung disease
June 2021	51	Both upper limb paraesthesia with dyspnoea on exertion and referred to a heart failure specialist.
July 2021	51	Underwent diagnostic exams including transthoracic echocardiography, genetic test, and endomyocardial biopsy.

Case presentation

A 51-year-old woman was referred to a heart failure clinic for the evaluation of progressive cardiomegaly. She underwent dual-chamber pacemaker (Adapta ADD01 [the last generator change in 2015], Medtronic, MN, USA) implantation because of a high-degree atrioventricular block (AVB) 24 years ago and was followed up by an electrophysiology specialist. She was also treated for Type 2 diabetes mellitus for 23 years and underwent right total thyroidectomy for papillary thyroid cancer. She was taking subcutaneous insulin glargine 8 units once daily, metformin 1000 mg once daily, alogliptin 25 mg once daily, and glimepiride 4 mg once daily for Type 2 diabetes mellitus. Under these medications, her haemoglobin A1c level was 7.1%. She had been using hearing aids for 12 years after being diagnosed with sensorineural hearing loss and had been receiving antibiotic treatment, including azithromycin and ethambutol, for non-tuberculous mycobacterial lung disease for 2 years prior to this medical event. She had no family history of cardiac disease or genetic syndrome. A chest radiography revealed that her heart size increased progressively over the past 2 years (*Figure 1*).

When visiting a heart failure clinic, she complained of dyspnoea on exertion for 1 month. She also suffered from paraesthesia of her upper and lower extremities. Her blood pressure was 139/75 mmHg, and her pulse rate was 89 b.p.m. On physical examination, no abnormal finding other than a chronic ill-looking appearance was observed. A regular heartbeat without a murmur was observed, and her lung sounds were clear.

A transthoracic echocardiography revealed severe global hypokinesia of the left ventricle (LV) with an enlargement of the cardiac chambers (LV end-diastolic dimension was 56 mm); LV ejection fraction was estimated to be 26%. The myocardium showed a sparkling texture with fine bright particles, and the thickness of the interventricular septum and LV posterior wall increased to 11 mm from an echocardiography measurement of 7 mm in 2012. A small pericardial effusion was also noted. No valvular dysfunction was observed, except for Grade 1 mitral regurgitation. Mitral inflow showed a pseudonormalization pattern with elevated LV filling pressure (*E*/*e*′ 20.2) (see Supplementary material online, *Video*). Interrogation from her pacemaker showed a 100% ventricular pacing record with an underlying complete AVB rhythm, which suggested complete dependency on the pacemaker. Her thyroid function was within the normal range in laboratory tests, but her serum sodium level was slightly low (126 mmol/L), whereas N-terminal pro-B-type natriuretic peptide (1961 pg/mL; reference range, 0–249 pg/mL) and troponin-T (39 pg/mL; reference range, 0–14 pg/mL) levels increased. Urinary tests showed heavy proteinuria (spot urine protein-to-creatinine ratio, 7.22 g/gCr; albumin-to-creatinine ratio, 5811 mg/gCr). Urine electrophoresis of 24-h-collected urine showed non-selective proteinuria. A nerve conduction velocity study confirmed the presence of bilateral sensorimotor polyneuropathy.

Several diagnostic examinations were performed for cardiac amyloidosis or other infiltrative diseases. Screening tests for Fabry disease revealed normal α-galactosidase activity. Serum and urine immunofixation revealed no abnormal monoclonal band, and the ratio of serum kappa and lambda light chains was also within the normal range (1.0; reference range, 0.26–1.65). ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy showed no definite DPD uptake in the myocardium. Cardiac magnetic resonance imaging could not be carried out because of the old-generation pacemaker leads. Coronary angiography was performed to exclude ischaemic cardiomyopathy, and a concomitant EMB was performed to investigate the possibility of unusual cardiomyopathy or chronic myocarditis. Coronary angiography revealed no significant stenosis in either the right or left coronary artery systems. Myocardial tissue of the right ventricle was obtained and analysed. Haematoxylin-eosin staining showed hypertrophy of myocytes (*Figure 2A*), and an electron microscopy revealed a disarrangement of mitochondrial cristae (*Figure 2B*), which were compatible with mitochondrial cardiomyopathy; Congo red staining was negative. Genetic testing was performed to identify genes related to cardiomyopathy. Although common mutations known to cause dilated cardiomyopathy, such as those in *TTN*, *LMNA*, *MYH7*, and *TNNT2*, were not found in next-generation sequencing, the m.3243A > G heterozygote mutation of the *MT-TL1* gene was confirmed by Sanger sequencing (see Supplementary material online, *Figure S1*). However, no mutation of the *MT-TL1* gene was identified in her mother. Of note, the patient never suffered from stroke-like episodes, serum lactic acid levels were found to be within the normal range (1.5 mmol/L; reference range, 0.5–2.2 mmol/L), and she never complained about headaches or recurrent vomiting episodes during the recent follow-ups.

