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Idiopathic Dilated Cardiomyopathy Associated with Bicavitary Thrombi: Case Report, Diagnostic Approach and Literature Review

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ABSTRACT

Dilated cardiomyopathy is considered as a dysfunction of the left ventricle systolic function or even both ventricles associated with myocardial dilation. Approximately 50% of cases have an identifiable cause such as genetic mutations, infectious, autoimmune or metabolic diseases, among others. When the origin of dilated cardiomyopathy is not identified, it is considered idiopathic, which constitutes the other 50% of cardiomyopathies. The diagnostic approach is based on laboratory and image studies trying to identify the known causes of dilated cardiomyopathy, the treatment consists in those cases of known etiology cardiomyopathy in the treatment of the underlying disease as well as the heart failure if it presents, if the etiology is unknown we only focus in improve the symptoms caused by cardiomyopathy.

We present a case of a 27-year-old man with history of sudden cardiac death in a second degree relative, who initially presented signs of heart failure with later pulmonary thromboembolism secondary to biventricular intracardiac thrombi. A complete diagnostic approach was performed, ruling out genetic and non-genetic causes of dilated cardiomyopathy, without being perform an endomyocardial biopsy to complete the diagnostic approach due to the risk that the procedure involved and the patient's refusal.

KEYWORDS: Dilated cardiomyopathy, Systolic dysfunction, Biventricular intracardiac thrombi, Heart failure, Endomyocardial biopsy.

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INTRODUCTION

Dilated cardiomyopathy (DCM) is defined as the presence of isolated left ventricle dilation with or without systolic dysfunction of the or both ventricles. Likewise, is well known that the hypokinesia of the left ventricle without initially dilation could lead us to suspect DCM [1].

Approximately 50% of patients with DCM have an identifiable etiology, of which around 30 to 40% are secondary to a genetic mutation. However, in the remaining 50% the cause is often not identified and is called idiopathic DCM [1,2]. Idiopathic DCM is an exclusion diagnosis that is reached unequivocally after ruling out other identifiable causes.

Among the genetic origin causes, the majority come from mutations that are transmitted in an autosomal dominant, mainly those involved in the titin and laminin genes [3].

In the identifiable group of non-genetic origin, inflammatory causes (such as infectious or autoimmune diseases), metabolic, toxic and even peripartum cardiomyopathy, among others, stand out.

The clinical picture of DCM is very heterogeneous, the vast majority manifests with signs of left sided heart failure, being the dyspnea the most characteristic symptom generally accompanied by other manifestations such as lower limb edema and cough [4].

During the initial evaluation of DCM various diagnostic tools are useful, such as: Laboratory studies to establish

metabolic or inflammatory causes, 12-lead electrocardiogram and echocardiogram, which are essential for the diagnosis and initial and subsequent monitoring of systolic function[1,3,5].

In difficult cases when it's not possible to reach an etiological diagnosis by the initial methods previously mentioned, comes into the role the cardiovascular magnetic resonance (CMR) which evaluates the hearth anatomy and is very useful to differentiate storage disorders from those caused by congenital heart diseases and the endomyocardial biopsy (EMB), which is the gold standard to confirm the etiology [1].

The treatment goal for idiopathic DCM is improve the quality of life mitigating the symptomatology and minimizing the exposure to risk factors [6].

We present the case of a 27-year-old male, in whom despite an exhaustive search for the etiology, a final diagnosis was not reached, considering it to be an idiopathic DCM, so in this review the currently existing diagnostic methods will be analyzed, which will allow us to reach the etiological diagnosis, since some causes may benefit by receiving additional treatment and can improve the prognosis of our patients.

CASE REPORT

We present a case of a 27-year-old male patient with a history of a second-degree relative who died due to a sudden death of apparent cardiac origin at the age of 45-year-old. He has not significative personal pathological history. His symptomatology began 2 months prior to our evaluation with medium exertion dyspnea accompanied with cough and salmon-like expectoration, sometimes associated with hemoptysis, as well as edema of the lower limbs. This symptomatology had a progressive development, so he decided to go to assessment.

