



RESEARCH ARTICLE



Natural course of inflammatory cardiomyopathies

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ABSTRACT

Introduction. Refractory heart failure with a poor prognosis is a key feature of dilated cardiomyopathy. Inflammatory cardiomyopathy, often diagnosed via *in vivo* subendomyocardial biopsy, is considered a potential precursor to dilated cardiomyopathy. The Dallas criteria, applied to morphometric and electron microscopic studies of biopsy samples, are essential for differentiating the features of various inflammatory stages. Building upon these established diagnostic principles, our study integrates immunohistological analysis with measurements of intramyocardial indices and intracardiac hemodynamics. This comprehensive approach aims to characterize the natural course of inflammatory cardiomyopathy, seeking to improve the understanding of the clinical trajectories and tissue structures that define both inflammatory cardiomyopathy and its progression to dilated cardiomyopathy.

Material and methods. The study included 75 patients with inflammatory cardiomyopathies and 75 patients with dilated cardiomyopathies. The following procedures were performed: coronary angioventriculography, repeated subendomyocardial biopsy, immunohistologic analysis, and assessment of intracardiac and intramyocardial hemodynamics.

Results. Morphohistologic analysis of inflammatory cardiomyopathies at different stages revealed a maximum of 10-12 lymphocytes, which decreased to only isolated lymphocytes in late stages. In biopsies from early-stage inflammatory dilated cardiomyopathies, the morphologic appearance showed lymphocytic infiltration of the myocardial stroma, vasculitis of intramural arteries and arterioles. The biopsies performed after 36 months showed dystrophic structures, microfocal and diffuse replacement fibrosis, predominantly perivascular, which are indistinguishable from the features of dilated cardiomyopathy. Intracardiac hemodynamic indices in patients with dilated and inflammatory cardiomyopathies did not differ. Similarly, left ventricular regional contractility, as verified by radiopaque ventriculography, was not significantly different. The degree of radiotracer detection on thallium-201 scintigraphy was statistically insignificant between the two conditions. Immune complexes and immunoglobulins G, M, and A in the blood were elevated in both groups, likely as a consequence of heart failure.

Conclusions. Morphostructural analysis of biopsies taken from patients with inflammatory dilated cardiomyopathies, at different stages of its natural course reveals the progressive development of dilated cardiomyopathies. These structural changes correlate closely with findings from intracavitary and hemodynamic assessments and measures of regional contractility, supporting a direct link between dilated and inflammatory cardiomyopathies.

Keywords: cardiomyopathy, cardiomyocyte, scintigraphy, heart failure.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

The specific markers and progression patterns that would allow clinicians to predict when inflammatory cardiomyopathy will transition into dilated cardiomyopathy are still unknown.

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The research hypothesis

The study utilized a complex morphohistological analysis of submyocardial biopsies and intracardiac hemodynamic indices for assessment of traits regarding inflammatory cardiomyopathy evolution during 36 months in a comparison with hallmarks of dilated cardiomyopathy.

The novelty added by the manuscript to the already published scientific literature

Myocardial morphostructural analysis at 36 months revealed that inflammatory cardiomyopathy evolution exhibit features, such as dystrophic changes, microfocal and diffuse fibrosis, that are indistinguishable from those in dilated cardiomyopathy. Likewise, functional assessments showed no significant differences in either intracardiac hemodynamic indices or left ventricular regional contractility, as verified by radiopaque ventriculography. These findings provide strong evidence suggesting inflammatory cardiomyopathy progresses to dilated cardiomyopathy.

Introduction

In primary diseases of the heart, particularly dilated cardiomyopathy (DCM), the heart is subjected to significant hemodynamic volume overload, leading to heart failure that is often refractory to conventional treatment [1-4]. The complexity of DCM lies in a wide array of causative factors that serve both as a basis in the initiation and development of acquired and familial dilated cardiomyopathy [5-8]. Among these, inflammatory cardiomyopathy (ICM) is recognized as an important potential precursor to DCM, a diagnosis confirmed by morphological analysis of the myocardium [9, 10]. The identification of myocardial inflammatory processes, particularly those with an insidious evolution such as inflammatory dilated cardiomyopathy (IDCM), is a difficult endeavor due to the heterogeneous nature of the clinical and diagnostic findings. Currently, the most sensitive and definitive method for confirming the existence of an inflammatory process and viral infection in the heart muscle is the subendomyocardial biopsy, which is considered the “gold standard”. The use of the 1986 Dallas morphological classification of inflammatory cardiomyopathy or the 1997 Marburg Agreement on the Diagnosis of Inflammatory Cardiomyopathy increases the order of differentiation of acute and chronic inflammatory processes [10, 11]. These classifications, combined with the ability to type different immunocompetent cell populations, expand the understanding of viruses with cardiotropic potential in patients with IDCM and

DCM [11, 12]. By applying these methods, it becomes feasible to track the natural history of ICM from its early, asymptomatic phases, where risk stratification is critical, to the late stages of cardiomyopathic syndromes. This approach facilitates a better understanding of the clinical course and shared morphofunctional features of these pathologies, aiming to open new avenues for therapeutic development.

