Dilated cardiomyopathy: etio-morphologic investigation

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TABLE OF CONTENTS

1. ABSTRACT

The heart is the first organ to form and to function during vertebrate embryogenesis and its correct functionality is a "conditio sine qua non" for life. If the heart's pumping power is compromised, chambers dilate and pulmonary and systemic circulations are altered. Dilated cardiomyopathy can appear along a wide spectrum of presentations, including no symptoms, subtle symptoms or heart failure, which occurs when the heart is unable to pump blood to the periphery and oxygenate the organs. Dilated cardiomyopathy, the most common form of cardiomyopathy, is characterized by a particular complex of nonspecific pathologic features that do not necessarily identify the different etiologies. In this study, we review the etiologic and morphologic features of 86 explanted recipient adult hearts with dilated cardiomyopathy undergoing orthotopic heart transplantation between 1997 and 2008.

2. INTRODUCTION

The heart is the first organ to form and to function during vertebrate embryogenesis and its correct functionality is a "conditio sine qua non" for life. If the heart's pumping power is compromised, chambers dilate and pulmonary and systemic circulations are altered. Dilated cardiomyopathy can appear along a wide spectrum of presentations, including no symptoms, subtle symptoms or heart failure, which occurs when the heart is unable to pump blood to the periphery and oxygenate the organs. Dilated cardiomyopathy (DCM) is the most common cardiomyopathy, a group of heart diseases resulting from a primary abnormality in the myocardium (1), accounting for approximately 55% of the cases. DCM is characterized by progressively impaired cardiac contractility and ventricular dysfunction. (2) DCM most commonly presents between 18 and 50 years of age, and occurs more frequently in men than in women. (3) DCM is associated with significant

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Table 1. Clinical and Morphologic Features in 86 Dilated Cardiomyopathy (UA Hospital, Edmonton Data)

No. Cases (percent)	Age (range)	F:M	Etiologies/Associated Factors	Gross Morphologies (Weight, shape, ventricular dilation)	Histomorphologic Features
10 (12%)	38 (19-62)	8:2	Viral Infections (Viral prodrome/ infections)	468 g (range: 342-640), globular shape, biventricular dilation	Inflammation – mixed T-B-cells; fibrosis
1 (0.86%)	27	M	WPW syndrome, DCM in mother	447 g, biventricular dilation	Inflammation, fibrosis
1 (0.86%)	36	F	LGMD	327 g , biventricular dilation	Fibrosis
1 (0.86%)	45	F	Mucopolysaccharidosis	290 g, RV dilation	Fibrosis, myocyte vacuolar degereration
1 (0.86%)	32	F	Genetic hemochromatosis	382 g, biventricular dilation, mild	Fibrosis, hemosiderin-deposits
1 (0.86%)	59	M	Familial (1st degree relative) DCM	446 g, hypertrophy + dilation	Fibrosis
1 (0.86%)	21	M	Chemotherapy-related for HD)	350 g, dilation, mild	Fibrosis
1 (0.86%)	41	F	Mixed connective tissue disease	320 g, LV apex thinned	Inflammation, fibrosis, thickened arteriole
2 (1.72%)	22-45	F	Peripartum	391 g, biventricular dilation	Fibrosis
67 (78%)	51 (21-70)	22:45	Idiopathic	511 g (range: 295-1045) globular shape, biventricular dilation, hypertrophy, mural thrombus	Inflammation – mild, fibrosis

DCM: Dilated Cardiomyopathy, WPW: Wolff-Parkinson-White syndrome, LGMD: Limb-girdle muscular dystrophy, HD: Hodgkin's disease, RV: Right ventricle, LV: Left ventricle.

morbidity and mortality, and is a leading indication for cardiac transplantation in adults and children worldwide. (3, 4)

