HYPERTROPHIC CARDIOMYOPATHY WITH UNUSUAL EXTENSIVE SCARRING PATTERN: DANON DISEASE

Dan D. Le, M.D.^a; Paulino Alvarez, M.D.^b; Roberto Barrios, M.D.^b; Michael Arriaga, M.D.^b; Mariyam Cherry, M.D.^b; Dipan Shah, M.D.^b; C. Huie Lin, M.D.^b

^aEast Carolina Heart Institute at East Carolina University, Greenville, North Carolina; ^bHouston Methodist Hospital, Houston, Texas

Introduction

Danon disease is a rare X-linked dominant disorder caused by a primary deficiency in lysosome-associated membrane protein 2 (LAMP2). It is characterized by the development of hypertrophic cardiomyopathy in male teenagers, mild myopathy, and mental retardation.^{1,2} Electrocardiogram (EKG) usually displays a Wolff-Parkinson-White (WPW) syndrome. Females who carry the mutation in the LAMP2 gene on chromosome X could develop dilated or hypertrophic cardiomyopathy in their early 40s. Unfortunately, there is no causal therapy for Danon disease. Heart transplantation is the only therapeutic option once heart failure occurs and should be considered as early as possible due to the disease's rapid progression.³

Since Danon disease is rare, it is often misdiagnosed with hypertrophic cardiomyopathy or other causes of left ventricular hypertrophy (LVH). It should be highly suspected in the male teenager with LVH, especially if the patient has an extensive scarring pattern in the lateral wall on late gadolinium enhancement cardiac magnetic resonance (CMR), elevated creatine kinase and liver transaminase enzymes, and/or WPW syndrome. Endomyocardial biopsy and genetic analysis can confirm the diagnosis.⁴⁻⁷ This report demonstrates the clinical value of CMR for the diagnostic work-up of Danon disease, with diagnostic confirmation by endomyocardial biopsy and genetic analysis.

Case Presentation

A 21-year-old Pakistani male college student with a 7-year history of muscle cramps and easy fatigability and dyspnea on exertion for the past few months presented to the local emergency department complaining of shortness of breath. He was found to have an enlarged heart on chest X-ray along with an abnormal EKG and was referred to our hospital for further evaluation. His mother had died of unknown etiology at age 40. His physical examination was significant for tachypnea, tachycardia, mild limb muscle weakness, and atrophy. Electrocardiogram showed sinus tachycardia with biventricular hypertrophy and short PR interval (Figure 1 A). Laboratory testing revealed elevations of serum creatine kinase and liver transaminase enzymes. Transthoracic echocardiography (TTE) demonstrated massive concentric LVH (septum 27 mm, lateral wall 21 mm) and severe globally depressed left ventricle (LV) systolic function with ejection fraction (EF) of 25% (Figure 1 B). The patient was further evaluated with CMR, which revealed morphologic findings similar to those of the TTE: severe symmetric LVH, severe LV systolic dysfunction, and moderate globally depressed right ventricular (RV) systolic function with a RVEF of 38%. There was diffuse late gadolinium enhancement in the RV insertion points and mid-myocardium, most prominent in the LV lateral segments, with total scar burden of 63%. These unusual extensive scarring patterns were suggestive of Danon

Figure 1. (A) Electrocardiogram showed sinus tachycardia with Wolff-Parkinson-White pre-excitation pattern. (B) Transthoracic echocardiogram apical 4-chamber view showed severe concentric left ventricular hypertrophy; the thickness of interventricular septum and lateral wall were 27 mm and 21 mm. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

Figure 2. Late gadolinium enhancement (LGE) cardiac magnetic resonance. The top row (4-chamber, 3-chamber, and 2-chamber LGE images) and the bottom row (from basal to apical short axis LGE images, left to right) showed diffuse LGE in the right ventricular insertion points and mid-myocardium, most prominent in the left ventricular lateral segments (arrows).

disease (Figure 2). A definite LV apical thrombus was also found (Figure 3). Cardiac biopsy was performed in the subendocardial muscle of the RV septum, and no fibrosis, amyloid, or inflammation was observed. There was mild focal architectural disarray. The cardiomyocytes were hypertrophic, with enlarged and irregular nuclei and vacuolated cytoplasm (Figure 4 A). Ultrastructural examination showed numerous vacuoles containing degenerating mitochondria, glycogen, small vesicles, and granular debris (Figure 4 B).

Due to the constellation of findings, the patient underwent a hypertrophic cardiomyopathy genetic panel and was found to be heterozygous for a novel frameshift mutation in the LAMP2 gene, thus confirming the diagnosis of Danon disease. An electrophysiologic study was performed and failed to demonstrate any evidence of accessory pathways. In light of the patient's family history, symptoms, and echocardiographic findings, he was discharged home with a LifeVest™ device (ZOLL Medical Corporation, Burlington, MA), anticoagulant therapy, and optimal heart failure medications. Unfortunately, 3 months after discharge from Houston Methodist Hospital, the patient returned to his home country and died suddenly while hiking with his father.

Conclusion

We present the case of Danon disease confirmed by endomyocardial biopsy. In our case, the late gadolinium enhancement was mainly visible in the mid-myocardium and more extensively in the lateral segments in a distribution that would be unusual in more common pathologies.² Given the poor prognosis of this disease, early recognition is important to guide therapeutic interventions.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Figure 3. Cardiac magnetic resonance delayed enhancement TI 600 ms showed a definite left ventricular apical thrombus (arrow).

Keywords: Danon disease, LAMP2, hypertrophic cardiomyopathy, left ventricular hypertrophy

References

1. Maron BJ, Roberts WC, Arad M, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA*. 2009 Mar 25;301(12):1253-9.
2. Silva C, Moon JC, Elkington AG, John AS, Mohiaddin RH, Pennell DJ. Myocardial late gadolinium enhancement in specific cardiomyopathies by cardiovascular magnetic resonance: a

Figure 4. (A) Endomyocardial biopsy showed enlarged and vacuolated cardiomyocytes, hematoxylin-eosin stain, original magnification 400x. (B) Ultrastructure of myocardial biopsy showed myocardial fibers with accumulation of autophagic vacuoles, with degenerating mitochondria, glycogen, small vesicles, and granular debris. Magnification 8000x.

- preliminary experience. *J Cardiovasc Med (Hagerstown)*. 2007 Dec;8(12):1076-9.
3. Maron BJ, Roberts WC, Arad M, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA*. 2009;301(12):1253-9.
 4. Danon MJ, Oh SJ, DiMauro S, et al. Lysosomal glycogen storage disease with normal acid maltase. *Neurology*. 1981 Jan;31(1):51-7.
 5. Sugie K, Yamamoto A, Murayama K, et al. Clinicopathological features of genetically confirmed Danon disease. *Neurology*. 2002 Jun 25;58(12):1773-8.
 6. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med*. 2005 Jan 27;352(4):362-72.
 7. Dougu N, Joho S, Shan L, et al. Novel LAMP-2 mutation in a family with Danon disease presenting with hypertrophic cardiomyopathy. *Circ J*. 2009;73:376-80.