ORIGINAL ARTICLE

CME

Etiologic Diagnosis of Cardiomyopathy in Heart Transplant Recipients. Agreement Between Pretransplant Clinical Diagnosis and Pathology

Diagnóstico etiológico de la miocardiopatía en pacientes receptores de trasplante cardíaco. Concordancia entre el diagnóstico clínico pretrasplante y la anatomía patológica

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ABSTRACT

Introduction: Etiologic diagnosis in patients with end-stage cardiomyopathy can be challenging. A large number of patients remain undiagnosed despite a thorough evaluation, so they are classified as idiopathic dilated cardiomyopathies.
Objectives: To describe the etiology of cardiomyopathy in heart transplant recipients according to pretransplant clinical diagnosis and its degree of agreement with the anatomopathological diagnosis of the explanted heart.
Methods: We performed a retrospective analysis of consecutively transplanted patients in a high complexity hospital of the Autonomous City of Buenos Aires from 2003 to the end of 2013. An agreement analysis between pretransplantation clinical diagnosis and anatomopathological diagnosis of the explanted heart was done using the kappa coefficient.
Results: One-hundred patients with mean age of 49.7 ± 12.5 years at the time of transplantation and median ejection fraction of 26.6% were analyzed. The most common pretransplant clinical diagnosis was idiopathic dilated cardiomyopathy (37%), followed by ischemic-necrotic cardiomyopathy (32%) and Chagas cardiomyopathy (10%). The most common histopathological diagnoses were ischemic-necrotic cardiomyopathy (35%), hypertrophic cardiomyopathy (10%), Chagas cardiomyopathy (10%) and myocarditis (8%); a causal diagnosis was not reached in 25% of cases (idiopathic dilated cardiomyopathy). The kappa coefficient was 0.64 (CI 0.52 - 0.76).
Conclusions: Approximately one third of patients reach transplantation without an etiologic diagnosis. Anatomopathological analysis allows identifying the cause in more than half of these patients. Although the correlation between pretransplant diagnosis and pathological anatomy was statistically adequate, a significant percentage of patients could benefit from a more specific etiologic diagnosis, which may have prognostic, therapeutic and/or family assessment implications.

Key words: Cardiomyopathy - Etiology - Heart Transplant - Pathology.

RESUMEN

Introducción: El diagnóstico etiológico en pacientes con miocardiopatías en estadio avanzado puede ser un desafío. Un gran número de pacientes permanecen sin diagnóstico a pesar de una evaluación exhaustiva, por lo que quedan rotuladas como miocardiopatías dilatadas idiopáticas.
Objetivos: Describir la etiología de la miocardiopatía en pacientes receptores de trasplante cardíaco según el diagnóstico clínico pretrasplante y su grado de concordancia con el diagnóstico anatomopatológico del corazón explantado.
Material y métodos: Se realizó un análisis retrospectivo de pacientes consecutivos trasplantados en un hospital de alta complejidad de la Ciudad Autónoma de Buenos Aires desde 2003 hasta fines de 2013. Se efectuó un análisis de concordancia entre el diagnóstico clínico pretrasplante y el diagnóstico anatomopatológico del corazón explantado utilizando el coeficiente kappa.
Resultados: Se analizaron 100 pacientes con una edad media en el momento del trasplante de 49,7 ±12,5 años y una mediana de fracción de eyección del 26,6%. El diagnóstico clínico pretrasplante más frecuente fue el de miocardiopatía dilatada idiopática(37%), seguida por la miocardiopatía isquémico-necrótica(32%) y la miocardiopatía chagásica (10%). Entre los diagnósticos histopatológicos más frecuentes se encontraron el de miocardiopatía isquémico-necrótica (35%), de miocardiopatía hipertrófica (10%), de miocardiopatía chagásica (10%) y de miocarditis (8%); no se arribó a un diagnóstico causal en el 25% (miocardiopatía dilatada idiopática). El resultado del coeficiente kappa fue de 0,64 (IC 0,52-0,76).
Conclusiones: Aproximadamente un tercio de los pacientes llegan al trasplante sin un diagnóstico etiológico. El análisis anatomopatológico permite identificar la causa en más de la mitad de estos pacientes. A pesar de que la concordancia entre el diagnóstico pretrasplante y la anatomía patológica fue estadísticamente buena, un porcentaje importante de pacientes podría beneficiarse con un diagnóstico etiológico más preciso, que podría tener implicaciones pronósticas, terapéuticas y/o en la evaluación de familiares.

