The Heart Is Just a Muscle

Robert W. McGarrah, MD; Tariq Ahmad, MD, MPH; Dwight D. Koeberl, MD, PhD; Chetan B. Patel, MD

Foreword

Information about a real patient is presented in stages (boldface type) to expert clinicians (Dr Chetan B. Patel, heart failure cardiologist, and Dr Dwight D. Koeberl, medical geneticist) who respond to the information and share their reasoning with the reader (regular type). A discussion by the authors follows.

A 25-year-old white woman was referred to the outpatient cardiology clinic at our institution for a second opinion regarding a newly diagnosed cardiomyopathy. She was in a normal state of excellent health, without a significant past medical history, when she began to develop exertional fatigue, dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Her primary care provider diagnosed her with pneumonia. The following day she developed severe, cramping pain in her right leg associated with paresthesias. Physical examination was notable for a heart rate of 97, blood pressure of 100/70, and body mass index of 18.1. She was remarkable for aortic dissection in her father at 49 years of age but otherwise was without cardiovascular disease. Her family history was remarkable for aortic dissection in her father at 49 years of age but otherwise was without cardiovascular disease. Physical examination was notable for a heart rate of 97, blood pressure of 100/70, and body mass index of 18.1. Her jugular venous pressure was estimated at 10 to 12 cm of water. She had an audible S3 gallop without murmurs and no lower extremity edema. ECG showed normal sinus rhythm with bialtrial enlargement and a QRS duration of 84 ms.

Dr Patel: The patient is presenting with New York Heart Association functional class II to III symptoms and echocardiographic evidence of a dilated cardiomyopathy. Although she did not undergo an ischemic evaluation on initial presentation, she has no obvious risk factors for coronary artery disease, so this likely represents a nonischemic cardiomyopathy. The differential diagnosis is broad; for example, in a review of ≈1200 patients with initially unexplained cardiomyopathy who underwent endomyocardial biopsy, half had no cause identified (ie, idiopathic cardiomyopathy) during follow-up. Those with identifiable causes had myocarditis (9%), ischemic heart disease (7%), infiltrative disease (5%), hypertension (4%), connective tissue disease (3%), and substance abuse (3%). Among patients with idiopathic dilated cardiomyopathy, clinical screening of family members can diagnose a familial cause in ≤50%. The arterial thromboembolic event may be unrelated to her cardiac issues; however, heart failure with systolic dysfunction increases the risk of thromboembolism and a LV thrombus or predisposing atrial arrhythmia should be ruled out. While attempting to identify an underlying, possibly reversible, etiology, it is important to initiate optimal medical therapy for heart failure as was done in this case. The next diagnostic step could include cardiac magnetic resonance (CMR). CMR would allow for better characterization of the myocardium and would rule out ischemic disease. In addition to detailed morphological assessment (mass, size, function), gadolinium contrast enhancement techniques can identify and characterize areas of myocardial scar and fibrosis, the pattern of which may suggest specific etiologies.

Patient presentation (continued): The patient was referred for CMR, which revealed a mildly dilated LV with mild concentric LV hypertrophy, a LV EF of 32%, no LV mass or thrombus, normal right ventricular size and function, mild mitral regurgitation, and no other significant valvular abnormalities. Stress perfusion imaging was negative for ischemia. Delayed enhancement imaging for viability was abnormal with diffuse myocardial delayed enhancement preferentially involving the midmyocardium.

Dr Patel: The delayed enhancement pattern suggests myocarditis, whether viral-induced or secondary to another process (eg, connective tissue disease). Cardiac amyloidosis is also a consideration but typically involves the subendocardium and generally presents in an older patient population;

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however, hereditary forms (transthyretin deposition) may be seen in a younger age group and have variable imaging findings. The findings are not suggestive of sarcoidosis, which tends to have more focal enhancement. The role of endomyocardial biopsy (EMB) to aid in the diagnosis of new-onset heart failure is controversial, and major society guidelines recommend against this procedure in the routine evaluation of patients with heart failure.2–5 However, certain myocardial disorders have unique prognoses and treatments necessitating the need for EMB in situations where the diagnostic benefits outweigh the procedural risks (Table 1).2 Based on the diffuse findings of her CMR and the lack of significant improvement in her symptoms, proceeding with EMB is reasonable.

