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HEART FAILURE AND CARDIOMYOPATHIES

CASE REPORT: CLINICAL CASE

Successful Simultaneous Heart-Kidney Transplant in a Patient With *MT-TL1* MELAS Cardiomyopathy

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ABSTRACT

Here we describe the first reported case of a patient with *MT-TL1*:m.3243A>G MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes)-associated cardiomyopathy who successfully underwent simultaneous heart-kidney transplantation. (JACC Case Rep. 2024;29:102523) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 30-year-old man with MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) syndrome and biventricular cardiomyopathy presented to clinic because of repeated admissions for decompensated heart failure. On examination, the patient exhibited signs of heart failure, including jugular venous distention, peripheral edema, and rales on lung auscultation. Neurologic examination revealed muscle weakness and bilateral sensorineural hearing loss.

TAKE-HOME MESSAGES

- To understand the complexities of managing MELAS syndrome with multiple organ involvement.
- To recognize the potential of simultaneous heart-kidney transplantation in patients with mitochondrial disease.
- To acknowledge the need for further research and guidelines for transplantation in primary mitochondrial diseases.

PAST MEDICAL HISTORY

Pertinent history included Wolff-Parkinson-White syndrome, intellectual disability, left ventricular apical mural thrombus complicated by embolic phenomena and stroke, muscle weakness, short stature, delayed puberty, congenital left renal dysgenesis, and chronic kidney disease stage IV.

DIFFERENTIAL DIAGNOSIS

Diagnoses that were initially considered were Fabry's disease, given his renal involvement, and a *PRKAG2* variant associated with cardiomyopathy and Wolff-Parkinson-White syndrome. However, genetic testing later confirmed MELAS syndrome.

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ABBREVIATIONS AND ACRONYMS

MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

mtDNA = mitochondrial DNA

INVESTIGATIONS

Initial genetic testing included a comprehensive cardiomyopathy panel revealing a paternally inherited variant of unknown significance in *PLEKHM2*. Further testing, including trio exome with mitochondrial genome sequencing, identified a heteroplasmic maternally inherited pathogenic variant *MT-TL1*:m.3243A>G at 53% heteroplasmy from a peripheral blood draw.

MANAGEMENT

The patient was started on CoQ10 and arginine supplementation. Because of advanced heart and kidney failure, he underwent evaluation for heart and kidney transplantation, requiring outpatient milrinone infusion as a bridge to candidacy. He was not considered for a left ventricular assist device because of his renal dysfunction and cognitive impairment. Multiple transplant committee meetings determined he was an elevated but acceptable risk candidate for dual-organ transplantation.

A multidisciplinary meeting was held to plan the surgery and anesthesia, with specific measures to avoid lactic acidosis and cerebrovascular accidents. The multidisciplinary team also developed an emergency guideline to address and treat emergency situations such as stroke-like episodes. It was decided to use propofol for intravenous induction, with midazolam and fentanyl, and ketamine as needed for maintenance anesthesia. Perioperative management included the use of 10% dextrose-containing saline with intravenous insulin to prevent hypoglycemia and catabolism during fasting. An arginine infusion was maintained to mitigate metabolic complications.

The patient underwent a successful heart transplant, followed by a kidney transplant 15 hours later. Postoperative management included antiarrhythmia medications, prolonged inotrope wean, and intensive monitoring.

DISCUSSION

Primary mitochondrial diseases are diverse disorders caused by genetic variations in mitochondrial or nuclear DNA, resulting in impaired mitochondrial respiratory chain function and abnormal adenosine triphosphate production.[1] Common genetic changes include large-scale mitochondrial DNA (mtDNA) deletions and the m.3243A>G point variant.[2] These diseases often affect organs with high energy demands, such as the cardiovascular, renal, and neurologic systems.[3]

Cardiac involvement in mitochondrial disorders is significant. Kearns-Sayre syndrome is linked to cardiac conduction defects, myoclonus-epilepsy-ragged fibers syndrome often presents with asymmetrical septal hypertrophy, and MELAS syndrome can lead to hypertrophic or dilated cardiomyopathy, end-stage heart failure, or Wolff-Parkinson-White syndrome.[4] MELAS syndrome is maternally inherited and associated with pathogenic or likely pathogenic variants in mtDNA or inherited through Mendelian inheritance patterns.[1] The most frequent cause of maternally inherited MELAS syndrome is the adenine-to-guanine transition at position 3243 of the mtDNA in transfer RNA,[5] which was identified in the patient reported here. This syndrome is characterized by the presence of ragged red fibers on muscle biopsy, cardiomyopathy, renal failure, encephalopathy, lactic acidemia, embolic-like events, short stature, cortical blindness, and seizures.[4]