Initially, the follow vital signs were obtained:

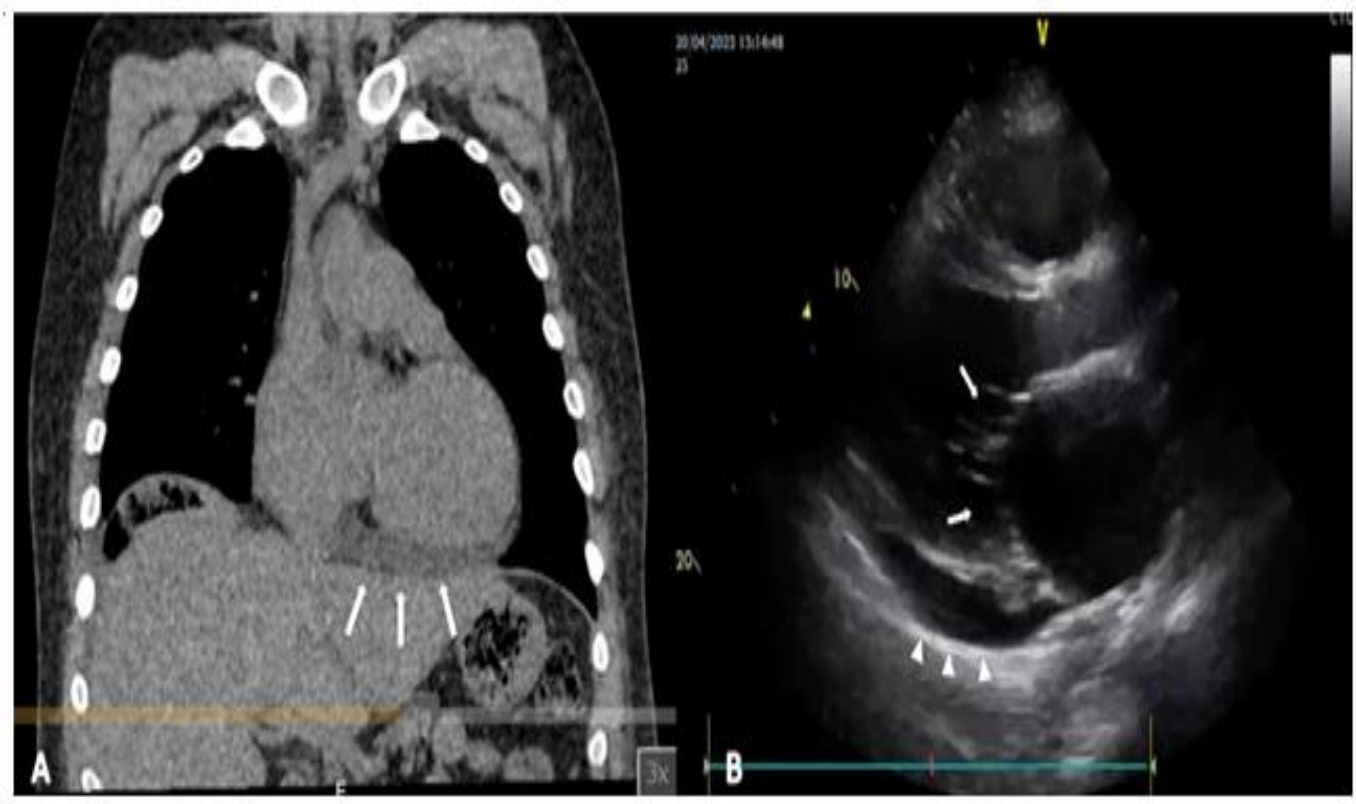

Figure 1. A) Simple chest tomography in coronal section cardiomegaly associated with pericardial effusion is observed (Arrows). B) TTE that shows in the long parasternal axis an evident myocardial dilation associated with a dome-shaped mitral valve in the left ventricle (Arrows), as well as moderate pericardial effusion (Arrowhead).

