Circulation: Genomic and Precision Medicine

PERSPECTIVE

Frameshifts in Code and in Care

The Importance of Timely Genetic Evaluation

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In the coming years, remarkable advances in understanding the genetic underpinnings of rare and common disorders will transform the clinical care of patients with inherited cardiovascular conditions. Discoveries from genome-wide association studies, next-generation sequencing studies, and novel bioinformatics approaches have already revolutionized our diagnostic capabilities for monogenic and polygenic disorders. Translating and implementing this information into daily clinical practice lags considerably. We are confronting a significant genetics/genomics literacy gap in the clinical workforce that threatens to widen without dedicated efforts to address it. Here, we present a case that highlights the importance of a soliciting a minimum 3-generation family history in all cases of cardiomyopathy and the pitfalls of ordering genetic testing without a sufficient infrastructure for interpretation and return of results.

CLINICAL CASE

A 58-year-old woman was referred to our institution for management of recurrent atrial and ventricular arrhythmias. She first experienced palpitations at age 14 years, which were initially attributed to atrial arrhythmias and were well controlled on medical therapy. In her early 40s, they became refractory to antiarrhythmic medications. She underwent multiple electrical cardioversions and catheter ablations for atrial flutter, atrial fibrillation, and atrial tachycardia with a decrease in atrial arrhythmia burden but incomplete control. At age of 50 years, a dual chamber pacemaker was implanted for sinus node dysfunction. On routine device interrogation 19 months later, she was noted to have recurrent nonsustained ventricular tachycardia (VT) and was referred for cardiac magnetic resonance imaging (MRI) to evaluate for left ventricular (LV) and right ventricular fibrosis. Cardiac MRI demonstrated extensive multifocal patchy midmyocardial delayed gadolinium enhancement thought to be consistent with myocarditis versus cardiac sarcoidosis. Her moderately decreased LV ejection fraction of 43% was attributed to poor ventricular rate control with recurrent atrial arrhythmias. Subsequent evaluation with F-18 fluorodeoxyglucose (^{18}F-FDG) cardiac positron emission tomography/computed tomography (PET/CT) showed no foci of abnormal uptake to suggest active sarcoid involvement (Figure 1A). Given her history of atrial and ventricular arrhythmias, she was referred for further risk stratification with an electrophysiological study. During the electrophysiological study, programmed stimulation easily induced rapid sustained monomorphic VT that degenerated into ventricular fibrillation. With this result, her dual chamber pacemaker was upgraded to an implantable cardioverter defibrillator. She continued to have brief episodes of atrial arrhythmias that were managed with β-blockade.

Key Words: cardiomyopathies ■ genetic testing ■ glycogen ■ heart failure ■ tachycardia, ventricular

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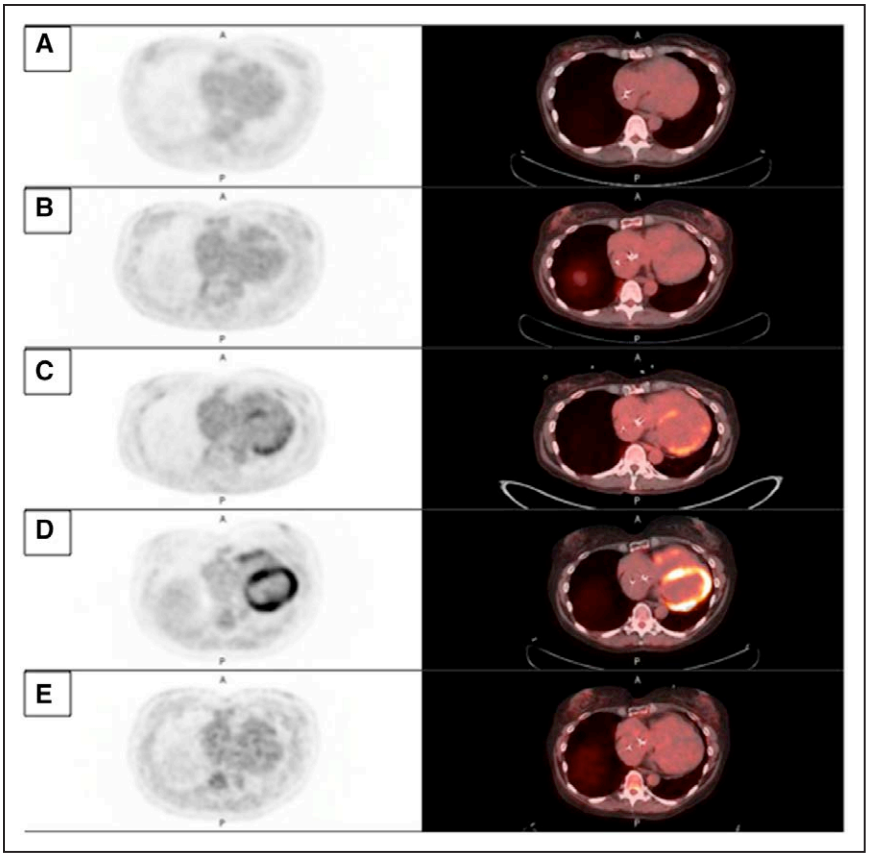