Palabras clave: Miocardiopatía- Etiología- Trasplante cardíaco- Anatomía patológica.

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Abbreviations

CA	Coronary angiography	**INC**	Ischemic-necrotic cardiomyopathy
IDC	Idiopathic dilated cardiomyopathy	**SPECT**	Single-photon emission computed tomography
CMR	Cardiac magnetic resonance		

INTRODUCTION

Heart failure prevalence is increasing, and coronary disease is one of its main causes. (1, 2) However, dilated cardiomyopathy is the final result of multiple aggressions such as poorly controlled hypertension, toxics (alcohol, chemotherapy), valve diseases, infections (viral myocarditis, Chagas cardiomyopathy), inflammatory diseases and even genetic alterations (hypertrophic cardiomyopathy, family history of dilated cardiomyopathies, arrhythmogenic right ventricular dysplasia, etc.). (3) Therapeutic advances have improved the prognosis of patients with moderate to severe heart failure; however, once the end-stage is reached survival is poor, (4-6) leaving heart transplantation as the best therapeutic option. The etiologic diagnosis of end-stage cardiomyopathies requiring transplantation is a challenge and 40-50% of cases remain undiagnosed despite a thorough evaluation, and are therefore labeled as idiopathic dilated cardiomyopathies (IDC). (7-9) Anatomopathological examination of the explanted heart helps to identify the cause of ventricular dysfunction in a significant number of these cases, modifying the initial diagnosis made in the pretrasplant stage. (7, 8, 10, 11) The aim of this study is to describe the etiology of cardiomyopathy in patients receiving heart transplantation and its agreement with the anatomopathological diagnosis of the explanted heart.

METHODS

A retrospective analysis of consecutive patients transplanted at the Hospital Italiano of Buenos Aires from 2003 through 2013 was performed. Data were obtained from the electronic medical records. The diagnosis made by the treating physicians in the period prior to the procedure was considered pretransplant clinical diagnosis. Anatomopathological analysis was performed by a cardiovascular pathologist (HGR) and consisted in a macroscopic and microscopic study. The explanted hearts were fixed in buffered formalin. Standard samples were taken from the two ventricles (free walls), septum, coronary vessels and valvular system. Histological 5 micron thick sections and routine staining (hematoxylin and eosin, Masson's trichrome) were performed. In selected cases, special dyes (e.g. Congo red and thioflavin in patients with suspected amyloidosis) and inmumohistochemical techniques (e.g. viral myocarditis) were employed. The histological diagnosis of myocarditis was made according to the Dallas criteria. (12) The general guidelines used for clinical, and anatomopathological diagnoses are listed in the Annex.

An agreement analysis between pretransplant diagnosis and the anatomopathological diagnosis of the explanted organ was performed using the Kappa coefficient, including in the analysis the eight most common diagnoses. Continuous variables are expressed as mean and standard deviation or median and interquartile range according to normal or non-normal distribution. Categorical variables are expressed as percentages.

RESULTS

The analysis included 100 patients, 76% male, with mean age of 49.7±12.5 years and median ejection fraction of 26% (interquartile range 20 -30%). Population characteristics are shown in Table 1. All patients underwent transthoracic echocardiography and 52% a coronary angiography (CA) 6 months prior to transplantation, although rescue of clinical history data failed in 17% of cases. Gadolinium cardiac magnetic resonance (CMR) was performed in 26% of patients and 10% underwent endomyocardial biopsy as part of the diagnostic evaluation.

The most common pretransplant clinical diagnosis was IDC (37%), followed by ischemic-necrotic cardiomyopathy (INC) (32%) and Chagas cardiomyopathy (10%) (Table 2). The most frequent histopathological diagnoses were INC (35%), hypertrophic cardiomyopathy (10%), and myocarditis (8%), whereas a causal diagnosis was not reached in 25% of cases (IDC) (see Table 2).

The agreement between the pretransplant clinical diagnosis and the anatomopathological diagnosis was good, with a kappa coefficient of 0.64 (CI 0.52-0.76). Diagnosis disagreement was found in 27 of the 100 cases analyzed. The highest ratio of agreement was found for Chagas cardiomyopathy (1; CI 0.65-1) and INC (0.91; CI 0.75-0.97) and the lowest ratios for myocarditis (0.09; CI 0.004-0.43), hypertrophic cardiomyopathy (0.22; CI 0.039 to 0.59) and sarcoidosis (0).