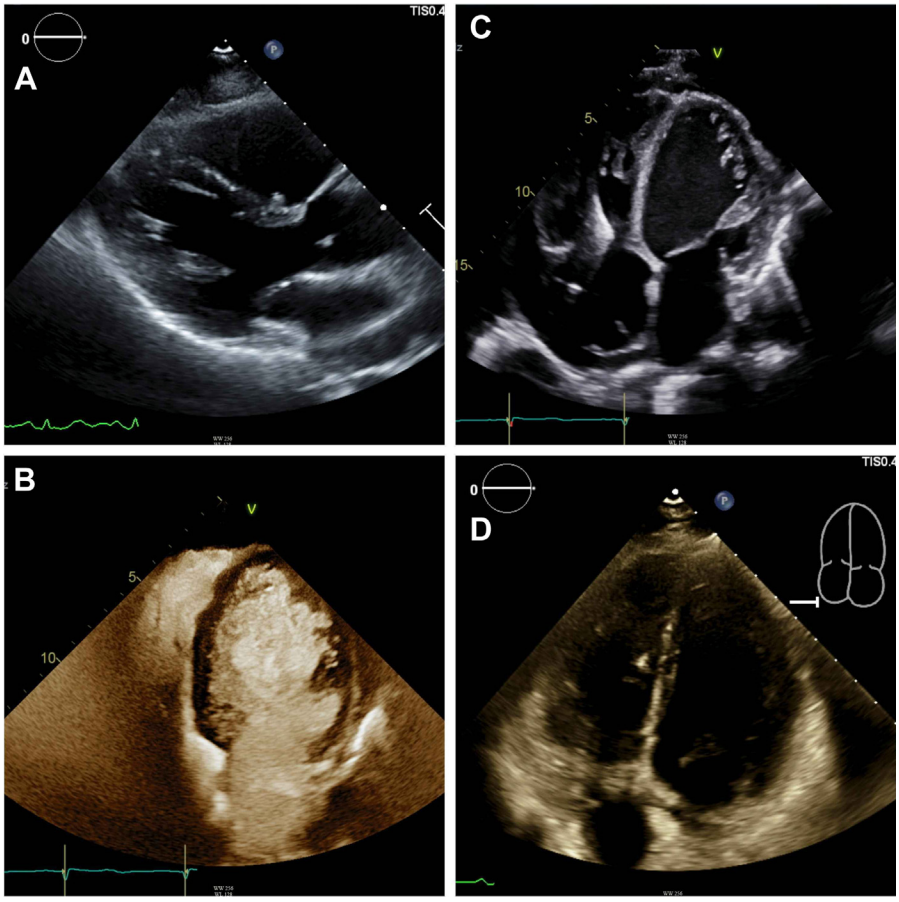
Although cardiac involvement is not a defining characteristic of MELAS syndrome, it can present as a severe and potentially life-threatening manifestation. The presence of hypertrophic, concentric, nonobstructive cardiomyopathy characterizes the cardiac phenotype in MELAS syndrome. This cardiac phenotype often progresses, leading to left ventricular dilation and dysfunction accompanied by systolic heart failure, similar to the features observed in dilated cardiomyopathy.[6]

In addition to cardiac involvement, our patient also presented with end-stage renal failure. Kidney involvement is a rare and late diagnosis of MELAS syndrome. The usual forms of renal dysfunction include focal segmental glomerulosclerosis, tubular disorders (such as Fanconi syndrome or in the form of salt-losing nephropathies), or end-stage renal failure.[7]

The management of patients with MELAS syndrome during a perioperative period poses significant challenges because of complications arising from the disease itself and potential fatal interactions with medical treatments. To mitigate these potential complications, a multidisciplinary guideline with specific indications was developed for our patient. The primary objectives were to ensure the correct administration of anesthetics, prevent extended fasting conditions, maintain an appropriate balance of oxygen supply and demand, minimize the risk of malignant hyperthermia, manage any metabolic acidosis, and treat stroke-like episodes.