**Patient presentation (continued):** She was referred to the cardiac catheterization laboratory for EMB. This revealed marked myocardial hypertrophy without apparent disarray and multifocal myocardial degeneration (Figure 1). There were nonspecific ultrastructural findings, including increased free and vacuolar glycogen stores without dense inclusions more typical of glycogen storage disorders; prominent focal myocyte nuclear membrane proliferation; nonspecific mitochondrial changes typical of end-stage heart failure; and no light chain or complement deposition. Immunofluorescence showed mild diffuse capillary IgM; and trace focal IgG, κ- and λ-light chain, and complement C3. Special stains were negative for amyloid and there was no evidence of sarcoid or active myocarditis. The biopsy was not reviewed under electron microscopy.

**Dr Patel:** Overall, the pathological findings are nonspecific and do not strongly indicate a specific form of cardiomyopathy. Many of the findings can be observed in hypertrophic myocytes, and the degeneration can be seen in cardiomyocyte stress and failure. Only rare lamellated bodies are not sufficient to suggest Fabry disease. The immunofluorescence findings and lack of active myocarditis do not support lupus carditis. The increased IgM deposition along interstitial capillaries with slight C3 and κ and λ can be seen in mixed cryoglobulinemia; however, this deposition may only be in response to injury and degeneration. Based on her CMR and histological findings, and her demographic (young white female), the

<table>
<thead>
<tr>
<th>Scenario Number</th>
<th>Clinical Scenario</th>
<th>Class of Recommendation (I, IIa, IIb, III)</th>
<th>Level of Evidence (A, B, C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New-onset heart failure of &lt;2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure of &gt;3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Heart failure associated with a dilated cardiomyopathy of any duration associated with suspected allergic reaction and eosinophilia</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Heart failure associated with suspected anthracycline cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
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<td>6</td>
<td>Heart failure associated with unexplained restrictive cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
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<tr>
<td>7</td>
<td>Suspected cardiac tumors</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>Unexplained cardiomyopathy in children</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>9</td>
<td>New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1–2 wk</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>Heart failure of &gt;3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1–2 wk</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>Heart failure associated with unexplained hypertrophic cardiomyopathy</td>
<td>IIb</td>
<td>C</td>
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<tr>
<td>12</td>
<td>Suspected arrhythmogenic right ventricular cardiomyopathy</td>
<td>IIb</td>
<td>C</td>
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<tr>
<td>13</td>
<td>Unexplained ventricular arrhythmias</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>14</td>
<td>Unexplained atrial fibrillation</td>
<td>III</td>
<td>C</td>
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etiology of her cardiomyopathy is likely due to previous viral myocarditis.

Patient presentation (continued): For the year after initial presentation, her symptoms remained stable, New York Heart Association class II to III, including ongoing fatigue requiring daily naps and exertional dyspnea. Repeat transthoracic echocardiography demonstrated a persistently depressed EF of 35%. Her carvedilol was uptitrated, and she was started on a low-dose angiotensin receptor blocker and an aldosterone antagonist. Further titration of heart failure medication was limited by hypotension. She underwent implantation of a single-chamber implantable cardioverter-defibrillator for primary prevention.