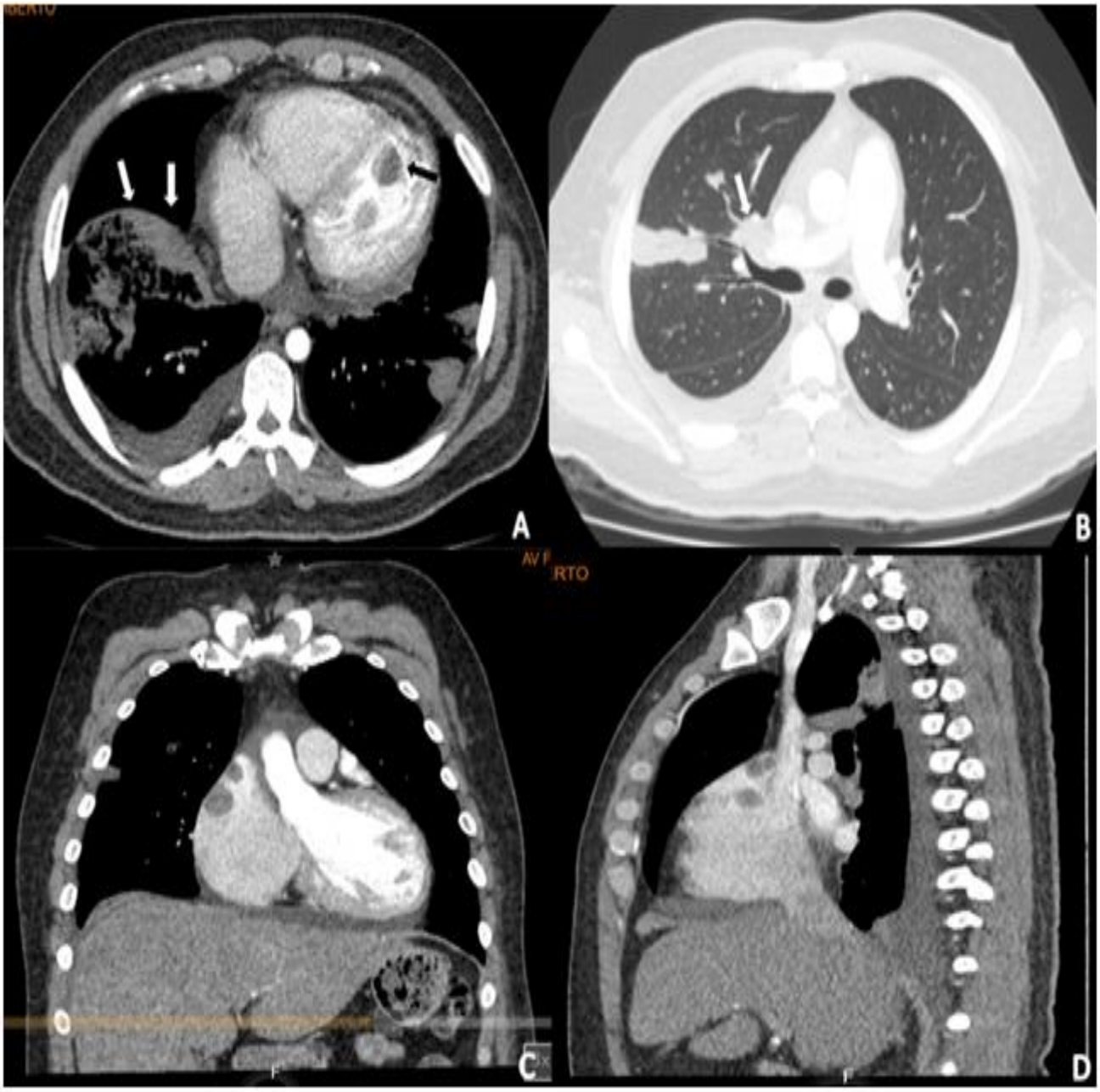

Figure 2. Simple and contrast-enhanced chest tomography. A) In the mediastinal window, intracavitary thrombus is seen in the left ventricle (Black arrow), as well as a region of alveolar ischemia in the right lung (White arrows); B) In the pulmonary window, a thrombus is seen in the right pulmonary artery (white arrow) with subsequent area of pulmonary ischemia; C) Coronal section, bicavitary thrombi are observed; D) Sagittal section that shows multiple thrombi in the right atrium.

T/A 100/60 mmHg, Fc 95x´ Fr 23x´ T 36.3º, and laboratories: D-dimer 8125 mg/L, leukocytes 10.4 K/ul, hemoglobin 13.6 g/dl, platelets 234 K/ul, DHL 316 U/L, urea 42.8 mg/dl, BUN 19.97 mg/dl, creatinine 1.08 mg/dl.