In idiopathic cardiomyopathies according to pretransplant clinical diagnosis (n = 37), an etiologic diagnosis was obtained from the study of the explanted heart in 46% of cases: 18.9% myocarditis, 13.5% hypertrophic cardiomyopathies, 8.1% INC and 5.4% sarcoidosis cardiomyopathy (see Table 2). However, 54% persisted without diagnosis. Table 3 summarizes the different pretransplant etiologies and the corresponding anatomopathological diagnosis.

All pretransplant cardiomyopathies diagnosed as ischemic-necrotic prior to transplantation were confirmed in the anatomopathological analysis. The same occurred with Chagas cardiomyopathies.

The analysis of patients who underwent CMR (n = 26) showed that the CMR diagnosis agreed with the anatomopathological study in 65.3% of cases, 9 of which were INC, 4 IDC, 1 amyloid cardiomyopathy,

Table 1. Population characteristics

Variable	(n=100)
Age (years)	49.7 ± 12.5
Female gender, %	24%
Pretransplant EF, %	26 (IQR 20-30)
WU	2.7 (IQR 2-3.5)
Pretransplant Cr mg/dL	1.18 ± 0.47
Condition in waiting list	
Emergency, %	25
Urgency, %	55
Elective, %	20
IABP, %	19
MVA, %	10
Inotropics, %	74
CA	
Yes, %	52
No, %	31
NR, %	17
CMR	
Yes, %	26
No, %	60
NR, %	14
Endomyocardial biopsy, %	10

EF: Ejection fraction. IQR: Interquartile range. UW: Wood units. Cr: Creatinine. IABP: Intra-aortic balloon pump counterpulsation. MVA: Mechanical ventilatory assistance. CA: Coronary angiography. NR: Not reported. CMR: Cardiac magnetic resonance

Table 2. Etiologic diagnosis

	Pretransplant diagnosis %	Anatomopathological diagnosis %
IDC	25	25
INC	35	35
Hypertrophic cardiomyopathy	10	10
Chagas cardiomyopathy	10	10
Myocarditis	8	8
Amyloidosis	2	2
NCM	1	1
Valvular cardiomyopathy	3	3
Congenital cardiomyopathy	1	1
Sarcoidosis	2	2
Restrictive	1	1
Secondary to CTA	1	1
Myocarditis/NCM	1	1

IDC: Idiopathic dilated cardiomyopathy. INC: Ischemic-necrotic cardiomyopathy. NCM: Non-compacted myocardium. CTA: Chemotherapy agents.

Table 3. Anatomopathological diagnosis according to pretransplant diagnosis

Variable	(n=100)
IDC (37%)	IDC 54% (20) INC 8.1% (3) Hypertrophic cardiomyopathy 13.5% (5) Myocarditis 18.9% (7) Sarcoidosis 5.4% (2)
INC (32%)	INC 100% (25)
Hypertrophic cardiomyopathy (2%)	Hypertrophic cardiomyopathy 100% (2)
Chagas cardiomyopathy (10%)	Chagas cardiomyopathy 100%
Myocarditis (4%)	Myocarditis 25% (1) IDC 75% (3)
Amyloidosis (3%)	Amyloidosis 66.6% (2) Hypertrophic cardiomyopathy 33.3% (1)
NCM (4%)	NCM 25% (1) IDC 50% (2) Hypertrophic cardiomyopathy 25% (1)
Valvular cardiomyopathy (3%)	Valvular 100% (3)
Congenital cardiomyopathy (1%)	Congenital cardiomyopathy 100% (1)
Restrictive cardiomyopathy (2%)	Hypertrophic cardiomyopathy 100% (1)
Secondary to CTA (1%)	Secondary to CTA 100% (1)
NCM/myocarditis (1%)	NCM/myocarditis 100% (1)

IDC: Idiopathic dilated cardiomyopathy. INC: Ischemic-necrotic cardiomyopathy.
NCM: Non-compacted myocardium. CTA: Chemotherapy agents.

1 myocarditis, 1 hypertrophic cardiomyopathy and 1 non-compacted myocardium with myocarditis.

In 7 out of the 10 patients who underwent endomyocardial biopsy, the diagnosis agreed with the explanted heart pathological anatomy: 1 myocarditis, 3 hypertrophic cardiomyopathies, 1 amyloid cardiomyopathy and 2 IDC.