Dr Patel: Despite a maximally tolerated heart failure medical regimen, her symptoms did not significantly improve nor did her ventricular function as measured by EF. Fortunately, she has remained clinically stable without hospitalizations for heart failure. Unfortunately, she is unable to tolerate guideline-recommended doses of standard heart failure medications (β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aldosterone antagonists) which is an indicator of patients with more severe disease and with a worse short-term prognosis. In general, several factors have been associated with failure of myocardial recovery in recently diagnosed nonischemic dilated cardiomyopathy including lower baseline EF, higher baseline LV diameter in diastole, black race, and higher New York Heart Association functional class. In 1 large prospective study, transplant-free survival in these patients was favorable at 88% over 4 years; higher New York Heart Association functional class and black race portended a higher risk of death/transplantation over this time period, whereas female sex was associated with a lesser risk. Several risk score calculators exist to determine the prognosis in patients with chronic systolic heart failure that can help to determine the timing of referral for consideration of advanced heart failure therapies such as left ventricular assist device (LVAD) or cardiac transplantation. One such calculator is the Seattle Heart Failure Model that takes into account numerous clinical, hemodynamic, and laboratory parameters. Based on this model, the patient has a 1-, 2- and 5-year expected survival of 96%, 92%, and 78%, respectively. Referral to an advanced heart failure specialist could be considered based on her anticipated clinical course and her likely good candidacy for transplantation. Implantation of an implantable cardioverter-defibrillator is appropriate at this stage given her lack of recovery of EF on medical therapy. She is not a candidate for cardiac resynchronization therapy based on her QRS duration, although her sex and nonischemic etiology would favor a positive response to cardiac resynchronization therapy.

Patient presentation (continued): On the next follow-up visit 3 months later, she reported a significant change in her symptoms. She had developed intermittent nausea with decreased appetite. She noted more frequent paroxysmal nocturnal dyspnea and increasing orthopnea, and she was often experiencing dyspnea at rest. Lung examination had decreased breath sounds at the bases and dullness to percussion. Her N-terminal probrain natriuretic peptide was elevated to 2713 pg/mL. Transthoracic echocardiography demonstrated an EF of 20% with an increasing LV dimension. She subsequently underwent cardiopulmonary exercise testing (CPET). This revealed a peak oxygen consumption (VO₂) of 7.3 mL·kg⁻¹·min⁻¹ (17% of predicted) and a V̇E-V̇CO₂ slope of 58.4. She was referred to the advanced heart failure clinic. A right heart catheterization revealed a right atrial pressure of 8 mmHg, pulmonary arterial pressure of 43/20 mmHg with a mean pressure of 29 mmHg, and a pulmonary capillary wedge pressure of 16 mmHg. She had a severely depressed cardiac output of 2.6 L/min (cardiac index 1.76 L·min⁻¹·m⁻²).

Dr Patel: The rapid change in her symptoms is suggestive of decreased perfusion and worsening congestion. This is confirmed by her CPET and right heart catheterization that demonstrate severe functional impairment and a severe reduction cardiac index that qualifies as cardiogenic shock. Peak VO₂, in particular, is a useful indicator of patients who can continue on medical therapy versus those who should be considered for advanced therapies. In general, in patients receiving medical therapy for heart failure, including β-blockers, a peak VO₂ cutoff of 10 to 12 mL·kg⁻¹·min⁻¹ is used. Overall, her symptom complex, severely depressed ventricular function, and markedly abnormal peak oxygen consumption suggests that she has a poor short-term prognosis and cardiac transplantation evaluation should be initiated. While awaiting cardiac transplantation, one could consider mechanical circulatory support, namely LVAD, as a bridge. Considerations when making a decision between cardiac transplantation and bridge-to-transplant LVAD therapy are numerous. Major considerations include the clinical stability to await a suitable organ, anticipated wait time at that center based on blood type, body size, and degree of allosensitization, and the presence of any immediate contraindications, as well, that could be corrected with LVAD support (ie, pulmonary hypertension). Other factors that may play a role in this decision include, of course, patient preference, anticipated tolerance of multiple sternotomy procedures, and the potential for myocardial recovery with LVAD support that would be negated with transplantation.