3. ETIOLOGY

A number of conditions resulting in ventricular dilation and dysfunction, such as ischemic, valvular, hypertensive, congenital heart diseases and alcoholism should be primarily differentiated from DCM. In the majority of cases, DCM is idiopathic due to lack of an identifiable cause. Familial (genetic) forms of DCM have been identified in up to one-third of cases. (5) However, the true frequency is probably underestimated due to the diversity of clinical presentation, the variability in penetrance and expression. (6) Over 20 individual disease genes have been identified and screened for mutations in affected individuals. (7) The relevance of single nucleotide polymorphisms of the genome in individuals affected with DCM is under intense investigation. Some families have a clinical presentation that is characterized by DCM alone, while in others, DCM may be associated with additional cardiac manifestations, e.g. conduction-system disorders, valve defects, or non-cardiac manifestations, such as skeletal myopathy, or partial lipodystrophy. (8) Possible viral etiologies have been implicated in DCM. (1) It is also known that in a minority of cases, toxic, metabolic, or immunologic causes may play a predisposing or triggering role. (9) A high prevalence (67.4%) of viral genomes has been found in the heart of 245 consecutive DCM patients in a recent survey investigating a broad panel of viruses. (10) The frequent detection of viral genomes in human DCM hearts strongly suggests that viral infections may represent an important contributing factor in the pathogenesis of DCM. Interestingly, even a small cardiac virus load during chronic latent infections is able to sustain significant viral transcriptional activity over long periods of time, resulting in slow and progressive deterioration of cardiac function. (11).

4. THE EDMONTON EXPERIENCE

The University of Alberta Hospital in Edmonton, Canada is the leading tertiary care centre for cardiovascular surgery in Western Canada, performing 35-45 orthotopic cardiac transplantations annually. In this study, we summarize the etiology and morphologic features of explanted recipient hearts for DCM.

4.1. Clinicals

Diagnostic criteria for DCM are an ejection fraction of less than 0.45 and/or a fractional shortening of less than 25%, and a left ventricular end diastolic dimension of greater than 112% of the predicted value. By excluding ischemic, valvular, alcoholism (up to 30% of cases of heart failure can be linked to alcohol drinking in the Western world), hypertensive and congenital heart diseases, we have identified 86 explanted hearts from the Edmonton Database. All individuals are adults (age > 18 years) with DCM identified during an 11-year period (1997-2008). The patients' mean age is 48 years (range=19-70 years) with F/M ratio of 1:2. Five (6%) patients have familial or genetically inherited form of DCM (including one each of limb-girdle muscular dystrophy, mucopolysaccharidosis, Wolff-Parkinson-White syndrome, genetic hemochromatosis and one familial in which a first degree relative, who also showed the disease). One patient was affected with mixed connective tissue disease, one patient developed DCM on adriamycin treatment for Hodgkin's disease), two patients with peripartum history, 10 (12%) with viral prodrome or of previous viral infections, and the remaining 67 (78%) cases are idiopathic with unknown etiologies. (Table 1)