DISCUSSION

There is no diagnostic algorithm to guide the etiologic investigation in patients with end-stage cardiomyopathies. The proportion of patients reaching heart transplantation with IDC diagnosis varies widely accord-

ing to the depth of the evaluation. (7, 8, 10, 11). Even after performing an endomyocardial biopsy to all the patients without etiologic diagnosis, the cause cannot be identified in approximately 50% of cases. (9) One of the possible reasons for not intensifying the etiologic investigation is that in most cases the therapeutic management of these patients is not modified once an etiologic diagnosis is reached.

Although in our study the degree of agreement between pretransplant clinical diagnosis and pathological anatomy was good according to the Kappa coefficient (0.64), the diagnoses did not match in approximately 1 out of every 3 patients. Part of this discrepancy is explained by the fact that in more than half IDC the diagnosis was made in the explanted heart. These findings are similar to those reported by Luk et al. (7)

Three of the patients with pretransplant IDC received an ischemic-necrotic diagnosis after the anatomopathological analysis. One of these patients had undergone a CA 15 years before transplantation to evaluate his cardiomyopathy and had no significant angiographic lesions; another patient had low pretest for coronary disease and cardiac SPECT without inducible ischemia, and the third patient was referred from another center in cardiogenic shock with a 10-year evolution dilated cardiomyopathy. These results are similar to those of Bortman et al. reporting that from 38 cardiomyopathies classified as idiopathic in the pretransplant study, 9 had anatomopathological ischemic-necrotic diagnosis, 6 of them with CA in the previous year. In our study, the percentage of patients undergoing CA as part of the pretransplant diagnostic assessment is probably low, although it could be underestimated, since as it is a reference center, many patients could have undergone the procedure prior to contact with our hospital. Moreover, a significant proportion of patients are referred to our institution with end-stage cardiomyopathies and low cardiac output syndrome to be included in waiting list for heart transplantation, and the CA result would probably not modify the indication. A point to be taken into account is that in the presence of dilated cardiomyopathy with coronary lesions, a coronary disease etiology cannot be always confirmed. Nevertheless, the ischemic-necrotic etiology is possibly the most relevant diagnosis to identify in the pretransplant stage, as some of these patients could benefit from revascularization.

In two patients with pretransplant IDC diagnosis, anatomopathological findings were compatible with sarcoidosis (see Figure 1A). Cardiac sarcoidosis without overt systemic involvement is uncommon; the diagnosis is based on a high suspicion index, late gadolinium enhancement pattern in CMR and an endomyocardial biopsy. Its etiologic diagnosis has important implications, since it not only has specific treatment (immunosuppression) which could reduce disease progression, but there is also risk of recurrence in the implanted heart. (13, 14)

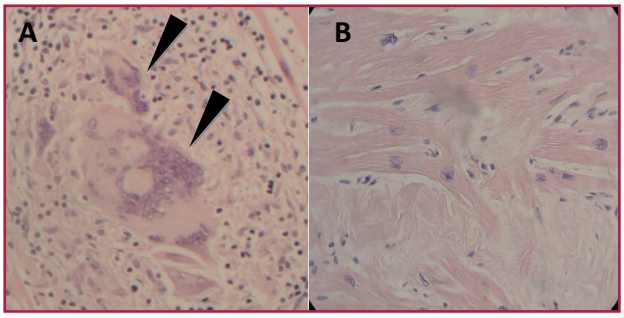

Fig. 1. Histological image of the explanted heart of one of the patients diagnosed with cardiac sarcoidosis showing inflammatory cells forming granulomas without evidence of necrosis and multinucleated giant cells (arrows). B. Histological image of a patient carrying hypertrophic cardiomyopathy showing hypertrophied myocytes and myocyte disarray foci.

In all cases with anatomopathological diagnosis of hypertrophic cardiomyopathy (Figure 1B), classified as idiopathic in the pretransplant evaluation, wall thickness in the transthoracic echocardiogram was normal or slightly increased (< 1.3 cm). Three of these patients had CMR and two, non-diagnostic endomyocardial biopsy. This shows the heterogeneous presentation of this pathology, where different genes produce the same phenotype and the same gene gives different phenotypes, among them hypertrophic cardiomyopathy with restrictive pattern where wall thickness is generally only slightly increased. (15) Dilated hypertrophic cardiomyopathy in which wall thickness may decrease is another possibility. The importance of arriving to this etiologic diagnosis resides in the need of electrocardiographic and echocardiographic screening of all first degree family members of hypertrophic cardiomyopathy carriers. (16) The genetic diagnosis would be useful in relatives without evidence of hypertrophy in complementary studies (15), although its availability in our country is limited.