Patient presentation (continued): She was admitted to the hospital and was listed for cardiac transplantation, status 1B. She underwent cardiac transplantation without immediate complications 1 month later. Postoperative transthoracic echocardiogram showed an EF >55% with normal right heart function. Routine posttransplantation EMB demonstrated multifocal moderate acute cellular allograft rejection. She was treated with several days of pulsed high-dose steroids and discharged on a standard immunosuppressive regimen that included mycophenolate, tacrolimus, and a prolonged oral prednisone taper. Subsequent follow-up visits included normal allograft function by echocardiography and resolved cellular rejection on EMB. She returned to the cardiac transplant clinic 4 months posttransplantation for an unscheduled appointment owing to progressive weakness, fatigue, exertional dyspnea, and abdominal fullness.
Dr Patel: Her presentation is concerning for allograft rejection, which occurs in ≤30% of patients within 1 year after transplantation. She has several characteristics that place her at increased risk for rejection including female sex, young age, time interval since transplantation, and a previous episode of rejection. Because routine surveillance such as EMB and echocardiography, many patients with allograft rejection are asymptomatic. Symptoms to suggest rejection include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, presyncope/syncope, arrhythmias, or gastrointestinal symptoms due to bowel/hepatic congestion. Another possible cause for her symptoms is medication side effect. Her immunosuppressive agents—tacrolimus, mycophenolate, prednisone—can cause a variety of symptoms, including those she is experiencing; however, medication side effects are a diagnosis of exclusion. I would recommend right heart catheterization and EMB to exclude allograft rejection.

Patient presentation (continued): She was referred for urgent transthoracic echocardiogram, right heart catheterization, and EMB. These revealed normal LV and right ventricular function, normal filling pressures with preserved cardiac output, and no evidence of rejection on pathology. She continued to report ongoing and progressive fatigue during cardiac rehabilitation, difficulty walking up stairs and performing chores around the house. Pravastatin was discontinued, and mycophenolate was switched to azathioprine without resolution of these symptoms.

Dr Patel: With a cardiac etiology of her progressive symptoms ruled out, and with no improvement despite the discontinuation of potential offending medications, a more systemic process must be considered at this point and the diagnostic approach must be broadened. A full infectious workup should be performed to evaluate for community-acquired, opportunistic, and donor-derived infections. The risk of infection by specific pathogens changes according to the particular posttransplant interval. Early infections within the first month include nosocomial organisms such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococcus, and Candida species that are often related to the surgery and incisions, and donor-derived (herpes simplex virus) and recipient-derived (Aspergillus, Pseudomonas) infections, as well. From 1 to 6 months activation of latent infections (Mycobacterium tuberculosis, cytomegalovirus, Epstein-Barr virus) and opportunistic infections (Pneumocystis jirovecii pneumonia, hepatitis B and C viruses, endemic organisms such as Histoplasma capsulatum, Coccidioides spp, Cryptococcus gattii) predominate. After 6 months posttransplantation, patients are usually on a stable dose of immunosuppression and are therefore most susceptible to community-acquired pathogens. Her muscular concerns, generalized weakness, and fatigue could also suggest an inflammatory or rheumatologic process.

Patient presentation (continued): A comprehensive infectious workup was negative. Laboratory studies revealed an elevated creatine kinase level of >1000 U/L (normal 30–220 U/L), elevated aspartate aminotransferase, and elevated aldolase of 32.5 U/L (normal <7.6 U/L) suggestive of a myositis. Blood lactate levels were also elevated to 17 mmol/L (normal <2.5 mmol/L; previous level 9 months previously was 4 mmol/L) with an accompanying anion gap of 26. She was referred to rheumatology and her prednisone was increased for empirical treatment of presumed inflammatory myopathy. An electromyogram showed evidence of myositis in the upper and lower extremities. She was scheduled for a muscle biopsy. Pathological evaluation of the muscle biopsy was diffusely abnormal, with most fibers displaying markedly increased mitochondrial content by oxidative staining (Figure 2). Electron microscopic studies revealed mitochondria with widespread, marked morphological abnormalities, including large paracrystalline arrays in many mitochondria (Figure 3). The finding of type 1 fiber predominance indicated that this was a congenital disorder. There was no suggestion of an immune-mediated inflammatory myopathy or infectious process. Subsequent evaluation of her explanted heart showed increased numbers of abnormal mitochondria with dense inclusions (Figure 4).

Dr Patel: The presence of abnormal mitochondria in both cardiac and skeletal muscle is consistent with a primary mitochondrial disorder. This diagnosis unifies her presenting symptoms and her ongoing difficulties with exertional fatigue and generalized weakness.