The patient was prescribed guideline-directed medical treatment for heart failure, including sacubitril-valsartan (49/51 mg twice a day), carvedilol (12.5 mg twice a day), spironolactone (12.5 mg once daily), and dapagliflozin (10 mg once daily). Although upgrade to cardiac resynchronization therapy could be considered, given the high dependency on pacemaker, it was not proceeded because the patient was tolerable without exacerbation of any heart failure symptoms. In addition, 1 year after being on the guideline-directed medical treatment, a transthoracic echocardiography showed improved LV ejection fraction from 26 to 46%, but the LV wall remained thick.

Discussion

MELAS syndrome is a maternally inherited multi-organ disorder resulting from mtDNA mutations.[1] MELAS syndrome is characterized by some common manifestations included in the syndrome's name:

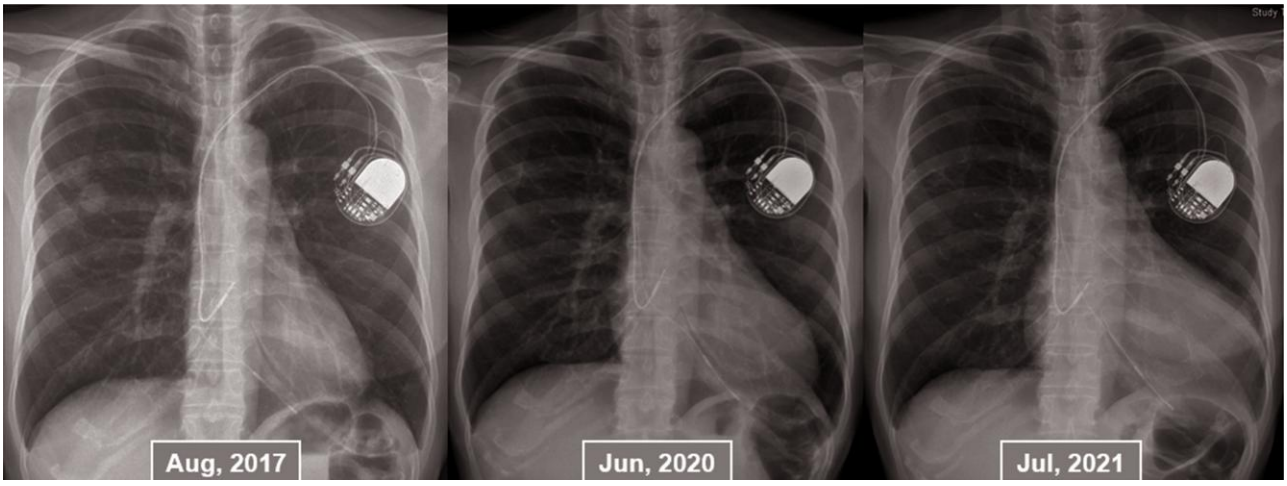

Figure 1 Serial chest radiography. Serial progression of cardiomegaly is observed. The presence of a dual-chamber pacemaker is noted.

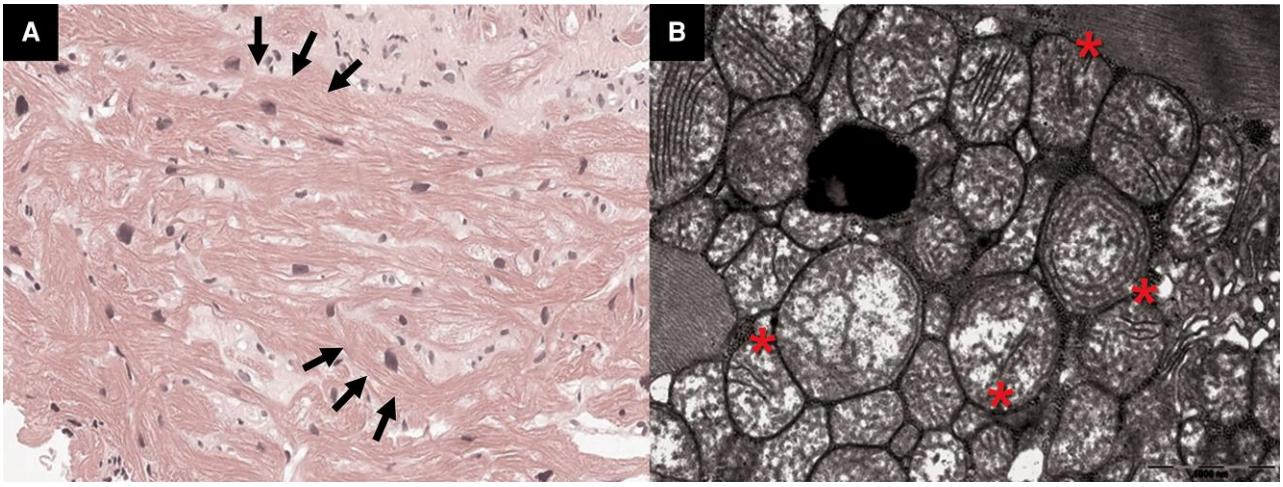

Figure 2 Histologic findings of the myocardium of the right ventricle obtained by endomyocardial biopsy. (*A*) Haematoxylin and eosin staining: hypertrophy of myocytes (black arrows) is observed; (*B*) Electron microscopy: a disarrangement of mitochondrial cristae (red asterisks) is observed.