As an initial approach to the dyspnea, a simple chest x-ray was performed with evidence of pulmonary congestion as well as an increased cardiothoracic index. A CT (Computed tomography) was requested, which didn't report data of pulmonary pathology, only cardiomegaly with associated pericardial effusion (Fig 1A). Given this finding, a transthoracic echocardiogram (TTE) was performed, highlighting the presence of grade III diastolic dysfunction, biventricular systolic dysfunction with LVEF of 32% associated with severe biatrial dilation, a 26mm diameter vena cava, and a moderate pericardial effusion of 1.2cm in the inferolateral wall (Fig 1B). The initial implemented treatment were with sodium-glucose cotransporter 2 inhibitor (SGLT-2i), beta-blocker (BB), angiotensin-converting enzyme inhibitor (ACEI), loop diuretic and potassium-sparing diuretic, with after symptomatic improvement. It was decided to discharge him from the hospital, however after two weeks he returned with signs of

acute heart failure associated with intermittent episodes of hemoptysis. New laboratories were performed: Leukocytes 11.5 K/ul, hemoglobin 14.5 g/dl, hematocrit 43.7%, platelets 314 K/ul, albumin 2.95 g/dl,

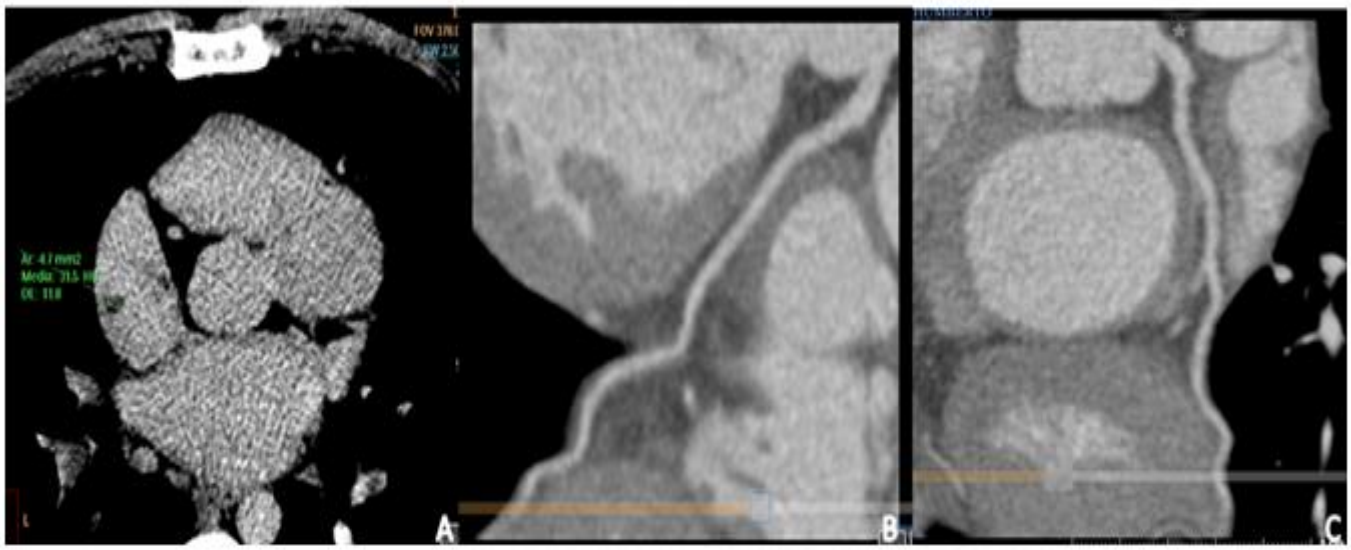

Figure 3. A) Cardiovascular computed angiotomography. Intracavitary thrombus in the right atrium of 5-7mm diameter is observed; It was reported a left ventricular diastolic diameter of 64 mm with diastolic volume of 245 ml, right ventricle of 203 ml without evidence of atherosclerotic disease. B) and C) Anterior descending and circumflex arteries can be seen, respectively, without anatomical alterations in their course.

ALT 115.5 U/L, AST 111.4 U/L, BD 2.95 mg/dl , BI 0.22 mg/dl, BT 3.17 mg/dl, DHL 418 U/L, Tp 42.2s, Tpta 31.7s, INR 3.82, potassium 6.04 mEq/l, urea 66.2 mg/dl, bun 30.89 mg/dl, creatinine 1.63 mg/dl, sodium 134 mEq/l, evidencing the presence of acute kidney injury and congestive liver, the treatment was readjusted, on this occa-

Table 1. Laboratory history. No alterations of any suggestive etiology of DCM were observed.