Patient presentation (continued): She was referred to medical genetics specialty clinic for recommendations on additional testing and treatment options. Further review of her family history revealed recent onset of excessive fatigue in her sisters but otherwise was negative for cardiomyopathy, congenital anomalies, sudden death, multiple pregnancy...
losses, or known genetic disorders. There was no history of hearing loss, diabetes mellitus, neurological involvement including seizures and strokelike episodes, developmental delay, or consanguinity. Physical examination was notable for proximal muscle weakness and ptosis. Blood and muscle tissue samples were sent for mitochondrial genome analysis, electron transport chain testing, and coenzyme Q10 levels to confirm the diagnosis and aid in treatment planning.

Dr Koeberl: The patient has a mitochondrial myopathy based on Modified Walker criteria of progressive myopathy with weakness and exercise intolerance, abnormal muscle biopsy

Table 2. Modified Walker Criteria for the Diagnosis of Mitochondrial Disorders

<table>
<thead>
<tr>
<th>Major diagnostic criteria</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Clinically complete RC encephalomyopathy or a mitochondrial cytopathy defined as fulfilling all 3 of the following conditions:</td>
<td></td>
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<tr>
<td>- Unexplained combination of multisystemic symptoms that is essentially pathognomonic for a RC disorder. Symptoms must include at least 3 of the organ system presentations described elsewhere, namely neurological, muscular, cardiac, renal, nutritional, hepatic, endocrine, hematologic, ophthalmologic, dermatologic, or dysmorphic.</td>
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<tr>
<td>- A progressive clinical course with episodes of exacerbation (eg, after intercurrent illnesses) or a family history that is strongly indicative of a mtDNA mutation (at least 1 maternal relative other than the proband whose presentation predicts a probable or definite RC disorder).</td>
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<tr>
<td>- Other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing, which may include metabolite, enzyme, or mutation analyses, imaging, electrophysiological studies, and histology.</td>
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<tr>
<td>Histology</td>
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<td>&gt;2% ragged red fibers in skeletal muscle</td>
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<tr>
<td>Enzymology</td>
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<tr>
<td>&gt;2% COX-negative fibers if &lt;50 y of age</td>
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<tr>
<td>&gt;5% COX-negative fibers if &gt;50 y of age</td>
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<tr>
<td>&lt;20% activity of any RC complex in a tissue</td>
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<tr>
<td>&lt;30% activity of any RC complex in a cell line</td>
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<tr>
<td>&lt;30% activity of the same RC complex activity in ≥2 tissues</td>
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<tr>
<td>Functional</td>
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<tr>
<td>Fibroblast ATP synthesis rates &gt;3 SD below mean</td>
<td></td>
</tr>
<tr>
<td>Molecular</td>
<td></td>
</tr>
<tr>
<td>Identification of a nuclear or mtDNA mutation of undisputed pathogenicity</td>
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(Continued)
of the mitochondrial genome present in these disorders is not always detectable in blood, whereas mutation testing of muscle samples has greater sensitivity. In addition, to help tailor treatment, a very important reason to confirm the mutation is the risk to relatives, which is very high for maternal relatives in the case of mitochondrial encephalomyopathy, lactic acidosis, and strokelike or myoclonic epilepsy with ragged-red fibers syndromes, but very low for Kearns-Sayre syndrome.

General treatment considerations and precautions in patients with mitochondrial disorders include the avoidance of medications that cause mitochondrial dysfunction such as aminoglycosides, chloramphenicol, valproic acid, and barbiturates. Precautions must be taken during anesthesia, including avoidance of depolarizing agents and certain inhaled anesthetics such as nitrous oxide. Blood glucose and lactate levels should be routinely monitored and infusions of high-glucose content should be avoided.

**Patient presentation (continued):** Genetic test results confirmed a causative mutation in the mitochondrial DNA associated with mitochondrial myopathy/encephalomyopathy. Mitochondrial DNA analysis by next-generation sequencing of leukocytes revealed an 89.7% homoplasmic m.3303C>T (tRNA Leu) mutation in the ML-TL1 (mitochondrially encoded tRNA leucine 1) gene, which was homoplasmic in skeletal muscle.