Materials and methods

This retrospective study analyzed morphofunctional data from 75 patients with inflammatory cardiomyopathy (IDCM) and 75 patients with dilated cardiomyopathy (DCM). The investigations performed included coronarography, scintigraphy of myocardium, intracardiac and intramyocardial hemodynamics, repeated subendomyocardial biopsy, immunohistology study, using the WHO expert group classification with mandatory use of the Dallas morphological criteria. Morphologically confirmation of the diagnosis was confirmed in 58 (77.3%) patients with IDCM and in 40 (53.3%) with DCM. At autopsy, the diagnosis was established in 17 (22.7%) IDCM patients and in 35 (46.7%) DCM patients. In 8 patients with IDCM, verified by intravital subendomyocardial biopsy, the diagnosis was established postmortem on histological analysis of the myocardium.

The distribution of patients according to age, sex and severity of heart failure (NYHA) are shown in Table 1.

Table 1. Patient distribution by gender, age and degree of heart failure

Index	ICM	DCM	P
Number of patients	75	75	Non-significant (NS)
Men	64 (85,3%)	66 (88%)	NS
Women	11 (14,7%)	9 (12%)	NS
Age (years) (M ± m)	38,5 ± 1,4 (15-58)	35,6 ± 1,3 (16-67)	NS
FC I	19 (25,3%)	2 (2,7%)	
FC II	30 (40%)	30 (40,0%)	
FC III	23 (30,7%)	41 (54,7%)	
FC IV	3 (4%)	2 (2,6%)	
Average FC (M ± m)	2,0 ± 0,1	2,6 ± 0,08	P < 0,05

Note: FC – Functional class, M ± m – Mean value, ICM – Inflammatory cardiomyopathy, DCM – Dilated cardiomyopathy, P – Student's-test, NS – Non-significant.

The groups of patients with IDCM and DCM did not differ in terms of age and sex, and both groups showed a clear predominance of male patients. The degree of heart failure in patients with IDCM was significantly lower compared to those with DCM ($p < 0.0005$).

Scintigraphy of myocardium with Thallium-201 (TL 201) was performed using a gamma camera equipped with a conversion collimator; in three positions: (1) anterior, (2) 45° left anterior oblique (LAO) and (3) left lateral. Image acquisition began 5-10 minutes after intravenous administration of 1.5-2.0 micrograms of TL-201 chloride, containing 2 mg of thallium substance, with an action of 55-74 MBq. The data were digitally stored as a 64x64 pixel matrix and the resulting scintigrams were processed using the RDR 11/34 computer program.

The following parameters were determined from *coronary angiography*: end-diastolic volume (EDV), end-systolic volume (STV), stroke index (BI), ejection fraction (EF), cytosolic index (CI), left ventricular myocardial mass (LVMM), mean velocity of circumferential fiber shortening (LVFSV), left ventricular end-diastolic volume (LVEDV), right ventricular pressure (RVP) and heart rate (HR). Regional contractility of the LV and RV was assessed after percentage shortening of 90 radii and percentage area restriction across 5 sectors of each ventricle.

Subendomyocardial biopsy (SEM) was performed at the end of the angiographic investigation. Multiple tissue samples (3-5 biopsies) were obtained from the septum, RV wall, LV apex and, less rarely, the inferior wall of the left ventricle. Morphological analysis was performed using both light and electron microscopy.

Results and discussion

Coronary angiography in patients with IDCM and DCM revealed wide, sinuous coronary arteries of typological significance. The passage of contrast medium and its subsequent washout, both in the large trunks and in the 3rd and 4th order arteries, were slowed. While coronary blood flow at rest was normal in both groups, the administration of coronary vasodilators resulted in increased vascular resistance and impaired arterial dilation, indicating increased vascular tone and reduced coronary reserve. Furthermore, there were no significant differences between the IDCM and DCM groups in the systolic and diastolic diameters of the coronary arteries or in the calculated extensibility index. **Ventriculography** revealed in both patient groups, significant changes in hemodynamics and left ventricular (LV) volumes: the end-diastolic (EDV) and systolic (STV) volumes were significantly increased and the ejection fraction (EF) and the mean velocity of circumferential fiber shortening (FSV) were reduced. The stroke index (BI) and systolic index (SI) were normal, likely due to the compensatory effect of the LV cavity.

