INTRODUCTION

Danon disease is a rare X-linked genetic disorder presenting typically as a triad of mental retardation, skeletal myopathy, and hypertrophic cardiomyopathy (HCM). Mutations of the lysosome-associated membrane protein 2 (LAMP2) gene lead to impaired lysosomal functioning and the accumulation of intracellular glycogen. Similarly to Pompe disease (glycogen storage disease type II), with which it was initially confused, Danon disease is seen as a glycogen storage disorder, but is not related to α-glucosidase enzyme deficiency. Instead, Danon disease results from an LAMP2-associated impairment of lysosomal membrane integrity.

Cardiac involvement is a prominent clinical feature of Danon disease, in which young, often adolescent patients present with apparent left ventricular hypertrophy (LVH) and arrhythmias. Danon disease is commonly mistaken for sarcomeric HCM, despite being a lysosomal storage disease. The distinction between these two disorders is important because Danon disease has a more rapid disease progression and higher mortality. Here we describe the importance of multimodality imaging of Danon disease in a patient with a novel LAMP2 mutation.

CASE PRESENTATION

A 15-year-old Caucasian boy presented with dyspnea on exertion. Since the age of 5 years, he had been noted to have exercise limitation and mild cognitive delay. There was not a family history of cardiomypathies, arrhythmias, or sudden cardiac death. On physical examination, he appeared well developed and there were no dysmorphic facial features. On cardiac auscultation, a grade 3/6 harsh systolic ejection murmur along the left middle sternal border was appreciated. His skeletal muscle strength and muscle tone were normal throughout.

Electrocardiography showed Wolff-Parkinson-White (WPW) syndrome and severe LVH by voltage criteria (Figure 1). Echocardiography demonstrated severe concentric LVH, including a septal thickness of 42 mm (Figure 2, Video 1), and a severely increased peak systolic intracavitary left ventricular gradient (Figure 3), but no significant left ventricular outflow tract obstruction was noted. The presumptive diagnosis was sarcomeric HCM. Subsequently, the patient was started on an oral β-blocker and received an implantable cardioverter-defibrillator.

Two years later, an episode of supraventricular tachycardia with rate of 214 beats/min, which was aborted via antitachycardia pacing, was noted on device interrogation. The patient then underwent radiofrequency ablation of two accessory pathways within the tricuspid valve annulus.

Upon continued assessment, an association between WPW and massive LVH introduced a suspicion for Danon syndrome. A positron emission tomography/computed tomographic scan demonstrated abnormal fluorodeoxyglucose uptake throughout the myocardium, indicative of altered glucose metabolism (Figure 4). Subsequent genetic testing revealed that the patient was hemizygous for a frameshift mutation in the LAMP2 gene, confirming the diagnosis of Danon disease. Moreover, his mutation (L141VfsX9) had not been previously reported. A myocardial biopsy was not performed.

At two years following the diagnosis of Danon disease, the patient continued to be symptomatic from episodes of supraventricular tachycardia and nonsustained ventricular tachycardia, despite cardiac ablation and implantable cardioverter-defibrillator placement. Antiarrhythmic agents were being titrated with the hope of controlling symptoms. The patient had not yet been considered for a heart transplantation.

DISCUSSION

Danon disease was first described by Moris Jak Danon and colleagues at the University of Illinois as a distinct form of lysosomal glycogen storage disease in two unrelated 16-year-old boys with mental retardation, cardiomegaly, and proximal skeletal myopathy. It was subsequently shown to be a result of LAMP2 gene mutations, leading to deposition of intracytoplasmic vacuoles and organ pathology. This rare genetic condition has been traditionally defined as a clinical triad of skeletal myopathy, mental retardation, and cardiomyopathy. However, on the basis of multiple clinical reports, including our case, the central nervous and skeletal myopathic symptoms are usually mild or clinically silent, with the cardiac symptoms consistently presenting as the dominant clinical feature.

Phenotypically, the cardiomyopathy associated with LAMP2 mutation can mimic the HCM caused by sarcomere protein gene mutations. However, it is distinguished by a high incidence of electrophysiologic patterns of preexcitation and has been noted as one of the most lethal cardiomyopathies in young patients. The clinical coupling of HCM and conduction abnormalities, including preexcitation, has also been described in the literature as a result of adenosine monophosphate-activated protein kinase disease. Mutations of the adenosine monophosphate-activated protein kinase gene γ2 subunit, PRKAG2, is associated with altered cellular metabolism, and the affected myocytes have been observed to have glycogen deposition on histologic review. However, the electrocardiographic pattern of
WPW is more frequently observed with Danon disease, and the pairing with both developmental delay and skeletal myopathy has not been described in adenosine monophosphate-activated protein kinase disease. Ultimately, it is of upmost importance to learn from cases of LAMP2 mutation–associated cardiomyopathy to detail the clinical characteristics and diagnostic evaluation of this rare condition and avoid misdiagnosis and delays in management.