Figure 1. F-18 fluorodeoxyglucose (^{18}F-FDG) cardiac positron emission tomography/computed tomography (PET/CT) images.
Left vertical panel (**A**–**E**) with 18F-FDG PET images. Right vertical panel (**A**–**E**) with axial fused PET/CT images.

During the following 2 years, the patient developed mild dyspnea on exertion and episodic wheezing and chest tightness in the setting of normalized LV systolic function. Her symptoms persisted despite trials of antibiotics and inhaled corticosteroids, so she was treated for possible pulmonary sarcoidosis with a 6-week course of prednisone. Her dyspnea and palpitations were unchanged on prednisone therapy, and she was monitored for the next 14 months without additional immunosuppression. She then underwent a sixth catheter ablation after presenting with a symptomatic sustained atrial tachycardia. Echocardiography was notable for mild concentric LV hypertrophy and LV ejection fraction 45%, which was thought to be secondary to tachycardia-induced cardiomyopathy. Post-ablation, LV ejection fraction improved to 55%. However, frequent nonsustained VT and a high burden of premature ventricular contractions led to repeat 18F-FDG PET/CT, which again showed no evidence of active cardiac sarcoidosis (Figure 1B).

Five months later, she was hospitalized for syncope and multiple episodes of sustained monomorphic VT requiring antitachycardia pacing, defibrillator shocks, and an eventual VT ablation. A new malar rash was also noted and thought to be consistent with lupus pernio. Laboratory workup revealed a strongly positive antinuclear antibody titer (1:5120), positive anti–Ro/SS-A antibody titer (5.4; reference range, 0–0.9), positive rheumatoid factor (89 IU/mL; reference range, 0–29 IU/mL), and elevated creatine kinase (665 U/L; reference range, 38–234 U/L). Cardiac PET/CT performed at this time revealed abnormally increased 18F-FDG uptake in the inferoseptal wall from base to midcavity and lateral and anterolateral wall from base to apex (Figure 1C). Cardiac MRI demonstrated global biventricular hypokinesis with LV ejection fraction 30%, right ventricular ejection fraction 25%, and multiple areas of midmyocardial and subendocardial delayed gadolinium enhancement. In the context of her dermatologic, laboratory, and cardiac imaging findings, a mixed connective tissue disease with characteristics of systemic lupus erythematosus was suspected in addition to active cardiac sarcoidosis. High dose prednisone was initiated; however, surveillance cardiac PET/CT showed continued diffuse heterogeneous patchy 18F-FDG uptake (Figure 1D).

Attempts to taper prednisone were complicated by recurrent sustained VT requiring hospital admission, and her regimen was escalated to pulse dose methylprednisolone and methotrexate. Voltage-guided LV endomyocardial biopsy yielded interstitial and subendocardial fibrosis and severe myocyte hypertrophy but no granulomas. Repeat cardiac PET/CT 2 months later showed interval complete resolution of abnormal 18F-FDG uptake and no evidence of an active inflammatory process (Figure 1E). Clinical suspicion for an

inherited metabolic storage disease was raised, and she was referred for genetic testing.

