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Case report

Mid-apical variant hypertrophic cardiomyopathy with filamin C mutation, an uncommon variant. Case report

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ABSTRACT

Hypertrophic cardiomyopathy presents with a broad spectrum of manifestations, including left ventricular outflow tract obstruction. The most common phenotype is the asymmetric septal variant, while the mid-apical variant is rare. Moreover, there are specific mutations associated with hypertrophic cardiomyopathy, with the filamin C variant being an unusual condition in these patients. We present the case of a 23-year-old male patient diagnosed with mid-apical variant hypertrophic cardiomyopathy, in whom a filamin C variant was documented. Due to an inadequate response and persistence of symptoms despite medical management, a myectomy procedure with a transapical approach was performed, resulting in subsequent improvement of clinical symptoms and outflow tract obstruction. This case illustrates an uncommon variant treated with a surgical approach different from the conventional transaortic method, leading to marked improvement of symptoms.

Palabras clave: Cardiomyopathy, Hypertrophic; Ventricular Outflow Obstruction, Left; Heart Failure (Source: MeSH NLM).

RESUMEN

Cardiomiopatía hipertrófica variante medio apical con mutación de la filamina C, una variante poco común. Reporte de caso

La Cardiomiopatía hipertrófica presenta diferentes espectros de presentación, entre ellos la obstrucción al tracto de salida del ventrículo izquierdo. El fenotipo más común es la variante septal asimétrica, siendo infrecuente encontrar la variante medio apical. Por otra parte, existen mutaciones puntuales asociadas a la cardiomiopatía hipertrófica siendo la variante de la filamina C una condición poco usual en estos pacientes. A continuación, se presenta el caso de un paciente sexo masculino de 23 años con diagnóstico de cardiomiopatía hipertrófica variante medio apical, en quien se documenta variante de la filamina C, ante la inadecuada respuesta y persistencia de sintomatología frente al manejo médico, se realizó el procedimiento de miectomía con abordaje transapical, con posterior mejoría de sintomatología clínica y obstrucción al tracto de salida. Este caso permite ilustrar una variante poco común con un abordaje quirúrgico diferente al convencional transaórtico con mejoría marcada de síntomas.

Keywords: Cardiomiopatía Hipertrófica; Obstrucción del Flujo de Salida del Ventrículo Izquierdo; Insuficiencia Cardiaca (DeCS-BIREME).

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary condition of the heart muscle which consists of an increase in the thickness of the left ventricular wall ≥15 mm in any myocardial segment, which cannot be explained solely by overload conditions [1]. HCM presents with various clinical manifestations, including left ventricular outflow tract obstruction (LVOTO) [2]. It commonly involves the septum in the basal portion; different phenotypes can be found, including the apical variant which varies in frequency depending on the studied population, up to 3 to 11% of HCM cases in the United States. It is more frequent in men than in women [3], with a proportion of cases with genetic diagnosis and Mendelian transmission being positive in up to 60% of patients [4] and is found mainly in individuals with sarcomeric or non-sarcomeric variants that generate different spectra of clinical presentation [5].

The filamin C (FLNC) variant is rare in HCM and has been associated with syndromic presentations and high risk of sudden death. This variant is more frequent in restrictive and non-dilated cardiomyopathy [1]. For this reason, we present the case of a patient diagnosed with asymmetric septal variant HCM, characterized by a significant intracavitary gradient and filamin C variant, in whom a transapical surgical approach was performed with subsequent improvement of symptoms.

Case report

A 23-year-old male patient, native of Itagüí - Colombia, with a family history of sudden death of unclear etiology in his grandfather at 50 years old, with no other significant family or personal medical history. He had been under external follow-up for recurrent syncopal episodes with a diagnosis of symptomatic sinus node dysfunction since childhood, for which a pacemaker was implanted.

During subsequent check-ups, there was no report of functional class deterioration until 2012 in Guayaquil-Ecuador. During his hospitalization, a generator change was performed; in the first postoperative month, he presented an early complication of pacemaker pocket infection, which required the explantation of the generator unit with subsequent abandonment of the previously implanted ventricular lead. A new pacemaker was implanted on the contralateral side without complications or records of new syncopal events in the following 10 years of follow-up.

Six months before admission, he presented deterioration to New York Heart Association (NYHA) functional class III, without other symptoms or reports of evaluations by the electrophysiology service since the last pacemaker generator implantation in 2012. During outpatient check-ups, the suspension of beta-blocker treatment was reported due to poor tolerance.