For example, our patient experienced stroke-like episodes before transplantation, necessitating the administration of a bolus of intravenous arginine, followed by a continuous infusion of intravenous

FIGURE 1 **Pre- and Post-Transplant Echocardiogram**



(A and B) Pretransplant echocardiogram with a left ventricular ejection fraction of 5% to 10%. (C and D) Post-transplant echocardiogram with a left ventricular ejection fraction of 60% to 65%.

arginine over the next 5 days. Medications such as propofol, midazolam, fentanyl, dexmedetomidine, ketamine, or quetiapine were used to manage intubation or anxiety. Although technically MELAS patients are at a higher risk of complications with anesthesia, we believed that because the patient had tolerated these previously, rather than try different agents for potentially the first time, the risk was tolerable. Given the impaired lactate metabolism in MELAS patients, infusion solutions containing sodium lactate were avoided, and normal saline was used instead. To address the risk of hypoglycemia, dextrose-containing intravenous fluids were administered during periods of fasting or stress events (see the Supplemental Appendix for guidelines).

Current treatment strategies for the initial cardiovascular and kidney involvement are supportive,[4] and in cases of advanced heart or kidney failure, transplants have been described to prevent death.[8] Transplantation has been considered a viable treatment option for cardiac and kidney failure in MELAS syndrome.[8]

However, there is a theoretical concern that patients with mitochondrial disease may have a worse prognosis and higher mortality after solid-organ transplantation or may be influenced by certain immunopharmacologic agents used post-transplant.[8] Parikh et al[8] reported a cohort of solid-organ transplantation in primary mitochondrial disease. In the case of MELAS patients, at least 50% of cases showed disease worsening immediately after heart and kidney transplant, presenting symptoms such as seizures, strokes, myopathy, gastrointestinal dysmotility, and diabetes mellitus; however, they achieved a 100% of survival rate. A recently published Italian study looked at 14 patients ultimately diagnosed with

MELAS from the *MT-TL1*:m.3243A>G variant, and although 10 were ultimately listed for transplant, none proceeded with transplant because of multiorgan failure from disease progression.[9] Savvatis et al[3] studied 600 adult patients from a multicenter registry with genetically confirmed mitochondrial disease in which 208 had the *MT-TL1*:m.3243A>G variant, 29 developed a heart failure major adverse event, and 2 ultimately underwent cardiac transplant. To our knowledge, we believe our patient is the first diagnosed with *MT-TL1*:m.3243A>G MELAS who successfully underwent simultaneous heart-kidney transplantation.

Unfortunately, patients with primary mitochondrial disease may have a shortened life expectancy because of the expected progression of their underlying disease. Successful organ transplantation, when feasible, allows for additional years of likely functional survival.[9] However, there are currently no guidelines for simultaneous solid-organ transplant in patients with mitochondrial disease, such as MELAS syndrome. Nevertheless, there are patients like ours who could benefit from a simultaneous transplant to avoid early mortality.

FOLLOW-UP

Fifteen months post-transplant, the patient remained stable and compliant with his medication regimen, including immunosuppressive therapy with tacrolimus, mycophenolate mofetil, and prednisone. He experienced 1 early donor-specific antibody episode that resolved, and biopsies showed no significant rejection. The patient's left ventricular ejection fraction after transplant was 60% to 65% (**Figure 1**).

CONCLUSIONS

Patients with mitochondrial disease, like our patient with MELAS syndrome, can have good survival rates post-transplantation, with treatable post-transplant complications. This case highlights the need for further research and development of guidelines for solid-organ transplantation in primary mitochondrial diseases.

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Dr John has received a research grant from Abbot Medical, which is not relevant to this current submission. Dr Alexy is part of the Speakers Bureau for Abbott Inc, scPharmaceuticals, and Endotronics, which are relevant to this current submission; and is a consultant for scPharmaceuticals, which is not relevant to this current submission. Dr Cogswell is part of the Speakers Bureau and a consultant for Abbott Inc, which is not relevant to this current submission; and is a consultant and advisory board member for Medtronic, which is not relevant to this current submission. Dr Maharaj is part of the Speakers Bureau for Pfizer, which is not relevant to this current submission. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS heart failure, kidney failure, MELAS, transplant

APPENDIX For a supplemental appendix, please see the online version of this paper.