encephalopathy, myopathy, stroke-like events, or elevated lactic acid level. Additionally, MELAS syndrome presents systemic manifestations. Other than stroke-like events or encephalopathy, recurrent headache, epilepsy, or hearing impairment can present as its neurologic manifestations. Diabetes or short stature is also one of the most common endocrinological manifestations of MELAS syndrome. Furthermore, as in this case, cardiomyopathy or conduction abnormality is a cardiac manifestation of MELAS syndrome.[1]

The prevalence of MELAS syndrome has been reported as 0.6–16 in 100 000 people; this figure varies based on the region.[2,3] Approximately 80% of patients with MELAS syndrome have the m.3243A > G mutation in the *MT-TL1* gene, which impairs mitochondrial protein synthesis, especially of the electron transport chain complex subunits.[4] Eventually, the mitochondrial capacity for energy production is impaired, leading to multiorgan dysfunction. Furthermore, nitric oxide (NO) deficiency occurs in mitochondrial disorders and is induced by the following two mechanisms. First, the activity of NO synthase is impaired because of additional oxidative stress from decreased energy production.[5] Second, *de novo* synthesis of NO donors (e.g. citrulline) from intestinal enterocytes decreases because of an energy shortage.[6] Nitric oxide deficiency of microvasculature results in angiopathy and perfusion impairment of organs.

According to previous studies, cardiac involvement has been reported in 18–30% of patients with MELAS syndrome.[7] It usually presents as cardiomyopathies, such as dilated cardiomyopathy and hypertrophic cardiomyopathy, or conduction abnormalities, such as Wolff–Parkinson–White syndrome and AVB.[1] In the case reported here, the patient complained of dyspnoea on exertion, and progressive cardiomegaly was noted. Finally, mitochondrial cardiomyopathy was confirmed by EMB, and genetic testing revealed the presence of the m.3243A > G mutation in the *MT-TL1* gene. Considering that her mother has the wild-type *MT-TL1* gene, the mutation is presumed to be sporadic. In addition to these confirmative key findings, the fact that the patient was suffering from cardiac diseases such as conduction abnormalities, endocrinological diseases such as diabetes mellitus, and sensorineural hearing loss over the past 25 years are pathognomonic findings of MELAS syndrome. According to these findings, the patient was highly likely to have

MELAS syndrome. Because past history including AVB leading to pacemaker implantation and hearing loss in young age are a generally rare feature among healthy population, further investigation for these morbidities should have been done. However, those symptoms and signs were not presented simultaneously, leading to difficulty in unifying those pieces of information into a single disease entity. By a retrospective systemic review after referral, we finally found the clue to evaluate the genetic background of the patient.

However, there are some concerns about her diagnosis. First, she never complained of neurological symptoms, including recurrent headaches, stroke-like episodes, and seizures, which are reported in over 90% of patients with MELAS syndrome. For clinical diagnosis of MELAS syndrome, two or more of the following three diagnostic criteria should be satisfied: (i) normal early psychomotor development, (ii) recurrent headaches, and (iii) recurrent vomiting episodes.[8] Further, her lactic acid level never increased. If these diagnostic criteria were strictly followed, diagnosing this patient with MELAS syndrome would be difficult.

Second, a differential diagnosis such as pacemaker-induced cardiomyopathy should be considered. Indeed, the patient was almost entirely dependent on her pacemaker, and it is possible that the pacemaker could have affected the myocardium and induced cardiomyopathy.[9] However, there is no reliable method to exclude pacemaker-induced cardiomyopathy from other aetiologies of cardiomyopathy. Given the above points, EMB and genetic testing should be performed to determine cardiomyopathy of unknown aetiology.[10]

The variability of the clinical manifestations of MELAS syndrome has not yet been fully understood. Heteroplasmy, in which mutant and wild-type mtDNA coexist within the same cell, is a key pathophysiology of mitochondrial disorders.[11] Each cell and organ has different mutational loads, leading to different degrees of dysfunction. Therefore, the clinical manifestations could also vary, even within families harbouring the same mutation.[12] In addition, recent research has reported that the copy number of mtDNA is a vital factor influencing disease severity in MELAS syndrome.[13] Although MELAS syndrome was named after its most common manifestations, theoretically, patients without typical symptoms could still exist because of the complex nature of mitochondrial disorders. As illustrated by this case, in patients with left ventricular dysfunction without a clear aetiology, a thorough medical history inquiry and a variety of tests for differential diagnosis, including genetic test, should be actively considered.

Lead author biography

Sang-Hyup Lee is a cardiology fellow at Severance Hospital, Yonsei University Medical Center, South Korea. He is interested in hemodynamics, circulations and nowadays also in interventional cardiology.

Supplementary material

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

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

Consent: The written consent for submission and publication of this case report containing images, videos, and laboratory data was obtained from the patient in line with COPE guideline.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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