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Clinical Case Report

A novel *LAMP2* mutation associated with severe cardiac hypertrophy and microvascular remodeling in a female with Danon disease: a case report and literature review

Irene Bottillo [a,*], Carla Giordano [b], Bruna Cerbelli [b], Daniela D'Angelantonio [a], Martina Lipari [a], Taisia Polidori [a], Silvia Majore [a], Enrico Bertini [c], Adele D'Amico [c], Diana Giannarelli [d], Carmelilia De Bernardo [a], Laura Masuelli [e], Francesco Musumeci [f], Andrea Avella [g], Federica Re [g], Elisabetta Zachara [g], Giulia d'Amati [b], Paola Grammatico [a]

[a] *Medical Genetics Laboratory, Department of Molecular Medicine, Sapienza University, San Camillo-Forlanini Hospital, Rome, Italy*
[b] *Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy*
[c] *Unit for Muscular and Neurodegenerative Disorders, Laboratory of Molecular Medicine, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy*
[d] *Biostatistic Unit, Regina Elena National Cancer Institute, Rome, Italy*
[e] *Department of Experimental Medicine, Sapienza University, Rome, Italy*
[f] *Department of Cardiac Surgery, San Camillo-Forlanini Hospital, Rome, Italy*
[g] *Cardiomyopathies Unit, Division of Cardiology and Cardiac Arrhythmias, San Camillo-Forlanini Hospital, Rome, Italy*

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ABSTRACT

Background: Danon disease (DD) is a rare disorder characterized by cardiomyopathy, intellectual disability, and proximal myopathy. It is caused by mutations in the *LAMP2* gene on X chromosome. Female patients most often present with late-onset cardiomyopathy and slow disease progression, but early-onset cases with unfavorable prognosis have been reported.
Case report: We describe the clinical, pathological, and molecular features of a novel *LAMP2* c.453delT mutation in a female patient with severe hypertrophic cardiomyopathy, Wolff Parkinson White (WPW) syndrome and rapid progression to heart failure, requiring heart transplant. Immunohistochemical analysis of *LAMP2* in the explanted heart revealed a mosaic pattern of distribution, with discrete clusters of either stained or unstained cardiac myocytes, the latter being more frequent in the septum. These findings paralleled X chromosome inactivation within the myocardium. Interestingly, multiple foci of microscarring were found on histology in the Left Ventricle (LV) free wall and septum, in a close spatial relationship with remodeling and severe stenosis of intramural coronary arterioles.
Conclusions: Our findings suggest that several features may contribute to the early and severe cardiac phenotype in female DD patients. The type of mutation may account for the early disease onset, while both the inhomogeneous distribution of *LAMP2* loss and the presence of microvascular remodeling may be determinant in the rapid progression to heart failure.

1. Introduction

Danon disease (DD) (MIM #300257) is a rare monogenic metabolic X-linked disorder characterized by early-onset cardiomyopathy with hypertrophic or dilated phenotype (frequently responsible for fatal outcome), intellectual disability, and proximal myopathy [1]. The accumulation of unprocessed autophagosomes filled with degraded cell debris represents the main ultrastructural finding in affected tissues [2]. The exact prevalence of DD is unknown; however, it has been reported in 1–6% of patients with unexplained left ventricle hypertrophy (LVH) [3–6] and in up to 17% of patients with LVH and other features such as elevated serum creatine kinase (CK) or Wolff–Parkinson–White (WPW) syndrome [5,6].

DD is caused by the primary deficiency of lysosome-associated membrane protein 2 (*LAMP2*), which coats the inner surface of the lysosomal membrane and is supposed to act as a receptor for proteins to be imported and degraded within lysosomes in chaperone-mediated autophagy [7]. *LAMP2* gene is located on chromosome Xq24, and its open reading frame consists of 1233 nucleotides spanning nine exons and encoding 410 amino acids [8]. Exon 9 undergoes alternative

Abbreviations: CK, creatine kinase; DD, Danon disease; ECG, electrocardiogram; EF, ejection fraction; ICD, Implantable Cardioverter Defibrillator; LVH, left ventricle hypertrophy; MRI, Magnetic Resonance Imaging; NSVT, Nonsustained Ventricular Tachycardia; VAD, Ventricular Assist Device; WPW, Wolff–Parkinson–White; XCI, X-chromosome inactivation.

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* Corresponding author at: Medical Genetics, Department of Molecular Medicine, Sapienza University, San Camillo-Forlanini Hospital, Circonvallazione Gianicolense, 87 – 00152, Rome, Italy. Tel.: +39-06-58704622; fax: +39-06-5870-4657.
E-mail address: i.bottillo@gmail.com (I. Bottillo).

