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Severe Cardiomyopathy from Limb Girdle Muscular Dystrophy: A Nidus for a Catastrophic Cascade

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Abstract We report a case of a 57-year-old female with Limb Girdle Muscular Dystrophy (LGMD) who initially presented to her outpatient physician a year ago with progressive shoulder and pelvic girdle muscle weakness associated with slight limitation of movement, gradual onset of easy fatigability, intermittent episodes of exertional dyspnea, and trace bipedal edema. On the day of admission, she had sudden onset of unresponsiveness due to massive cerebral infarct likely cardioembolic as evidenced by left ventricular thrombus, in the setting of severe cardiomyopathy associated from LGMD. The patient was treated with hemodynamic support and systemic anticoagulation but did not show any signs of neurologic improvement. Comfort care measures were initiated, eventually, the patient succumbed to death.

Keywords: *limb girdle muscular dystrophy, severe cardiomyopathy, congestive heart failure, cerebral infarction, cardioembolic stroke, left ventricular apical thrombus*

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1. Introduction

Severe cardiomyopathy in limb girdle muscular dystrophy is a rare complication that can be managed appropriately if considered early in the course of the disease. This would entail close surveillance to recognize symptoms and to prevent detrimental sequelae.

2. Case Presentation

A 57-year-old female diagnosed with limb girdle muscular dystrophy (LGMD) at age 52 when she presented with progressive weakness of her shoulder and pelvic girdles with associated worsening thigh muscle weakness resulting in slight limitation of movement. She had 4+/5 bilateral lower extremity motor strength. The diagnosis was confirmed by genetic testing with an unspecified genomic information and a muscle biopsy. No reported history of similar illness, cardiac disease, or sudden cardiac death in her family. She has been treated on intravenous immunoglobulin by her neurologist.

A year ago, besides her musculoskeletal complaints, she also noted gradual onset of easy fatigability and started complaining of intermittent episodes of exertional dyspnea. She denied any syncope, angina, orthopnea or paroxysmal nocturnal dyspnea. She had trace bipedal edema.

A week prior to her hospital admission, she complained of generalized malaise and worsening shoulder and thigh weakness but still managed to perform her activities of daily living. She continued to have progressive exertional dyspnea especially while climbing stairs such that she needed to rest in between flights. She had no dizziness, paroxysmal nocturnal dyspnea, orthopnea, palpitations or chest pain at this moment though had trace lower extremity swelling. On evaluation by her health care provider, her manifestations have been attributed to her LGMD.

On the day of admission, she was found unresponsive in the rest room with shallow and agonal breathing. She was intubated in the field and was subsequently admitted to the hospital at the intensive care unit. Patient had unstable hemodynamics and was started on pressors. She was comatose and was placed on ventilatory support. Cardiopulmonary assessment was unremarkable. Electrocardiogram showed sinus rhythm, left anterior fascicular block, and nonspecific T wave abnormalities. Troponin was not elevated. Transthoracic echocardiography revealed a large left ventricular apical thrombus and a severely reduced global right and left ventricular function with an ejection fraction of 25-30% (Figure A and Figure C). Chest radiography was consistent with pulmonary congestion (Figure B). Initial cranial computed tomography revealed no acute intracranial hemorrhage nor infarct but a subsequent cranial magnetic resonance imaging performed the next day exhibited extensive supratentorial infarction in the bilateral frontal, bilateral parietal, and right temporal lobes that appears to predominantly affect the anterior circulation (Figure D). She was started on systemic anticoagulation. During her course, she did not show any improvement in her clinical status and was declared by multidisciplinary team

specialist to have grave prognosis. Her family decided to initiate comfort care measures, thereafter, patient eventually expired. Autopsy showed cardiomegaly with an adherent thrombus in a dilated left ventricle and a cerebral infarct at bilateral anterior cerebral and right posterior cerebral artery territories.