On multidisciplinary review of the patient's putative diagnoses, she was referred to our Center for Inherited Cardiovascular Disease. Here, a notable maternal family history of cardiomyopathy was reviewed in the context of her clinical symptoms. The patient was of Slovakian and Polish ancestry. Her maternal grandmother died in her 20s with a history of dropsy and heart problems. The patient's mother died at age 39 years from cardiac complications with known cardiomyopathy. The patient's sister carried the diagnosis of Wolff–Parkinson–White syndrome and underwent orthotopic heart transplantation for cardiomyopathy at age 31 years, surviving for 14 years post-transplant (Figure 2). This sister's daughter had seizures, but her cardiac status was unknown. The patient had no personal history of intellectual disability or skeletal myopathy, and there was no known family history of cognitive deficits, childhood deaths, or birth defects. The results of her genetic testing were also interpreted at this visit.

GENETIC TESTING

The proband had undergone sequencing of 66 genes associated with arrhythmia and cardiomyopathy through a Clinical Laboratory Improvement Amendments–certified commercial laboratory. Sequencing revealed heterozygosity for a mutation in the *LAMP2* (lysosome-associated membrane protein 2) gene. The identified mutation (c.973dupC) in exon 8 of *LAMP2* leads to a frameshift at codon 325 (p.Leu325ProfsX25) and a premature stop signal that likely results in a truncated or absent protein product. Pathogenic loss-of-function variants in *LAMP2* have been previously characterized and carry a pLI score of 0.95 in the Exome Aggregation Consortium database.[1,2] The commercial laboratory classified this patient's c.973dupC mutation as pathogenic.

This variant is also known as c.973insC, which has been reported in association with Danon disease. c.973insC was first reported in a Hungarian boy who presented at age 14 years with mild mental retardation and exercise-induced tachycardia and was found