As our case demonstrates, the presentation of isolated ventricular hypertrophy in a young patient with Danon disease can often lead to an erroneous diagnosis of a sarcomeric HCM. The diagnosis of HCM is clinically defined as an unexplained left ventricular wall thickness ≥ 15 mm on cardiac imaging, a measurement criterion adopted from studies involving adults and children as young as 7 years of age. Mutations of sarcomere proteins remain the most common cause of HCM in genetic studies, with more than 200 mutations identified thus far. Stopping at this presumed diagnosis can result in rare cases of Danon disease going unrecognized. However, a young patient presenting with an impressive degree of LVH and ventricular preexcitation should prompt consideration for a LAMP2 mutation. In a genetic analysis of 75 unrelated subjects with unexplained

Figure 1 Twelve-lead electrocardiogram demonstrating WPW syndrome and voltage criteria for LVH.

Figure 2 Transthoracic echocardiogram in four standard views at end-diastole demonstrates extremely severe LVH.
LVH, only 9.3% had LAMP2 mutations, but the measurements of maximal left ventricular wall thickness for sarcomere protein gene mutations compared with LAMP2 mutations were 24 ± 10 and 35 ± 15 mm, respectively. This same study subsequently evaluated an additional cohort of 24 subjects with unexplained LVH and electrocardiograms suggesting ventricular preexcitation, and the incidence of LAMP2 mutations had increased to 16.6%.9

According to ClinVar archives of human genetic variations and phenotypes, hosted by the National Center for Biotechnology Information, there have been >500 genetic variants described of the LAMP2 gene, but <20% of those are deemed pathologic.10 The genetic sequencing in our patient revealed a novel frameshift variant in the LAMP2 gene (Xq24), denoted p.Leu141ValfsX9. This genetic variant causes a shift in the reading frame, changing a leucine to a valine followed by a premature stop codon. The genetic analysis of this novel frameshift variant will be detailed in a separate publication.

By nature of an X-linked inheritance, young men with LAMP2 deficiency are more affected than women and present with more advanced disease at an earlier age. The average age of disease onset is 12.1 years for male patients and 27.9 years for women.2 Cardiac symptoms typical of HCM, including chest pain, palpitations, and syncope, are the dominant clinical features at diagnosis. Conversely, there have been reported cases in which an isolated increase in creatinine kinase or abnormal electrocardiographic findings prompted the cardiac evaluation.11 Mental retardation or overt neurologic or musculoskeletal abnormalities tend to be minimal or absent in most documented cases.12

Danon disease is characterized by an adverse clinical course, despite treatment strategies. A longitudinal study by Maron et al.3 detailed the phenotype and clinical outcomes of a cohort of adolescent patients with HCM and identified LAMP2 mutations. The seven patients, with a median age of 14 years, were followed for mean of 8.6 years; all patients developed systolic dysfunction with ejection fractions of 20% to 35% (mean, 25%), and left ventricular wall thickness ranged from 29 to 65 mm. Five patients experienced lethal ventricular arrhythmias, and despite receiving implantable cardioverter-defibrillators, four died of progressive heart failure and one underwent heart transplantation.3

Multimodality imaging is a key to a successful diagnosis of Danon disease, as demonstrated by our patient’s case. A combination of WPW syndrome on electrocardiography and severe LVH on imaging, such as echocardiography, should immediately raise suspicion for Danon disease. Thereafter, positron emission tomography demonstrating glucose hypermetabolism in the myocardium further strengthens a diagnosis of Danon disease. The ultimate diagnosis requires genetic confirmation.

**CONCLUSION**

Danon disease is commonly mistaken for sarcomeric HCM. Because Danon disease has been associated with a more rapid disease progression and higher mortality, accurate diagnosis is essential and requires multimodality imaging. The combination of WPW syndrome on
Electrocardiography, massive LVH on echocardiography or other imaging modality, and glucose hypermetabolism on positron emission tomography is indicative of Danon disease. The ultimate diagnosis requires genetic confirmation.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2019.04.007.

REFERENCES

1. Danon MJ, Oh SJ, DiMauro S, Manaligod JR, Eastwood A, Naidu S, et al. Lysosomal glycogen storage disease with normal acid maltase. Neurology 1981;31:51-7.
2. D’Souza RS, Mestroni L, Taylor MRG. Danon disease for the cardiologist: case report and review of the literature. J Commun Hosp Int Med Perspect 2017;7:107-14.
3. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. JAMA 2009;301:1253-9.
4. Arad M, Moskowitz JP, Patel VV, Ahmad F, Perez-Atayde AR, Sawyer DB, et al. Transgenic mice overexpressing mutant PRKAG2 define the cause of Wolff-Parkinson-White syndrome in glycogen storage cardiomyopathy. Circulation 2003;107:2850-6.
5. Murphy RT, Mogensen J, McGarry K, Bahl A, Evans A, Osman E, et al. Adenosine monophosphate-activated protein kinase disease mimicks hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome: natural history. J Am Coll Cardiol 2005;45:922-30.
6. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivetto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol 2014;64:83-99.
7. Klues HG, Schieffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. J Am Coll Cardiol 1995;7:1699-708.
8. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379:655-68.
9. Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med 2005;352:362-72.
10. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res 2018;46:D1062-7.
11. Sugie K, Yamamoto A, Murayama K, Oh SJ, Takahashi M, Mora M, et al. Clinicopathological features of genetically confirmed Danon disease. Neurology 2002;58:1773-8.
12. Kim J, Pankhi P, Mahboob M, Arrighi JA, Atalay MK, Rowin EJ, et al. Asymptomatic young man with Danon disease. Tex Heart Ins J 2014;41:332-4.