On physical examination, a II/VI systolic murmur was found in the aortic focus without radiation, and there were no signs

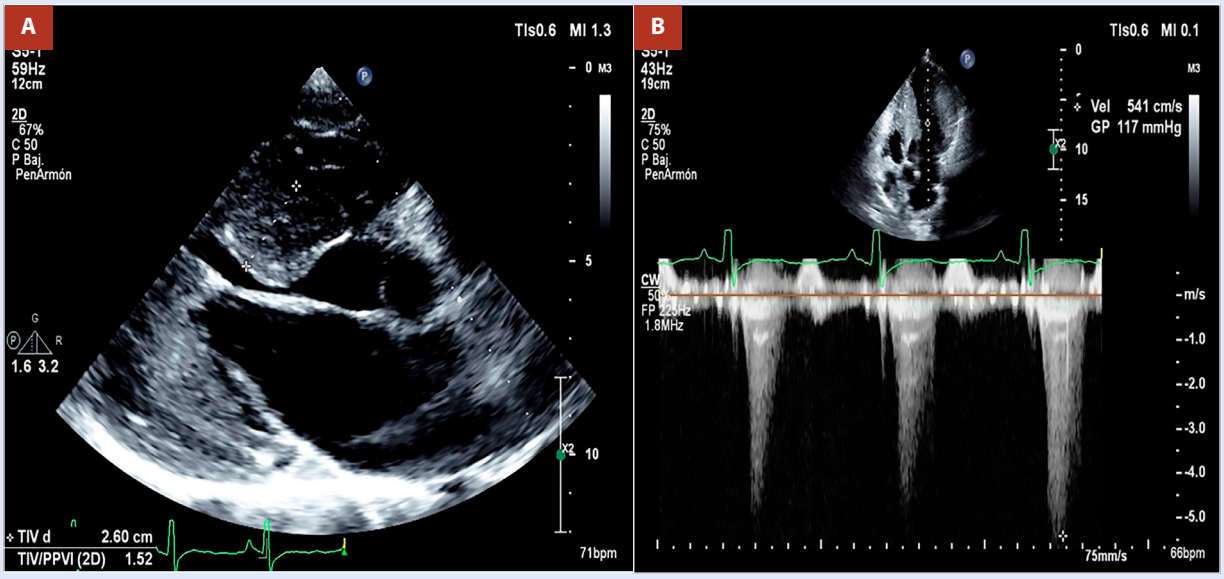

Figure 1. (A) Transthoracic echocardiogram in a long-axis parasternal view documenting a septum of 2.6 cm and evidence of mid-ventricular thickening. **(B)** Continuous wave Doppler of the left ventricular outflow tract (LVOT) showing a peak intracavitary gradient of 117 mmHg.

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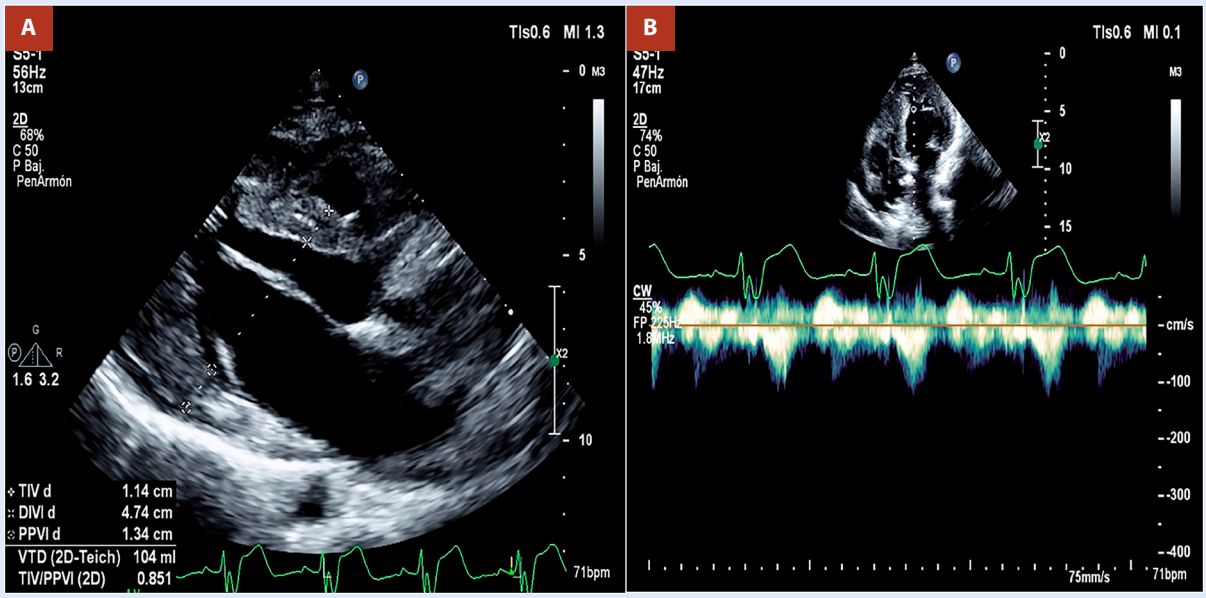

Figure 2. (A) Parasternal long-axis view showing a septum of 1.1 cm. **(B)** Continuous Doppler of the left ventricular outflow tract (LVOT) without evidence of intracavitary gradient.

of central or peripheral congestion. Laboratory tests showed no alterations in renal function, electrolytes, or hematological profile. The pacemaker was programmed with evidence of generator battery depletion. A transthoracic echocardiogram was performed, which showed severe concentric hypertrophy of the interventricular septum at the mid-ventricular level, measuring 26 millimeters with a peak intracavitary gradient of 117 mmHg **(Figure 1)** and systolic anterior motion of the mitral valve (SAM), which generated mild mitral regurgitation.