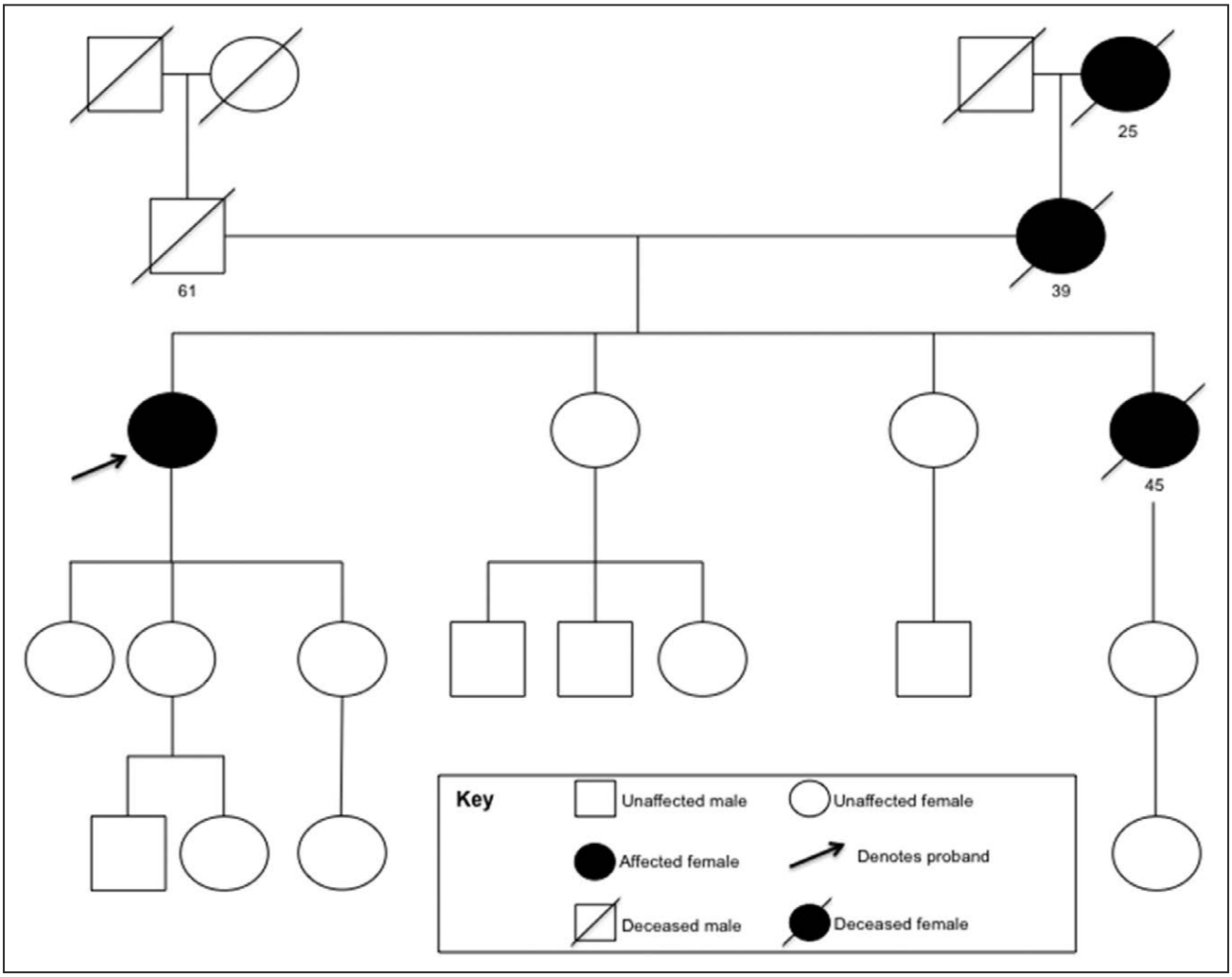

Figure 2. *LAMP2* c.973dupC family pedigree.
Numbers beneath individuals denote age at death.

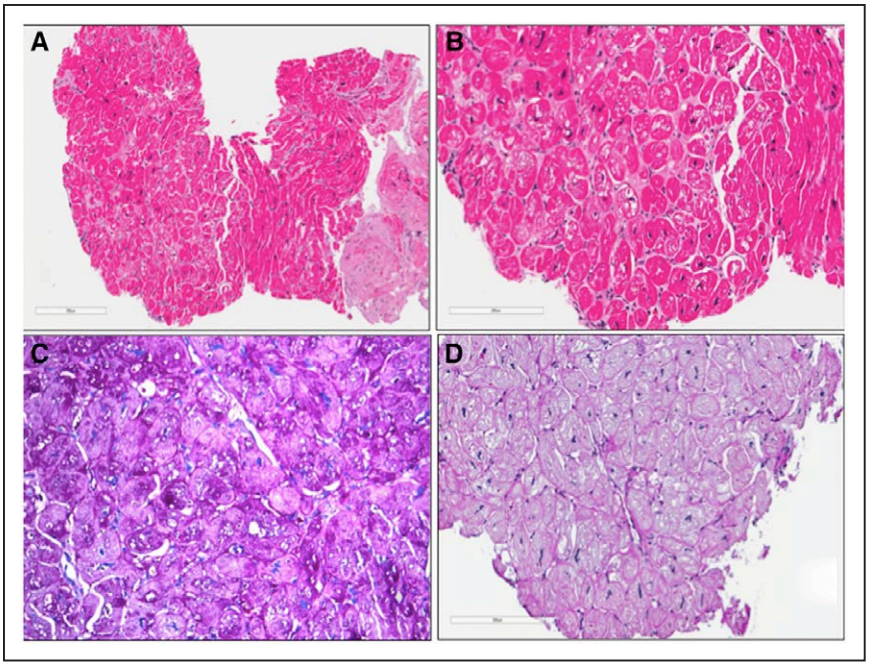

Figure 3. Endomyocardial biopsy histopathology. **A**, Hematoxylin and eosin stain of myocardial biopsy (×10). **B**, Hematoxylin and eosin stain demonstrating myocyte hypertrophy with interstitial fibrosis (×20). **C** and **D**, Periodic acid–Schiff stain alone and with diastase highlight presence of glycogen (×20).

to have elevated creatine kinase and transaminases, a short PR interval on ECG, and nonobstructive hypertrophic cardiomyopathy. For the next 6 years, he developed multiple atrial and ventricular arrhythmias, LV dilation, and eventually died from progressive biventricular heart failure. His mother was genotype positive and underwent catheter ablation of 2 atrial tachycardias at age 48 years but had normal LV dimensions and function.[3,4]