Infectious profile			
Ac. Anti-Cytomegalovirus (IgG): 174 UI/mL	**Ac. Anti-Cytomegalovirus (IgM):** 0.201 UI/mL	**Ac. Anti-Rubella (IgG):** 337 UI/mL	**Ac. Anti-Rubella (IgM):** 0.296 UI/mL
Ac. Anti-Toxoplasma gondii (IgG): 0.180 UI/mL	**Ac. Anti-Toxoplasma gondii (IgM):** 0.247 UI/mL	**VDRL:** Negative	**Ac. Anti-Trypanosoma cruzi:** Negative
HCV, HBV, HIV: Non-reactive	**CRP:** 2.6 mg/dl	**ESR:** 24 mm/h	
Rheumatological profile			
Lupus anticoagulant: Negative 1.12 UR/ml	**Anti-proteinase 3:** Negative <2.3 UR/ml	**Rheumatoid factor:** 10 UI/ml	**Anticardiolipin Antibodies (IgG):** Negative 2.5 U/ml
Anti-smith: Negative <3.3 UR/ml	**Anti-myeloperoxidase:** Negative <3.2 UR/ml	**Anticardiolipin antibodies (IgM):** Negative 2.3 U/ml	**Complement C3:** 175.0 mg/dl
Anti-beta 2 glycoprotein (IgM): Negative <1.1 UR/ml	**Anti-beta 2 glycoprotein (IgG):** Negative <6.4 UR/ml	**Antinuclear antibodies:**1:80 Negative	**Complement C4:** 27.8 mg/dl
Hematological profile			
Ferritin: 156.7 ng/ml	**Serum iron:** 81 µg/dL	**Iron-binding capacity:** 263 µg/dL	**Transferrin saturation:** 23.5%
Transferrin: 294 mg/dl	**Protein C:** 101%	**Antithrombin:** 105.0%	**Protein S:** 178%
Von-Willebrand factor: 212.7%	**Alpha-fetoprotein:** 3.25 ng/ml	**Carcinoembryonic antigen:** 2.58 ng/ml	**Human Chorionic Gonadotropin:** <2.30 mUI/ml
Fibrinogen: 409 mg/dl			
Cardiometabolic profile			
Pro BNP: 4255 pg/ml	**Troponin T:** 23.9 ng/l	**Total cholesterol:** 166 mg/dl	**Triglycerides:** 178 mg/dl
Cholecalciferol: (Vitamin D3):15.50 pg/ml	**Total T3:** 1.09 ng/dl	**Free T4:** 0.66 ng/dl	**TSH:** 1.63 mIU/L
Total T4: 4.66 ng/dl	**Free T3:** 2.81 ng/dl	**CPK:** 128 U/L	**CPK-MB:** 183 U/L
Genetic profile			
Titin: Negative	**Laminin:** Negative		