Despite normal left ventricular (LV) systolic and aortic diastolic pressures, LV myocardial mass was markedly increased in both patient groups. This was attributed to eccentric hypertrophy, characterized by LV cavity dilation with normal free wall thickness. Also, in IDCM, a significant difference in end-diastolic volume index (EDVI), ($P < 0.01$), end-systolic volume (ESV) ($P < 0.01$), and end-systolic volume index

(ESVI) ($P < 0.005$) were revealed. Thus, in IDCM-ST RV was 32.1 ± 1.9 versus 43.4 ± 3.6 ($P < 0.005$); differences were found in all pulmonary artery pressure indices: in IDCM-ST in PA (pulmonary artery) was equal to 32.3 ± 2.0 versus 44.8 ± 3.7 in DCM group ($P < 0.005$); DP AP was 14.3 ± 1.5 in IDCM and 20.6 ± 2.0 in DCM ($P < 0.05$); and mean PAP (mean pulmonary artery pressure) in AP in the group of patients with IDCM was equal to 22.0 ± 1.9 and in DCM – 32.6 ± 3.3 ($P < 0.005$). A comparison of right- and left-heart function revealed that in the IDCM group, hemodynamic parameters were similarly affected on both sides. In contrast, the DCM group exhibited predominantly left-sided hemodynamic compromise, which accounts for the more significantly elevated pulmonary pressures observed in these patients.

Compared to healthy individuals, patients in both the inflammatory cardiomyopathy (IDCM) and dilated cardiomyopathy (DCM) groups showed significantly elevated serum levels of circulating immune complexes (CICs) and immunoglobulins (IgG, IgM, and IgA). There was no significant difference in these levels between the two patient groups, suggesting that their elevation is likely a secondary phenomenon related to the severity of heart failure rather than a primary disease marker. Lymphocyte subpopulations in patients with DCM showed a significant decrease in T-lymphocytes as well as T helper inducer T-lymphocytes, with preservation of T-cytokine suppressors in normal parameters, respectively reduction of immunoregulatory index. The number of T-suppressors in patients with IDCM is obviously lower, with a higher immunoregulatory index than in those with DCM. The presented data show an appreciably greater increase in T-suppressors in patients with DCM than in those with a morphologically confirmed diagnosis of IDCM. The observed difference in T-cell profiles between the two conditions may be attributed to variations in the functional class of heart failure and the duration of disease at the time of assessment. It should be noted that these deviations from normal values were noted only in 5-25% of patients with DCM.

Myocardial scintigraphy revealed disturbances of local myocardial contractility. Areas of hypokinesia were recorded in the following regions of LV: in septum area – 2 (18.2%) patients with IDCM, in anterior wall area – in 1 patient with DCM, in antero-septal area – in 4 patients with IDCM (36.4%), in apex area – in 1 patient with ICM, in the antero-lateral area – in 2 patients with DCM (22.2%), in the lower apical area – in 1 patient with ICM and in 1 patient with DCM, in the diaphragmatic area – in 1 patient with IDCM and in 1 patient with DCM. Areas of akinesia: in the septal area – in 1 patient with DCM; in some patients there were areas of pathological asynchrony in the LV septal area – in 2 (27.3%) patients with IDCM, in the septal-apical area – in 1 patient with IDCM, in the inferior apical area in 1 patient with IDCM. In 3 patients with DCM and in 1 patient with IDCM, the areas of pathological asynchrony were combined with areas of akinesia and hypokinesia. Despite these individual findings, there were no statistically significant differences in the overall prevalence or distribution of wall motion abnormalities between the IDCM and DCM groups.

Morphological changes in inflammatory cardiomyopathies

Morphological and morphometric analysis of patients from different groups on subendomyocardial biopsy specimens detected similar features but also some differences between them. Patients in the first group with IDCM showed cardiomyocyte injury with pronounced cellular reaction in the interstitium. The lymphocyte count was 10-12. Electron microscopy revealed vacuolization of the sarcoplasmic reticulum, destruction of mitochondrial cristae and partial death of mitochondrial cristae were observed. In the 2nd group, the acuteness of the inflammatory process was moderate, the number of lymphocytes did not exceed 5, eosinophils and neutrophils were rarely detected. Electron microscopy revealed in the vicinity of the thinned capillaries with osmiophilic wall, flocculent masses and diapedesis hemorrhages. In group 3 the number of lymphocytes in the visual field was up to 5. In the interstitium, neutrophils were rare and macrophage elements were frequently present. Necrotized cardiomyocytes were uncommon. In the 4th group the structural changes were characterized by a chronic process or residual traces, reminiscent of the inflammatory process.

Conclusions

The double immunohistological analysis performed at different stages of the natural course in patients with inflammatory cardiomyopathy highlights morphological and morphometric elements in common with dilated cardiomyopathy. There is also a similarity of intracardiac hemodynamic indices, coronary and intramyocardial blood circulation and regional kinetic disturbances; the indistinct features found in both nosological entities point to direct links between dilated cardiomyopathy and inflammatory cardiomyopathy.

Competing interests

None declared.

Authors' contributions

AB launched the working hypothesis, elaborated the design of study, and analyzed the data. VN interfered with support in the statistical processing of results. VC structured and drafted the article, as well as selected the bibliographical references. TB participated in the results commenting and concluding. All authors critically reviewed the work and approved the final version of the manuscript.

Ethics approval

The research project was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes no. 1 from 04.12. 2020/ no. 90 from 31.10.2020).

Patient consent

Obtained.

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