4.2. Gross morphology

Hearts of patients with dilated cardiomyopathy showed a huge increase in mass with the mean heart weight of 491 g (range: 228 – 1045 g). The heart shape was usually globular with dilation of all chambers and the disappearance of a proper apex (apical rounding known as Roman arch). Four chamber or biventricular dilation was seen in 73 (85%) of our cases. The epicardium was usually smooth and the coronary arteries appeared stretched, but did not show high-grade atherosclerosis. The myocardium was flabby and the ventricular wall collapsed on section. Cardiac hypertrophy was shown by both weight increase and eccentric hypertrophy, although this finding was not
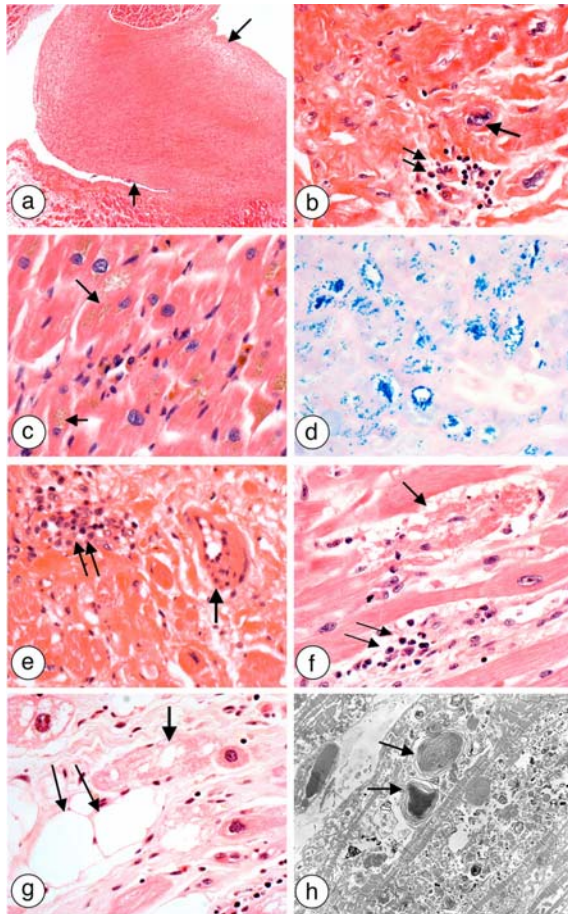
Figure 1. Peripartum DCM: Large organized thrombus adherent to endocardium, H&E, 40x. Peripartum DCM: Myocyte hypertrophy, nucleomegaly (arrow), mild interstitial fibrosis, lymphocytic infiltrate (double arrow), H&E, 400x. Hemochromatosis DCM: Myocyte hypertrophy, mild nucleomegaly, cytoplasmic iron deposits in myocytes (arrow) and reticuloendothelial cells, H&E, 400x. Hemochromatosis DCM: Abundant iron in myocytes. Perl's Prussian blue, 400x. Mixed connective tissue disease DCM: Thickened arteriole, interstitial fibrosis and lymphocytic infiltrate (double arrow), H&E, 400x. Viral Myocarditis DCM: Myocyte hypertrophy, slight nucleomegaly, myocytolysis (arrow), lymphocytic infiltrate (double arrow), H&E, 400x. Mucopolysaccharidosis DCM: Slight nucleomegaly, myocyte vacuolar degeneration (arrow), interstitial fibroadipose tissue replacement (double arrow), H&E, 400x. Mucopolysaccharidosis DCM: Ultrastructural: Myocyte degeneration, myofibrils separated by myelin figures (arrows), consistent with MPS accumulation.

evident in the majority of our cases because of ventricular chamber dilation. The mean thickness of the right ventricle wall was 0.35 cm (range: 0.2 to 0.7), whilst that of the left ventricle 1.4 cm (range: 0.75 to 1.6). The extreme thinning may be seen at left ventricle apex. Fibrosis was frequently found, but very variable with replacement fibrosis ranging from minimal to larger areas. Endocardial fibrosis was a common finding. In up to 10 (12%) cases, mural thrombi formed during the terminal stages of the disease. These latter findings are due to the reduced ejection fraction (a pattern of the cardiac apex that is also called: the change from *caput vivum* to *caput mortuum*). There were no primary valvular alterations, but rolling of leaflet edges may be seen in the mitral valves as a result of cardiac remodeling, ventricular dilation, and functional regurgitation.

4.3. Histopathology

DCM is characterized by a particular complex of nonspecific histopathologic features that are common to most end-stage cardiac conditions, and do not necessarily identify the different etiologies causing DCM. All our cases showed this complex of histopathologic features. It is important to emphasize that DCM change involves all myocardial components, including myocytes, interstitium, small vessels, and endocardium. The myocardium is both hypertrophied and dilated. Myocytes may appear thickened with hyperchromatic and often bizarrely shaped nuclei. Moreover, thinning, waving, and side-to-side slippage of myocytes, characteristics associated with dilation, are seen interspersed between the hypertrophied myocytes. Enlarged, rectangular and hyperchromatic nucleus may be transversely arranged and occupies the entire cross-sectional area of the attenuated myocytes. Loss of intracellular myofibrils may result in hydropic changes of the myocytes, which are often localized in the subendocardial layer and ranges from perinuclear halo to a pattern of colliquative myocytolysis.