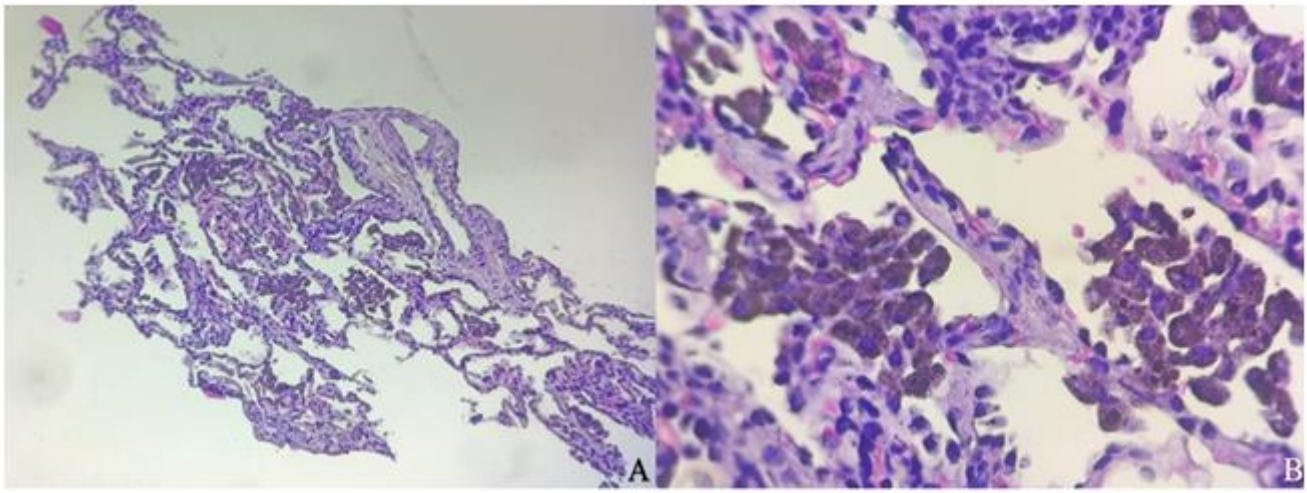

Figure 4. Pulmonary biopsy A) Histopathological staining with H&E 400x. Multiple inclusions of macrophages with hemosiderin are seen around the alveoli. B) H&E 100x Histopathological staining we can observe the multiple and dispersed macrophage inclusions through the alveoli.

sion due to recurrent hemoptysis, secondary pulmonary embolism (PE) was suspected, chest angiotomography was performed and it reported thrombosis in the right pulmonary artery as well as presence bicavitary cardiac thrombi, anticoagulation with rivaroxaban was started with subsequent cessation of the hemoptysis episodes (Fig 2).

Given no etiological evidence of his heart failure, his diagnostic approach began with multiple laboratory and image studies (Table 1), (Fig 3). However, none of them were conclusive, ruling out the possibility of ischemic, infectious, rheumatological, or metabolic etiology, and even after the negativity of titin and laminin, a probable genetic disease was ruled out. As part of the PE follow-up, a new chest CT was performed, reporting data of chronic PE associated with multiple lung nodules. Sarcoidosis was suspected as the origin of said nodules and the cardiomyopathy. However, after performing a transthoracic lung biopsy, the possibility was ruled out after report only macrophages with hemosiderin around the alveoli (Fig 4).

During the rest of the approach, an endomyocardial biopsy was offered, however, given the risk that the procedure implied, our patient refused, so symptomatic management of the heart failure was continued. After two months of follow-up, he remains with adequate control without evidence of new decompensation.

DISCUSSION

The definition of DCM requires the presence of left ventricular dilation with systolic dysfunction in the absence of alterations during the afterload that could justify it, such as hypertension, valvular disease or coronary disease. DCM is considered one of the most frequent causes of heart failure, having an annual incidence between 5 to 8 cases per 100,000 habitants [3].

According to the DCM classification of the European Society of Cardiology, DCM are divided in two large groups, from genetic and non-genetic origin [5].

In the group of non-genetic etiologies, the most common causes are those from an infectious origin (Chagas disease, enterovirus infection), metabolic diseases (Thyroid disorders), toxic (Alcohol, drugs), peripartum cardiomyopathy, cardiac sarcoidosis among others (Table 2).

Although non-genetic causes tend to be quite frequent, it's essential to consider genetic causes since most of them are mutations with autosomal dominant inheritance (Table 3).

In general, as part of the initial approach, an adequate anamnesis should be taken aimed at ruling out important history such as: family history of heart disease or sudden death, systemic arterial hypertension, coronary disease, valvular disease, exposure to cardiotoxic drugs, chemotherapy and radiation [3].

Laboratory and image studies are an essential part of the approach, such DCM has a varied etiology, these diagnostic elements must be aimed as the clinical history, to ruling out each of the possible etiologies of DCM.

With the wide range of laboratory studies available today, certain infectious etiologies can be ruled out by performing a viral panel (Hepatitis B, hepatitis C, human immunodeficiency virus), serology for Toxoplasma gondii and Trypanosoma cruzi (Chagas disease) [7]. Chagas disease represents one of the main etiologies of DCM and an endemic cause in our country despite that its prevalence has been decreasing, going from 16-18 million people in

Table 2. Main non-genetic causes of DCM [1,3,7,8].