CLINICAL COURSE

Based on genetic testing results, review of relevant literature, and clinical expert consensus, the patient was diagnosed with Danon disease, resulting in major changes to her clinical management. Her systemic lupus erythematosus and sarcoidosis diagnoses were dismissed, and her immunosuppression was weaned. Cascade testing was recommended for at-risk relatives. Of her 2 surviving sisters, 1 tested negative for the variant and the other has not yet been tested. The patient has 3 daughters, all of whom have tested negative for the variant. She has no brothers or sons (Figure 2). Heart transplant evaluation was promptly initiated; she underwent successful orthotopic heart transplantation 6 months after her revised diagnosis because of progressive low-output heart failure requiring inotropic support. On pathological rereview, the patient's cardiac biopsy tissue was notable for glycogen deposits and excess vacuolization (Figures 3A–3D and 4).

DISCUSSION

Danon disease is a multisystem disorder caused by disruptions in LAMP2 protein expression. It follows an X-linked dominant inheritance pattern although de novo mutations have been reported.[5,6] Danon disease was first described in 1981 in young men with cardiomyopathy, skeletal myopathy, and intellectual disability and was thought to be a glycogen storage disease until its genetic underpinnings were elucidated in 2000.[7,8] The *LAMP2* gene, located on chromosome Xq24, consists of an open reading frame of 1233 nucleotides and encodes 410 amino acids over 9 exons.[8] Exons 1 to 8 and a portion of 9 encode a large lysosomal luminal domain. The remainder of exon 9 encodes a transmembrane region and a small carboxy-terminal cytoplasmic tail. Alternative splicing generates 3 major LAMP2 protein isoforms: LAMP-2A, LAMP-2B, and LAMP-2C, each of which vary at the carboxy-terminal lysosomal transmembrane domain and cytosolic tail.[9] Differences in quaternary structure and tissue-specific expression levels suggest that each isoform may have distinct functions. The LAMP-2A cytoplasmic tail acts as a lysosomal membrane receptor for chaperone-mediated autophagy. LAMP-2B isoform expression has been observed to be higher in myocardial, skeletal muscle, and brain tissues, and all known mutations affect at least this isoform.[10–12]

The majority of *LAMP2* mutations are of the nonsense or frameshift types and result in protein truncation and loss-of-function although splicing, large deletion, large duplication, insertion/deletion, and missense mutations have also been described. *LAMP2* mutations causing attenuated protein expression are thought to disrupt the protein's transmembrane and cytoplasmic domains. The breakdown of intracellular transport mechanisms causes accumulation of autophagic material and cell debris, including glycogen, in

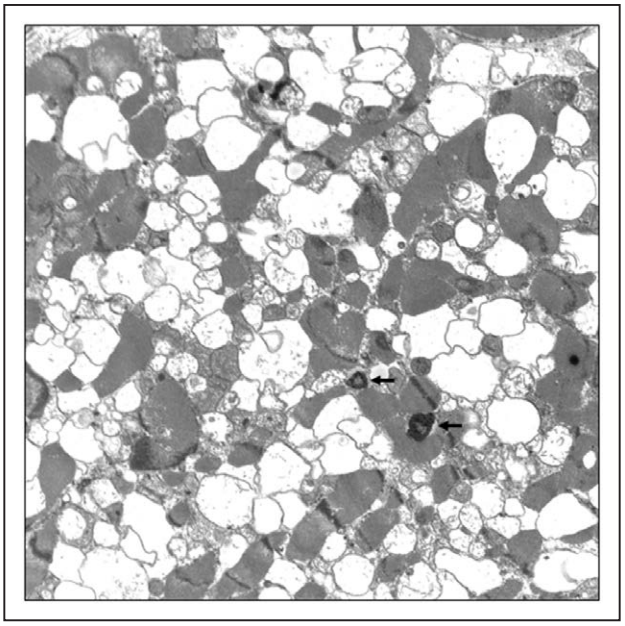

Figure 4. Endomyocardial biopsy electron micrograph. Electron microscopy shows myocardium with dilated mitochondria, numerous vacuoles, and lysosomes with autophagic material (arrows). Electron micrograph, ×3000.