Dr Koeberl: There have been only 4 previous reports (16 total cases) in the literature associating this mutation in the leucine transfer RNA (tRNA Leu) mitochondrial gene with cardiomyopathy. These reports described patients with a wide range of clinical phenotypes, including cardiomyopathy, encephalopathy, diabetes mellitus, and peripheral neuropathy. The clinical phenotypes vary widely among individuals, making it difficult to predict the specific manifestations of the disorder. Further research is needed to better understand the natural history and management of this rare disorder.
because of the nature of the inheritance of mitochondrial mutations and range from fatal infantile cardiomyopathy to asymptomatic LV hypertrophy to sudden cardiac death. Some patients have predominant myopathic symptoms, whereas others have no apparent skeletal muscle involvement. Overall, this patient’s clinical presentation with both cardiomyopathy and myopathy was consistent with the majority of previous reports of the m.3303C>T mutation; moreover, higher heteroplasmy >70% is more consistent with more severe clinical involvement.\textsuperscript{13–16} Treatment for such mitochondrial RNA mutations includes coenzyme Q10, creatine monohydrate, and α-lipoic acid.

**Patient presentation (continued):** After initiation of the above treatment, her myopathic symptoms improved. Her lactate and creatinine kinase levels decreased but remained chronically elevated on serial measurements.

Dr Koeberl: The primary therapy for mitochondrial myopathies is supportive. No clear evidence exists for pharmacological treatment, and current practice is based on limited clinical trial data and case reports. Evidence suggests that aerobic exercise improves mitochondrial function, increases peak work, prevents muscle deconditioning, and improves exercise tolerance. Long-term complications from a mitochondrial disorder include eye involvement, hearing loss, diabetes mellitus from insulin resistance, arrhythmias, seizures, and feeding intolerance, among others. Therefore, it is important to monitor for these effects by having medical evaluations and appropriate testing on a regular basis.

**Discussion**

Determining the cause of a newly diagnosed cardiomyopathy may help in prognostication and the guidance future therapy. The initial diagnostic workup should be guided by the epidemiology of various disease states, the results of laboratory-based testing, and noninvasive imaging. In this particular case, the etiology of the cardiomyopathy remained elusive after multiple diagnostic tests. Oftentimes, at this point in the diagnostic evaluation, a diagnosis of idiopathic nonscarring cardiomyopathy is made. Patients are started on evidence-based medical regimens and monitored for clinical improvement.

In this patient’s case, the characteristics of her CMR, and the failure to respond to standard therapy, as well, prompted the consideration of EMB to further pursue a potentially reversible etiology. According to current guidelines, she had a class IIa (level of evidence C) recommendation for EMB (Table 1).\textsuperscript{2} The EMB findings were nondiagnostic, likely because of the limited sampling area inherent in this procedure and the low diagnostic yield for many conditions, excluding those that result in global and transmural involvement such as amyloidosis or sarcoidosis. Moreover, functional studies such as cytochrome oxidase activity are not routine and thus were not performed on the biopsy samples owing to the lack of suspicion of a mitochondrial disorder.

As her symptoms continued to progress, subsequent studies that included CPET and right heart catheterization confirmed a diagnosis of profound cardiac failure. Cardiac transplantation at this juncture was likely lifesaving for the patient; those who progress to this advanced stage of disease have annual mortality rates approaching 50%.\textsuperscript{4} It was not until after her transplantation, when her fatigue and weakness continued to progress despite the correction of her heart failure, that an alternative or additional diagnosis needed to be considered. In retrospect, this worsening of symptoms was likely in large part due to the exposure to high-dose corticosteroids: immediately after transplantation, during her episode of early acute rejection and the subsequent prednisone taper, and during treatment of a presumed inflammatory myopathy. Corticosteroid therapy forms the cornerstone for treating episodes of acute rejection after cardiac transplantation and remains an effective strategy for T-cell suppression. Acute cellular rejection is the main target for immunosuppression in the posttransplant course and should be considered when the patient reports fatigue or a return of heart failure symptoms, even in the absence of decreased function by cardiac imaging. However, chronic corticosteroid administration has been shown to cause mitochondrial dysfunction in skeletal muscle with similar effects as seen in primary mitochondrial myopathies, such as increased circulating lactate during exercise and the impairment in respiratory chain subunit function.\textsuperscript{17} Evaluation into the causes of her muscle weakness led to a skeletal muscle biopsy that confirmed the diagnosis of a mitochondrial disorder. Although unlikely, it was possible that her cardiomyopathy and mitochondrial disorder were unrelated, so pathological examination of her explanted heart was critical to confirm a unifying diagnosis.