Seven patients with pretransplant idiopathic cardiomyopathy had anatomopathological diagnosis of myocarditis. These patients had variable presentations of the disease, ranging from cardiogenic shock with new-onset cardiomyopathy to dilated cardiomyopathy of 10-year evolution. Viral and post-viral infections are the most common causes of myocarditis. (17) Available molecular techniques allow detecting 38% to 67.4% viral genomes in endomyocardial biopsies from IDC patients. (18, 19) The evolution of patients with myocarditis is as diverse as their clinical presentation. (20) It is not easy to establish prognosis, as there may be an asymptomatic course of the infection which turns it indistinguishable from IDC and on the other hand, the diagnosis is not simple even using endomyocardial biopsy as diagnostic certainty. (21)

Prevalence of Chagas cardiomyopathy was 10% in our population, and they were all correctly diagnosed at the pretransplant stage. The diagnosis is helped with a Chagas disease serology test, which is routinely

performed in patients with dilated cardiomyopathy. This incidence is probably not representative of the rest of the country, as in some Chagas disease endemic regions it is one of the main causes of end-stage heart failure. Despite its high prevalence, heart transplantation in these patients is controversial due to the risk of disease recurrence and greater cancer incidence, although there has been a growing acceptance in recent years. (23)

From the 26 patients undergoing CMR, 17 had the same biopsy and CMR diagnosis. However, 9 were INC, where the diagnosis was probably obtained by different methods and the CMR was requested for other reasons, as ventricular function assessment, viability, etc. The best CMR resolution added to the pattern of late gadolinium enhancement enables a more precise etiologic diagnosis of different types of cardiomyopathies (myocarditis, amyloid cardiomyopathy, hypertropic cardiomyopathy, right ventricular arrhythmogenic dysplasia, etc). (24, 25) Taking into account that it is a noninvasive study, without radiation, that does not use nephrotoxic contrast (although it cannot be performed with creatinine clearance < 30 ml/min), it is to be expected that as its availability increases, the etiologic diagnosis of patients with end-stage cardiomyopathy will improve.

Ten out of 100 patients underwent endomyocardial biopsy and in 5 of them a diagnosis was reached (1 myocarditis, 1 amyloid cardiomyopathy and 3 hypertrophic cardiomyopathies). The role of endomyocardial biopsy in the etiologic search of end-stage cardiomyopathies is not clearly defined. Its usefulness is discussed, since low sensitivity is added to the potential complications. (26, 27) There are indications with greater degree of consensus as new-onset heart failure with conduction disorders or bad response to treatment and in the case of suspected infiltrative cardiomyopathies. (28).

CONCLUSIONS

Despite the progress of complementary methods, the etiologic diagnosis of cardiomyopathies requiring heart transplantation is still a challenge and approximately one third of patient reach transplantation without a diagnosis. The anatomopathological analysis of the explanted heart establishes the etiology in more than half of these cases. Although the agreement between the pretransplant clinical diagnosis and the anatomopathological analysis was statistically satisfactory, a high percentage of patients could benefit from a more precise etiologic diagnosis, allowing the identification of potentially reversible causes that require a specific treatment and/or the evaluation of relatives of cardiomyopathy carriers with a hereditary component.

Conflicts of interest

None declared.