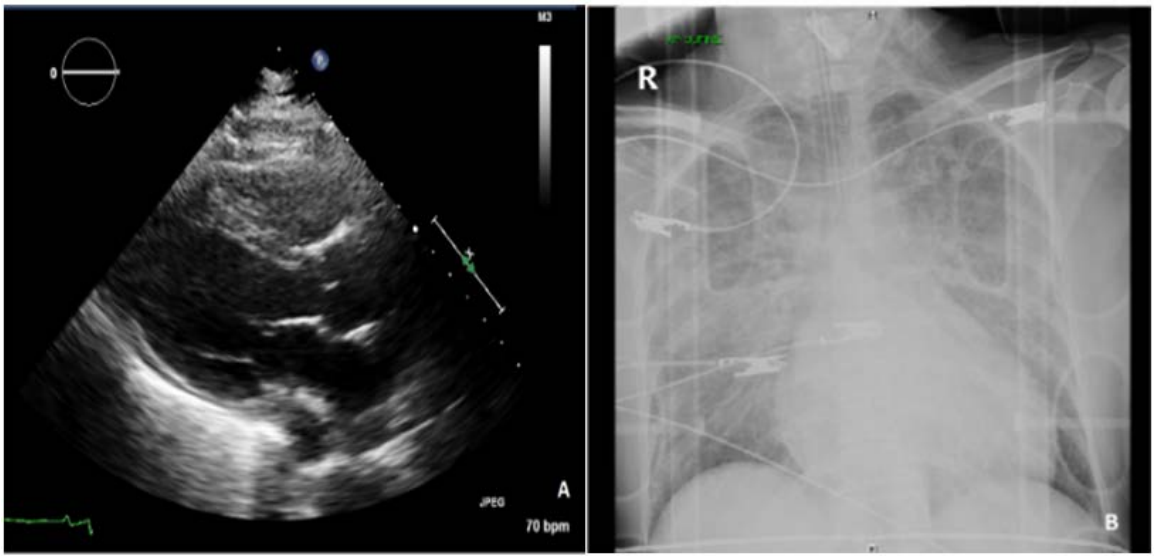

Figure A. Echocardiographic parasternal long axis revealing severe global left ventricular dysfunction with an estimated ejection fraction of 25-30%. **Figure B.** Anteroposterior chest radiograph showing pulmonary edema

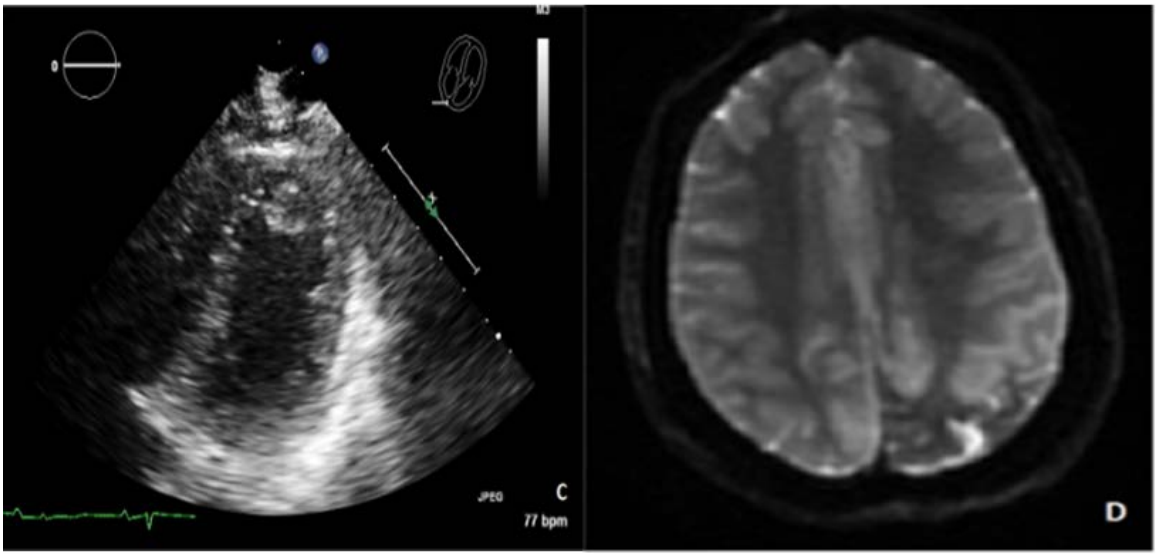

Figure C. Transthoracic echocardiogram showing left ventricular hyperechoic structure probably thrombus versus mass. **Figure D.** Diffusion weighted imaging sequence from cranial magnetic resonance imaging demonstrates diffuse bilateral cerebral restricted diffusion compatible with infarction

3. Discussion

Limb Girdle Muscular Dystrophy (LGMD) is a rare progressive muscular dystrophy genetic disorder that is characterized by wasting and predominantly proximal weakness of the voluntary muscles of the hip and shoulder areas. It is inherited either as an autosomal dominant or an autosomal recessive scheme [1] with indeterminate pattern of inheritance in some families [2]. Autosomal dominant LGMD is known as LGMD1 with eight subtypes (LGMD1A-1H) while autosomal recessive LGMD is known as LGMD2 has seventeen subtypes (LGMDA-Q) [3]. Because of the rarity of the other specific LGMD disorders, the estimated prevalence of LGMD varies from specific subtypes and ranges from 0.07 per 100,000 (LGMD2D and LGMD2E) to 0.43 per 100,000 (LGMD2I) [4].