Mitochondrial diseases are a group of disorders caused by defects in the mitochondrial respiratory chain that impair oxidative phosphorylation. Therefore, organ systems that rely on aerobic metabolism are primarily affected. When skeletal muscle is involved, alone or in conjunction with other organ systems, the term mitochondrial myopathy is used. Although once considered rare, these disorders are being increasingly recognized with a prevalence of up to 13.1 per 100 000 births based on some studies.\textsuperscript{18} Myocardial tissue is highly dependent on mitochondria for energy production and is therefore highly susceptible to defects in mitochondrial function. Apparent isolated cardiac involvement in mitochondrial disorders has been described.\textsuperscript{19,20} A pathological analysis of 601 patients with idiopathic dilated cardiomyopathy who underwent endomyocardial biopsy revealed that 85 (14%) had ultrastructural evidence of abnormal mitochondria. Of these, 19 patients (22%) had mitochondrial DNA mutations that were found neither in 111 normal controls nor in 32 patients who had dilated cardiomyopathy without ultrastructural mitochondrial abnormalities.\textsuperscript{19} This study and others suggest that mitochondrial mutations may be an underappreciated cause of idiopathic dilated cardiomyopathy that should be considered in the evaluation of this condition, although the question remains whether these mutations are indeed causal or whether they are acquired during the process of gradual cardiac failure.\textsuperscript{21,22}

Because heart failure and peripheral myopathies share similar symptoms such as exertional fatigue, weakness, and dyspnea, the CPET can be helpful in distinguishing between these 2 entities.\textsuperscript{23} A cardiovascular pattern of VO\textsubscript{2} responses may represent impaired cardiac output or impaired peripheral
oxygen consumption as is observed in mitochondrial myopathies.24 The general physiological response to exercise in peripheral myopathies is an increase in cardiac output (Q) and ventilation (Ve). Therefore, the measurement of exercise cardiac output may help to distinguish these disorders from primary cardiovascular disease by demonstrating a high rather than low cardiac output relative to peak VO2.35 Based on this fact, calculation of the VO2/Q ratio and the slope derived from change in cardiac output and change in VO2 (ΔQ/ΔVO2) can be helpful. The findings on CPET of early fatigue during times of illness and physiological stress.

ongoing treatment will focus on standard maintenance and a primary mitochondrial myopathy offers a unique and formidable clinical scenario that requires heightened vigilance. The distinguishing findings on CPET that are typical of peripheral myopathies are obscured because of her profound cardiac insufficiency and low cardiac output. It was only after her heart failure was cured, via cardiac transplantation, and after she was exposed to mitochondrial-toxic medication that her myopathy became fully apparent.

This patient’s cardiomyopathy has been effectively treated with transplantation. Her prognosis is now dictated by her myopathy became fully apparent. Her heart failure was cured, via cardiac transplantation, and her underlying mitochondrial disorder, as well. The combination of cardiac transplantation and a primary mitochondrial myopathy offers a unique and challenging clinical scenario that requires heightened vigilance. Ongoing treatment will focus on standard maintenance and surveillance of her cardiac allograft, continued nutritional supplementation, aerobic exercise as tolerated, avoidance of mitochondrial toxins, and prevention of the worsening of her symptoms during times of illness and physiological stress.

Conclusion

Nonischemic cardiomyopathy is a common diagnosis among patients with systolic heart failure, and specific etiologies are often not identified despite extensive diagnostic testing. As this case demonstrates, suspicion for a systemic illness underlying newly diagnosed cardiomyopathy must exist for a diagnosis to be made. When symptoms persist despite definitive treatment, clinicians must broaden their view to consider conditions that may more completely explain the clinical data available. Clinical insights from rare cases such as these can shed light on heart failure pathogenesis, result in an improved understanding of disease mechanisms, and eventually lead to novel therapeutics.25

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Disclosures

None.

References


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