cardiac and skeletal muscle. In a systematic review of genotype–phenotype correlations of 35 mutations and 73 cases, nonsense, frameshift, and large deletion/duplication mutations manifest with the earliest ages of disease onset for both men and women, followed by splicing mutations, and then missense mutations.[12] Most mutations have been reported as private, in single families, with recurrent mutations in exons 3 (Q83X, W98X) and 7 (R293X, V310I) reported in unrelated families.[3]

Danon disease has been reported in 1% to 6% of patients with unexplained LV hypertrophy.[5,6,13,14] The exact disease prevalence is difficult to estimate as an increased number of individuals are now being diagnosed through the expansion of genetic testing into clinical practice and the inclusion of *LAMP2* into cardiomyopathy genetic testing panels since the early 2000s.[15] Genetic testing for *LAMP2* mutations is now the preferred method of diagnosis. Acid maltase level measurement on muscle biopsy or blood-spot analysis, immunohistochemistry analysis, and histopathology and electron microscopy of skeletal muscle and myocardial tissue are supportive diagnostic tools.[12]

Cardiac manifestations of Danon disease are often life limiting and include hypertrophic and dilated cardiomyopathies; hypertrophy predominates in men whereas women exhibit both phenotypes.[3] Conduction abnormalities, including Wolff–Parkinson–White syndrome, atrial and ventricular arrhythmias, and sudden cardiac death, occur in both sexes. Neurological and musculoskeletal symptoms, such as proximal muscle weakness, learning disabilities, and cognitive defects, are more common in men, whereas pulmonary, gastrointestinal, and ophthalmologic involvement are reported less frequently in both sexes.[12] Because of haploinsufficiency of the X-linked *LAMP2* gene, men are generally affected at earlier ages with more severe phenotypes. Early-onset cardiac disease in young women and phenotypic differences among related men have been reported. Proposed explanations for this heterogeneity include skewed X-chromosome inactivation, uneven myocardial distribution of cardiomyocytes lacking LAMP2, diffuse microvascular disease in women, and unidentified influences of background modifier genes.[14,16,17] Importantly, the phenotypic umbrella of Danon disease may continue to expand as novel *LAMP2* mutations are identified.

Heart transplantation is the only definitive therapy for Danon cardiomyopathy, which is otherwise characterized by an early, accelerated, and lethal course. Currently, there are no consensus screening, diagnosis, or management guidelines for these patients. Extrapolating management strategies from the 2011 American College of Cardiology Foundation/American Heart Association Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy could be considered for this cardiomyopathy; however, it is crucial to recognize the differences in inheritance pattern, pathophysiology, disease course, and prognosis among other genetic or idiopathic cardiomyopathies, including hypertrophic cardiomyopathy, and Danon disease.[5,18] Regarding clinical management of affected individuals, experts advocate for guideline-directed heart failure management with a low threshold for implantable cardioverter defibrillator implantation and early listing for heart transplantation. Annual echocardiography, electrocardiography, Holter monitoring, and stress testing have been recommended for screening of first-degree family members of individuals with hypertrophic cardiomyopathies when a known pathogenic or likely pathogenic variant has been detected. Genetic testing, including sequencing of *LAMP2*, should be recommended for individuals with otherwise unexplained LV hypertrophy or dilated cardiomyopathy, especially in the presence of other associated features, including Wolff–Parkinson–White syndrome, proximal skeletal muscle myopathies, and cognitive deficits. At-risk relatives should be offered cascade testing to inform clinical screening practices and to facilitate reproductive decision making.[12,19]

In this patient's case, 4 major issues contributed to the delay in diagnosis. First, she presented with numerous and challenging atrial arrhythmias. The poorly controlled arrhythmias were often associated with rapid ventricular rates. Initial fluctuations in LV function were attributed to tachycardia-induced cardiomyopathy rather than a primary myocardial process.

Second, despite the patient's engagement with various subspecialty providers for many years, her multigenerational family history of cardiomyopathy was not elicited until late into her disease course. Family history has been demonstrated as an important predictor of gene-positive status in multiple inherited cardiac conditions.[20] There are many benefits in obtaining a comprehensive family history in cardiovascular genetic disease, which include the identifications of affected and at-risk family members, of phenotypic behaviors (eg, penetrance, expressivity, and lethality) of known genetic mutations, and of individuals who may qualify for disease-modifying treatment.[21] Had they been elicited, the family's high-risk features of early-onset, severe disease along with a female predilection would have likely provided an indication of the genetic basis of her disease to her providers.