Areas of myocyte death was evident in all our DCM hearts by the presence of interstitial and perivascular fibrosis predominantly, whereas replacement and endocardial fibrosis were seen focally. In four cases (5%), fibroadipose tissue replacement was significantly more prominent in the right ventricle, reminiscent of that seen in arrhythmogenic right ventricular dysplasia (ARVD). Significant iron overload with intramyocellular iron deposition resulting in myocellular degeneration indicative of hemochromatosis was seen in one patient. Inflammatory cellular infiltrates were seen in 25 cases (29%) ranging from a single microscopic focus to patchily and often around areas of fibrosis. The inflammatory cells were composed almost exclusively of lymphocytes of mixed T- and B-cells by immunophenotyping studies. These findings were consistent with an activated immunologic process within the myocardium in DCM. (12) (Figure 1)

A disordered arrangement of desmin intermediate filaments also characterizes a myocellular derangement of the myocytes as detected by immunohistochemistry. In particular, an immunohistochemical procedure may also be needed to demonstrate an abnormal type I/type III fibrillar collagen ratio. In a recent study, atrial natriuretic protein (ANP) and CD34 (an endothelial and stem cell marker) were significantly over-expressed in IDCM compared to normal heart (NH). Patients with a difference of more than 20 myocardial fibers in the compared expression between CD34 and troponin T were associated with a quite less favorable survival although the difference was not significant (13). The increase in ANP positive cells in

IDCM could be a consequence of neuro-hormonal activation due to a decline of the impaired myocyte contractility. Further, since it was already shown that ANP could be important in the control of vascular remodeling, we postulated that the increment of CD34 positive cells could be functionally correlated to the increase of ANP production. Differential expression of CD34 and troponin T might be used for future studies to evaluate their prognostic value. (13)

4.4. Ultrastructural morphology

Electron microscopy studies of DCM are usually nonspecific, revealing characteristics associated with myofibril loss, and increased numbers of fibrocytes and adipocytes in the areas of replacement fibrosis. However, there are a few characteristics that are often found during the ultrastructural examination of the cardiac specimens. The electron microscopic studies showed frequently nuclear enlargement with irregular shape, deep infolding of the nuclear membrane, multiple nucleoli, dilation and proliferation of T tubules, rough endoplasmic reticulum and increased numbers of sarcomeres and mitochondria, and myocellular hypertrophy (Figure 1).

5. CONCLUSIONS

Dilated cardiomyopathy is a common cardiac diagnosis that may result from a number of acquired myocardial insults and ultimately yield similar clinicopathologic patterns. The etio-morphologic investigation of DCM may represent a looking for a needle in a haystack procedure because of the number of conditions that need to be screened and complicated procedures used. The clinical and family history is most probably a very essential factor. The clinical data from Edmonton are consistent with those reported in the literature: DCM most commonly presents between 18 and 50 years of age and occurs more frequently in men than in women. In the majority of cases (78%), DCM is idiopathic, and in the remaining 22%, familial or identifiable etiologic factors are present. Of note are the associations of cardiac conduction abnormality, and non-cardiac myopathy in the familial (genetic) cases, and in patients with autoimmune diseases or viral infections that may play predisposing or triggering roles in the development of DCM. Our morphologic data are also similar to those reported in the literature, including huge increase of heart mass, with cardiac hypertrophy and cardiac chambers dilation, myocytes and interstitial changes, fibrosis and the presence of mixed T- and B-immune cells. The complex histopathologic features seen in DCM do not necessarily identify specific etiologies, nor the severity reflects the degree of dysfunction or the patient's prognosis. However, a thorough morphological investigation may uncover the etiology in a number of cases. Pathology may provide important parameters supporting the clinical diagnosis, while further elucidation of the familial (genetic) defects may provide a molecular link between the genome and environment interaction during the pathogenesis of DCM and the basis for future research.

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