To establish a specific type of LGMD, genetic testing for the specific gene alteration must be done first and a muscle biopsy should be contemplated if the genetic testing is not available or equivocal. Patients with LGMD subtypes linked with cardiac involvement and those with an LGMD phenotype without a specific genetic diagnosis should have a cardiology appraisal that includes electrocardiogram, structural heart studies with echocardiography or cardiac magnetic resonance imaging, and cardiac event monitoring to guide treatment [5].

LGMD may affect the myocardium in the form of hypertrophic or dilated cardiomyopathy as well as cardiac arrhythmias especially in LGMD2C-F,2l,and LGMD1B forms of the disease, rarely in the LGMD1C and 2B subtypes, and has not been reported in type 2A [6]. LGMD1B patients often exhibit findings of both

cardiomyopathy and dysrhythmia [7]. The arrhythmia in LGMD1 may present with an atrioventricular block, atrial fibrillation with high degree atrioventricular block and junctional escape rhythm, bradycardia, atrial standstill, and syncopal attacks [8]. Ten percent of LGMD patients have clinically relevant abnormalities that includes atrioventricular conduction disturbances in an autosomal dominant subtype and dilated cardiomyopathy in some advanced cases of the autosomal recessive and sporadic group [9]. In many cases of patients with subtypes including LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C to 2K, and LGMD2M to 2P lack overt symptoms of cardiac disease that may herald cardiac morbidity or sudden death [10]. Cardiac involvement exhibited as conduction disorders and/or myocardial abnormality are those connected with a defect in the genes coding for the α-(LGMD2D), β-(LGMD2E), γ-(LGMD2C), or δ-(LGMD2F) subunits of the dystrophin-associated sarcoglycan complex in cardiac and skeletal muscle [11]. Cardiomyopathy is also very common in LGMD2I, caused by a mutation in the enzyme fukutin-related protein (FKRP), which normally allows α-dystroglycan (peripheral membrane component of the dystrophin-associated glycoprotein complex) to bind with the extracellular matrix as an essential element in cytoskeleton linkage and sarcolemmal dystrophin-associated glycoprotein complex [10].

There is an increased risk for LV thrombus formation in heart failure with reduced ejection fraction whereas severe mitral regurgitation may have a protective effect by decreasing blood stasis [11]. Notably, up to 30% of patients with HF may have evidence of intracardiac thrombi on echocardiography [12] and studies suggest an increased embolic risk associated with LV thrombi, especially when they are associated with an apical aneurysm or are mobile [13]. Patients with documented LV thrombus who are not anticoagulated have a risk of embolization between ten to fifteen percent that usually occurs within the first three to four months [14] while anticoagulation with warfarin has an embolization rate reduction of eighty six percent [15].

Cardioembolic stroke may herald detrimental sequela especially in myopathic patients with cardiac manifestations such as arrhythmias and heart failure symptoms. An estimated fifteen percent of patients with primary myopathies have atrial fibrillation or flutter which significantly generated a stroke rate of around 6.5% [16]. Minimal available data regarding the incidence of ischemic stroke in laminopathy, mostly AD-EDMD and with a sole case of LGMD 1B have been reported; most suffered stroke on the fourth decade and have a documented cardiac arrhythmia [17]. Our patient is an addition to the rare case of LGMD who developed severe cardiomyopathy which lead to the formation of a substantial LV thrombus that culminated into massive cerebral infarction.

Cardiac transplantation has been effective in some patients with LGMD1B and other subtypes who succumbed to end stage congestive heart failure [18,19]. Pacemaker or ICD implantation should be considered to diminish the risk of sudden death due to bradycardia or ventricular tachyarrhythmia [20]. Otherwise, supportive management had been advocated for LGMD since there has been no specific treatment to modify the disorder. The cardiologist plays a critical responsibility in the multidisciplinary team approach to the disease in order to screen and manage the significant cardiovascular comorbidities and possible complications.

4. Conclusion

Early consideration, recognition, and evaluation of cardiomyopathy in patients with LGMD would initiate timely and appropriate treatment to alleviate symptoms and avert deleterious complications.

List of Abbreviations

LGMD=Limb Girdle Muscular Dystrophy; FRP=Fukutin-Related Protein; AD-EDMD=Autosomal Dominant Emery-Dreifuss Muscular Dystrophy; ICD=Implantable Cardioverter Defibrillator

Conflict of Interests

The authors declare that they have no conflict of interest.

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