Third, we must consider the influence of anchoring bias in the diagnosis of cardiac sarcoidosis, which was largely made based on delayed gadolinium enhancement on cardiac MRI and abnormal 18F-FDG uptake on cardiac PET/CT, neither of which is specific for this disease. 18F-FDG is preferentially used by highly metabolically active tissues, which in the case of sarcoidosis are macrophage-dense regions and areas of granulomatous inflammation. These macrophages are more reliant on external glucose to drive basic cellular processes. In patients with otherwise normal myocardium, a high-fat, high-protein, low-carbohydrate diet followed by a prolonged fasting period before 18F-FDG injection will suppress glucose and 18F-FDG use by the normal myocardium. However, increased 18F-FDG uptake is not specific to granulomatous inflammation in sarcoidosis. Indeed, numerous pathogeneses can result in a positive 18F-FDG PET/CT (eg, chronic ischemia, dietary noncompliance, poorly controlled diabetes mellitus, myocarditis), and the diagnosis of myocardial sarcoidosis is made based on the preponderance of evidence and lack of other plausible explanations for myocardial glucose use despite appropriate preparation. Delayed gadolinium enhancement on cardiac MRI is similarly nonspecific and can be seen in several pathologies.[22] Published estimations of the sensitivity and specificity of cardiac PET for diagnosing cardiac sarcoidosis are severely limited by their basis in single-center retrospective data and the lack of a diagnostic gold standard.[23]

Myocardial 18F-FDG uptake in the setting of excess myocardial glycogen is largely unstudied. A small, hypothesis-generating single-center pilot study of in vivo myocardial glucose uptake assessed by ^{18}F-FDG PET in *PRKAG2* cardiac syndrome, another inherited cardiac disease leading to excess glycogen storage, demonstrated a reduction in myocardial glucose uptake in 6 subjects compared with 6 healthy, matched controls.[24] The consequences of dysfunctional or absent LAMP2 protein and the resultant excess cardiac glycogen accumulation on myocardial glucose or ^{18}F-FDG uptake is a prospect for further exploration. In this case of excess cardiac glycogen combined with the altered myocardial energetics of a failing heart, the contributions of intramyocardial and peripheral glucose availability and of the reduced expression of the glucose transporter protein GLUT4 should be considered in discriminating the pattern of ^{18}F-FDG uptake.[25] The varying doses of immunosuppression at each study and lack of concomitant perfusion imaging presented more layers of complexity in this patient's PET/CT interpretation.[26]

Last, the return of the patient's genetic testing was delayed, in part, because of the lack of an infrastructure to interpret and act on results. There are numerous considerations on the incorporation of genetic testing into clinical practice: appropriate selection of patients and families for testing and of the genetic test, pretest counseling with informed consent, review and interpretation of results, disclosure and post-test counseling, and management of at-risk relatives.[27] Cardiovascular practitioners who order genetic testing should have a plan for interpreting and returning the results to the patient in a timely manner. Referral to centers with expertise in genetic evaluation and family-based management is being increasingly encouraged. Clinical and genetic evaluations of the inherited cardiomyopathies are rapidly evolving, and professional societies have issued scientific and guideline statements to assist cardiovascular providers in maintaining core competencies for practice in this field.[28,29]

CONCLUSIONS

This case emphasizes the critical importance of soliciting a detailed family history for any patient who presents with cardiomyopathy, ensuring proper workflows for the incorporation of genetic testing into clinical practice, and maintaining awareness of heuristics and biases in diagnostic reasoning. Conditions, such as Danon disease, can present more subtly than established epidemiological phenotype data would suggest. Recognition of this disease enables cost-containment and appropriate resource use, a potentially life-saving therapeutic approach, and risk stratification for family members. Reporting of genotype–phenotype correlations is imperative to achieve a greater understanding of this rare disease and for the development of future therapeutic targets.

ARTICLE INFORMATION

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Disclosures

None.

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