The patient was evaluated by the Heart Team due to the sudden death risk score (16.8%) and family history of sudden death, considering a EUROSCORE II of 0.67%. Regarding the previously abandoned electrodes and the contraindication for cardiac magnetic resonance imaging due to pacemaker incompatibility, a tomographic study was performed, and myectomy was considered due to symptoms and documented variant.

The patient was scheduled for mid-ventricular myectomy via a transapical approach with electrode removal. A left ventriculotomy was performed at the apex, followed by resection of the septum from the mid-ventricular part to the base, with subsequent removal of electrodes adhered to the tricuspid septal leaflet. There were no intraoperative complications, and subsequently, a decrease in the intracavitary gradient without the presence of the SAM phenomenon **(Figure 2)**.

During his stay in the Intensive Care Unit, the patient experienced two documented episodes of ventricular tachycardia with hemodynamic instability, for which an implantable cardioverter-defibrillator (ICD) compatible with magnetic resonance imaging (MRI) ST Jude was placed, with no new episodes of ventricular tachycardia occurring. The patient had no further complications, and outpatient genetic studies were initiated due to his family history.

The patient had a favorable postoperative evolution after ICD implantation. Genetic studies found a probably pathogenic variant in heterozygosis of FLNC, c.4636G>A, consistent with autosomal dominant familial hypertrophic cardiomyopathy type 26.

Currently, the patient is classified as functional class I, with no arrhythmias evidenced on telemetry and on regular treatment with Bisoprolol 5 mg. Expansion of genetic testing to direct family members was initiated; however, due to limited access to health services, its execution was limited.

Discussion

HCM is one of the most common cardiomyopathies worldwide, with an estimated prevalence of 0.2% (1). Most HCM cases are associated with eight established sarcomeric variants; this leads to an alteration in the coding of proteins involved in calcium homeostasis or genes that code for Z-disc proteins, such as FLNC, which occur less frequently in HCM [6].

FLNC is a large dimeric protein that binds to actin and is located in the premyofibrils, Z-discs, and intercalated discs where it intervenes in the mechanical stabilization and intracellular signaling of myocytes [6,7]. FLNC variants have been more associated with the development of restrictive and arrhythmogenic cardiomyopathies. However, mutations in this protein can alter the structure of the

sarcomere, generating an altered organization of the myofibrils. This structural alteration generates protein aggregates that ultimately lead to sarcomeric disorganization and the probable development of HCM [8]. Non-sarcomeric mutations, such as FLNC, have been more associated with the development of isolated basal septal hypertrophy, with less late gadolinium enhancement, but more LVOTO [5], as presented in the current case patient.

The implicated genetic finding is of vital importance due to the close relationship between FLNC and sudden death, which has been studied in patients with dilated, arrhythmogenic, and hypertrophic cardiomyopathy. This variant is associated with a 5-year prevalence of advanced heart failure, and development of ventricular arrhythmias between 22 to 27%, being the first reported case in Colombia.

Regarding myectomy, the extended transaortic septal technique is the best treatment option for patients with LVOTO whose symptoms are refractory to medical treatment. On the other hand, this approach is useful for patients with subaortic obstruction [9]. For patients with mid-ventricular obstructive (MVO) involvement as the underlying cause of the residual gradient, a transapical approach is effective [10]. In a cohort of 115 patients who underwent this technique between 1993 and 2012, of which 55 patients had an MVO phenotype (n=55), all patients showed a decrease in gradient and no subsequent complications such as ventricular septal defects, left ventricular pseudoaneurysm, or ventricular arrhythmias. The transapical approach proved to be safe and effective for MVO relief, with hemodynamic results similar to the transaortic approach [11,12]. This same approach was performed in our patient, with subsequent clinical success, decrease in gradient, and improvement of clinical symptoms.

In conclusion, the FLNC variant has been largely associated with restrictive and non-dilated cardiomyopathies, with infrequent presentation in patients with HCM. Genetic study is crucial in the diagnosis and prognosis of these patients due to the high risk of sudden death in populations with the FLNC variant. This information is essential for guiding our therapeutic approach, especially in relation to disease progression and the potential need for advanced medical devices. There are no reported cases in our context about myectomy with a transapical approach in these patients; however, it is another alternative for these patients with MVO, with significant improvement and safety in the patient's clinical outcomes.

Ethical aspects

For the preparation and presentation of this case, prior informed consent was obtained from the patient, clearly explaining the confidentiality and protection of their data. Subsequently, the patient signed and accepted the sharing of the case. The informed consent is kept in the research archives of the CardioVID clinic.

Authors' Contributions

JDOB and CHP: conceptualization, investigation and writing - original draft. **CIS:** conceptualization, investigation and writing - review & editing. **LFD y JCR:** supervision and writing - review & editing.

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