Inflammatory	
Infectious myocarditis	The main causal agents are viruses (Enterovirus, parvovirus B19, Herpesviridae, SARS CoV 2). Other infectious agent is Trypanosoma cruzi, which represents a very common cause of DCM in Latin America [1,7].
Autoimmune diseases	Rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, granulomatosis with polyangiitis and allergic granulomatosis [6]. They can cause acute or chronic myocarditis and it is estimated that 20% of patients with myocarditis may develop DCM within one year [1].
Metabolic	
Thyroid disorders	Thyroid hormones exert control over inotropism and lusitropism. Both hypothyroidism and hyperthyroidism can cause heart damage; But it is essential to differentiate heart failure from hypothyroidism since the clinical picture can be extremely similar (dyspnea, edema, pleural effusion, lower contractility and cardiac dilation) [3].
Toxic	
Alcohol	It is one of the main toxins, if it has been consumed excessively and chronically (> 80g per day for a period of at least 5 years) can cause DCM, its probability increases if an alteration occurs if the patient has a genetic variant of myosin isoforms. An excessively alcohol consumption can causes excessive production of free radicals and oxidative stress, the myocytes are highly sensitive to them and this interferes with calcium homeostasis, mitochondrial function in addition to the structure and function of contractile proteins [8].
Chemotherapeutics	Anthracyclines and imatinib can cause myocytes necrosis. Trastuzumab doesn't cause cell death, it adverse effects can be reversible and its associated with a better prognosis.
Cocaine and amphetamines	They damage the myocardium by vasospasm.
DCM: Dilated myocardiophaty	

the nineties to 8-10 million people at today [9]. Its diagnosis is established by at least two positive serological tests of the following: ELISA, immunofluorescence or hemagglutination, which detect antibodies against Trypanosoma cruzi [9], which were performed in our patient and were reported negative.

Likewise, other laboratory tests are of vital importance, such as antibodies, thyroid hormones, inflammatory markers, coagulation studies, cardiac enzymes, hematological panel and even genetic tests with the aim of ruling out the most common causes of DCM mentioned previously.

Genetic study is used when the etiology of the cardiomyopathy is unknown and other causes were ruled out since it has been shown that approximately 20-35% of DCM have a family association with at least 4 previous generations. Within the approach of our patient the main mutations were excluded. However it is worth mentioning that there are less common mutations that our genetic study did not detect.

Among the image studies that can be useful in the initial approach there are the chest x-ray, which serves as support to rule out other associated respiratory diseases, and electrocardiogram, despite it not being specific there are certain electrocardiographic criteria that can be useful if there are a high suspect of DCM like a complete left bundle branch blocks, evidence of atrial fibrillation or other arrhythmias, pathological Q waves that are usually associated with pre-existing coronary pathology, among others [3].

TTE is the study of choice to evaluate systolic and diastolic myocardial function of the right and left ventricles, as well as the identification of structural anomalies in patients with a high suspicion of coronary disease, myocarditis or valvular diseases and in turn helps to define whether are secondary to ventricular dilation or whether they have a primary origin, thus being the probable cause of dilated cardiomyopathy [3]. In the case of our patient, ventricular dilation was confirmed by TTE and the primary valvular disease was ruled out.

More specific studies used to rule out ischemic etiology are cardiac catheterization, cardiac magnetic resonance or coronary angiotomography, the last one was performed on

Table 3. Main genetic mutations related with DCM [1,3,10,11].

Mutation	Inheritance	Characteristics
Titin	AD	Thick filament binding protein to the Z line. It represents 25% of cases of congenital DCM and 8 to 15% in acquired DCM, and is associated with a higher risk of ventricular tachyarrhythmias.
Laminin	AD	Protein with nuclear membrane intervention. It represents 5% of DCM cases and presents with a high rate of ventricular arrhythmias and atrial fibrillation. Increased risk of sudden cardiac death.
Myosin heavy chain	AD	Early onset age. Lower LV remodeling.
Troponin T	AD	Mild dysfunction. It presents as HCM or DCM.

AD= Autosomal dominant, DCM= Dilated cardiomyopathy, HCM= Hypertrophic cardiomyopathy, LV= Left ventricle.

Our patient and it is very useful in the evaluation of patients with cardiomyopathy of ischemic origin to evaluate myocardial viability [3].

Despite the advances in image diagnosis of DCM, the gold standard continues being the endomyocardial biopsy (EMB), however its use has decreased over the time because it be an invasive study with a high rate of complications. EMB was impossible to do in our patient because he didn't accept the procedure due to the risks that it involved, given the lack of evidence of underlying etiology in the rest of the studies, we concluded our case as an idiopathic DCM.

For patients with DCM, treatment consists in symptomatology control and if it's necessary on the prevention and treatment of the underlying etiology. There is a group of patients in whom it's necessary provide anticoagulant treatment, such as those who have a history of atrial fibrillation, transient ischemic attack, stroke, deep venous thrombosis, pulmonary embolism, pregnant women with LVEF <30% due to the existing hypercoagulability state in pregnancy or when there is a demonstrable intracardiac thrombi as was the case of our patient [12].