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ANNEX. Diagnostic criteria

	Clinical diagnosis	Anatomopathological diagnosis
Ischemic-necrotic cardiomyopathy	More than 70 % injury in at least one main coronary artery associated with electrocardiographic, echocardiographic or CMR sequelae, in the territory corresponding to the coronary lesion.	Coronary artery disease with severe main coronary vessel atherosclerosis, associated to scarring myocardial infarctions (in the territory of the affected coronary artery), generally accompanied by ventricular dilation.
Chagas cardiomyopathy	Positive Chagas serology with global left-ventricular function impairment without CA coronary lesions in case of intermediate/high pretest and/or compatible CMR.	Presence of diffuse myocarditis with severe tissue injury and scant presence of T.cruzi parasite forms. Fibrotic tissue replacement of lesion areas and hypertrophy of the remaining myocytes.
Hypertrophic cardiomyopathy	First degree family history of hypertrophic cardiomyopathy and/or increased wall thickness (generally > 1.5 cm) in the absence of hypertension or valvulopathy, ECG disorders secondary to ventricular hypertrophy, left ventricular outflow tract dynamic obstruction, CMR compatible with hypertrophic cardiomyopathy and/or endomyocardial biopsy with myocyte hypertrophy, and myofibrillar disarray (myocyte disarray) (see anatomopathological criteria).	Left ventricular hypertrophy, mainly with septal involvement, generally without chamber dilation and in the absence of any other cardiac or systemic disease cause of hypertrophy. Myocyte hypertrophy, myofibrillar disarray (myocyte disarray) and presence of fibrotic scars.
Myocarditis	History of acute myocarditis or global left ventricular function impairment without CA coronary lesions in case of intermediate/high pretest, CMR with subepicardial or intramyocardial late gadolinium enhancement and/or intramyocardial biopsy with myocarditis-compatible findings (see anatomopathological criteria).	Presence of myocardial inflammatory infiltrates, consisting mainly of lymphocytes, with fiber injury (myocyte necrosis, myocytolysis vacuolization, apoptosis) and interstitial edema. Areas of reparative or scarring fibrosis in the case of chronic lesions.
Amyloid cardiomyopathy	Diffuse wall thickness increase in the absence of hypertension or valvulopathy, microvoltage in the ECG, CMR with diffuse subepicardial late gadolinium enhancement and nulled blood pool and/or endomyocardial biopsy with positive Congo-red or thioflavin staining (see anatomopathological criteria).	Presence of extracellular deposits of a pink protein-like, amorphous material, with beta-folded structure (amyloid) and pericellular, interstitial, subendocardial and arterial wall localization. Congo-red and thioflavin staining indicated amyloid presence.
Restrictive cardiomyopathy	Preserved or slightly increased wall thickness, generally with preserved systolic function and marked diastolic dysfunction in the absence of hypertrophic or amyloid cardiomyopathy, or other endomyocardial biopsy and/or CMR-diagnosed infiltrative cardiomyopathies.	Preserved or slightly increased wall thickness. Regions of scarring with inespecific focal fibrosis. Absence of lymphocytic infiltrates, myocyte disarray and negative Congo-red or thioflavin staining.

	Clinical diagnosis	Anatomopathological diagnosis
Non-compacted myocardium	Increased trabeculation with an echocardiographic or CMR compacted/non-compacted myocardium ratio > 2 or > 2.3, respectively, associated with global ventricular function impairment and in the absence of any other cause of cardiomyopathy.	Increased left ventricular trabeculation associated with left chamber dilation with preserved or slightly increased wall thickness. Regions of scarring with inespecific focal fibrosis. Absence of lymphocytic infiltrates, myocyte disarray and negative Congo-red or thioflavin staining.
Chemotherapy-induced cardiomyopathy	Global ventricular function impairment associated to cardiotoxic chemotherapy (e.g. doxorrubicin) in the absence of any other cause of cardiomyopathy.	Left chamber dilation with preserved or slightly increased wall thickness. Regions of scarring with inespecific focal fibrosis. Absence of lymphocytic infiltrates, myocyte disarray and negative Congo-red or thioflavin staining.
Valvulopathy-induced cardiomyopathy	Severe left valve disease associated with ventricular dilation and global systolic function impairment in the absence of any other cause of cardiomyopathy.	Left valve disorder associated to left chamber dilation with preserved or slightly increased wall thickness. Regions of scarring with inespecific focal fibrosis. Absence of lymphocytic infiltrates, myocyte disarray and negative Congo-red or thioflavin staining.
Idiopathic dilated cardiomyopathy	Dilated cardiomyopathy with global ventricular function impairment not fulfilling any of the aforementioned criteria.	Left chamber dilation with preserved or slightly increased wall thickness. Regions of scarring with inespecific focal fibrosis. Absence of lymphocytic infiltrates, myocyte disarray and negative Congo-red or thioflavin staining.
Sarcoidosis		Granulomatose myocarditis, characterized by the presence of non-necrotic and non caseating granulomas, formed by lymphocytes and giant cells.

CMR: Cardiac magnetic resonance. CA: Coronary angiography. ECG: Electrocardiogram.