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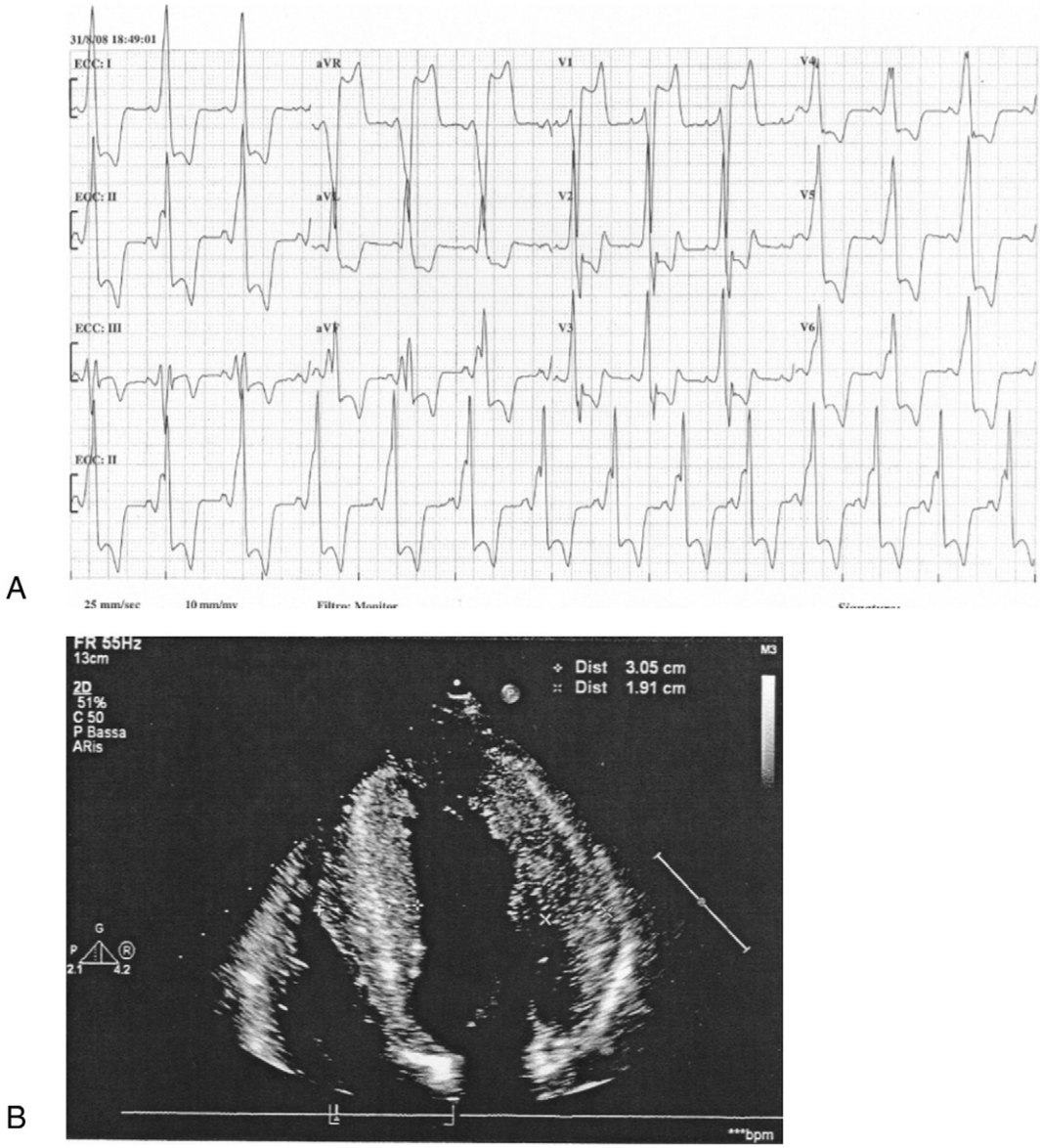

Fig. 1. Echocardiographic and electrocardiographic features of the patient. (A) Echocardiogram showing marked left ventricular hypertrophy involving interventricular septum and lateral wall with increased echogenicity of the myocardium. (B) Rest 12-lead electrocardiography showing sinus rhythm with large delta waves due to overt ventricular preexcitation associated with markedly abnormal ventricular repolarization.

splicing generating three splice isoforms (*LAMP2*A, *LAMP2*B, and *LAMP2*C) that differ in the transmembrane and cytoplasmic domains but have identical luminal domains [7]. *LAMP2*B isoform is mainly expressed in heart, skeletal muscle, and brain (the three "target tissues" of DD) [9], while isoforms *LAMP2*A and *LAMP2*C are nearly ubiquitous [10]. To date, more than 100 genetically proven cases of DD have been reported, and most of the mutations are small deletions/insertions, nonsense, or splicing alterations [11,12].

Clinical manifestations are variable but generally more severe in males due to the X-linked dominance [13]. However, early-onset cases with unfavorable prognosis have been seldom described in females [4,6,14–17]. These are believed to be caused mainly by an unfavorable skewing of X-chromosome inactivation (XCI) in the cardiac tissue [6,12,18].

Here, we report a novel *LAMP2* c.453delT mutation, found in a woman with severe hypertrophic cardiomyopathy and WPW syndrome requiring heart transplant. We demonstrate the skewed *LAMP2* gene inactivation both in peripheral white blood cells and in cardiac muscle, and in addition, we provide new histologic clues to the pathogenic mechanisms underlying the rapid progression to heart failure.

2. Case study

2.1. Clinical history

The patient, a 23-year-old female, was the only child born to unrelated Italian parents with a family history of cardiac disease. Her living father had developed chronic ischemic heart disease following a myocardial infarction at 52 years of age, while her mother began experiencing symptoms of progressive heart failure during the fourth decade of life, with the first hospital admission at age 39 with an ejection fraction (EF) lower than 30%. The diagnosis of idiopathic dilated cardiomyopathy was made in this woman who died 5 years later due to a cerebral hemorrhage complicating the implant of a ventricular assist device. Since childhood, the patient had manifested mild intellectual impairment. At the age of 20, she was referred to the cardiomyopathy unit, division of cardiology and cardiac arrhythmias, of our institution for supraventricular tachyarrhythmias.

Electrocardiogram (ECG) exhibited a normal sinus rhythm with a preexcitation pattern (Fig. 1A). Echocardiography revealed severe