The recommended symptomatic treatment which improves the functional capacity in heart failure with reduced LVEF in patients with DCM and which our patient is currently taking, is with ACEI (In case of not tolerating angiotensin/neprilysin receptor inhibitors (ARNI) which is the treatment of choice), BB, loop diuretics, aldosterone antagonist and iSGLT2.

This treatment basis on the "Fantastic four" provide a prognostic benefit reducing the cardiovascular and general mortality, the hospitalizations due to acute heart failure, as well it improves the symptoms and quality life, since they improve the cardiac output [6]. On the other hand, there is no evidence of antiarrhythmic prophylactic treatment different than BB for the prevention of sudden cardiac death. [13],[14],[15].

Sustained ventricular tachycardia and ventricular fibrillation in patients with dilated cardiomyopathy and heart failure with reduced LVEF are common and life-threatening arrhythmias, so primary prevention of sudden cardiac death should be considered based on risk stratification. Given the reported LVEF of our patient and based on a trial of sudden cardiac death in heart failure, he could benefit from the prophylactic placement of an implantable cardioverter-defibrillator, since it has been seen that there is a significant reduction in mortality in these patients [16],[17].

The two main surgical treatment options in patients with DCM are the long-term mechanical circulatory support and hearth transplant

The second option is the most viable in our patient given his age, life prognosis and lack of associated comorbidities [18].

The dilation and ventricular dysfunction that occurs in DCM induces an hypercoagulability state, it has been shown that there is an association of 37% risk of present thromboembolic events in patients with DCM without etiology and without anticoagulant treatment because these patients presents thrombi in left atrial in 68.9% and in the LV in 13.3% of cases [19].

Regarding the role of prophylactic anticoagulation, there are randomized clinical trials (Watch and Waref) that revealed that in patients with reduced LVEF secondary to ischemic heart disease or DCM and sinus rhythm there is only a slight benefit of anticoagulant therapy with warfarin compared with antiplatelet therapy in terms of decreased risk of ischemic stroke, however with increased bleeding risk [19].

There is more experience with vitamin K antagonists, however, currently the new oral anticoagulants

(NOACs) such as dabigatran, rivaroxaban, etc., Have proven to be a good option reducing the risk of thromboembolism and with lower bleed risk so they are considered a promising alternative [19,20].

In case of haven't receive prophylactic anticoagulation and when there are intracavitary thrombi associated, there are various treatment options, such as anticoagulation at therapeutic dose, thrombolysis, percutaneous removal and surgical intervention [21].

Warfarin has long been used in the treatment of intracavitary thrombi, reducing the risk of thromboembolism by 33% particularly in those thrombi located at the left ventricle [22], the recommended treatment duration by some groups is currently 3 months, others groups recommend it until resolution of intracavitary thrombi on follow-up images [23].

In those patients who are not candidates for warfarin, such as those with abnormal liver function, use of cytochrome P450 inhibitor drugs, a history of labile INR and poor monitoring with INR, NOACs have been used as a treatment for intracavitary thrombi, especially for those located in the left ventricle, having a successful response reported in some publications [24,25].

Despite NOACs being a promising treatment, due to the rarity and little evidence in anticoagulation zzbicavitarthrombi, are not considered as first-line therapy, so we consider that the management of our patient priority for risk stratification, prognostic and to evaluate iinteresting and could provide some evidence for future guidelines on the use of NOACs in those patients with similar conditions.

Monitoring of intracardiac thrombi resolution is performed with transthoracic echocardiography or cardiac magnetic resonance, generally 3 months after the start of anticoagulation [21]. If there is not resolution of the thrombi in repeated images or there is embolism, it is indicated surgical treatment or percutaneous intervention for thrombi removal [26].

CONCLUSION

At today dilated cardiomyopathy is one of the main causes of cardiovascular morbidity and mortality, the DCM has multiple etiologies which are important to identify by an adequate diagnostic approach to provide timely treatment focused on treating the triggering factor. However, there are cases in which the etiology is not determined after carrying out initial studies. Being necessary perform genetic studies and high-resolution imaging as appropriate, however due there are expensive and have little availability in the health system, there are cases in which an etiology is not identified. So it is essential to establish DCM as a new pharmacological therapies.

CONFLICT OF INTERESTS

The authors have declared no conflicts of interest.

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