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Original contribution

Mitogenic cardiomyopathy: A lethal neonatal familial dilated cardiomyopathy characterized by myocyte hyperplasia and proliferation

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Summary Pediatric cardiomyopathies are a heterogenous group of conditions of which dilated cardiomyopathies are the most common clinicomorphologic subtype. However, the etiology and pathogenesis of many cases of dilated cardiomyopathies remain unknown. We describe a series of 5 cases of a rare but clinically and histologically distinctive dilated cardiomyopathy that was uniformly lethal in early infancy. The 5 cases include 2 pairs of siblings. There was parental consanguinity in 1 of the 2 pairs of siblings. Death occurred in early infancy (range, 22-67 days; mean, 42 days) after a short history of general lethargy, decreased feeding, respiratory distress, or cyanosis. There was no specific birth or early neonatal problems. Autopsy revealed congestive cardiac failure and enlarged, dilated hearts with ventricular dilatation more pronounced than atrial dilatation, and endocardial fibroelastosis. Histology showed prominent hypertrophic nuclear changes of cardiac myofibers and markedly increased myocyte mitotic activity including occasional atypical mitoses. Immunohistochemical staining for Mib1 showed a markedly increased proliferative index of 10% to 20%. Ancillary investigations, including molecular studies, did not reveal a primary cause for the cardiomyopathies. This distinctive dilated cardiomyopathy characterized by unusual histologic features of myocyte nuclear hypertrophy and marked mitotic activity is lethal in early infancy. Its occurrence in 2 pairs of siblings suggests familial inheritance. Although the underlying molecular pathogenesis remains to be elucidated, it is important to recognize this distinctive entity for purposes of genetic counseling.

1. Introduction

Cardiomyopathies are defined in a recent statement of the American Heart Association as a heterogenous group of diseases of the myocardium associated with mechanical and/

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or electrical dysfunction that usually but not invariably exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic [1]. Significant differences in causes, clinical associations, and prognoses separate cardiomyopathy presenting in the pediatric age group from that affecting adults [2,3]. The differences are most marked during the perinatal period when cardiomyopathies due to a wide variety of metabolic, genetic, and syndromic etiologies constitute the key diagnostic considerations in this age-group that are usually not seen in the adult cardiomyopathy patient [2,3].

The annual incidence of pediatric cardiomyopathy is between 1.13 and 1.24 cases per 100 000 children [4,5]. The highest incidence occurs in the first year of life, and a second smaller peak occurs in adolescence [4,5]. Pediatric cardiomyopathies are a heterogenous group of conditions, of which a significant proportion (9%-20%) are familial [4,6].

Dilated cardiomyopathy is the most common clinicomorphologic type of pediatric cardiomyopathy [7]. The 2 most frequently identified causes are myocarditis and neuromuscular disease; but in a significant proportion of cases, the underlying cause is not known [8]. In the past 2 decades, mutations in more than 30 specific genes have been implicated in the pathogenesis of pediatric cardiomyopathy [9]. These include sarcomeric proteins [10] such as the myosin heavy chain, myosin-binding proteins, and troponins in hypertrophic cardiomyopathy, and cytoskeletal proteins such as dystrophin [11], desmin [12], taffazin, lamin, titin, and actin in dilated cardiomyopathy. Other mutations including mutations in calcium-metabolizing genes and cell-signaling molecules such as adenosine monophosphate–activated protein kinase, and mutations in enzymes and transporters essential for myocardial energy production in mitochondria, such as fatty-acid-oxidation enzymes, the carnitine transporter, and components of the respiratory chain oxidative phosphorylation pathway, are also known to cause cardiomyopathy. Identification of the spectrum of genetic mutational abnormalities remains at present the basis for understanding the causes of pediatric cardiomyopathy and is the first step toward the goal of developing specific curative treatments. In addition, a proportion of cases of dilated cardiomyopathy are familial, underlining the importance of accurate diagnosis for genetic counseling [8,13]. At present, the prognosis is grim in the majority of pediatric cardiomyopathies [8,14,15], and the current management remains that of cardiac transplantation.

The category of pediatric cardiomyopathies of unknown and uncharacterized etiology at present likely contains a large number of disparate and rare conditions. Clinically or pathologically distinct conditions can be culled out of this heterogenous "wastebasket" category as a start toward identifying distinctive conditions, their pathogenetic causes, and relevant molecular defects. With this in mind, we describe and characterize a clinically and pathologically distinctive familial form of dilated cardiomyopathy that we termed *mitogenic cardiomyopathy* occurring in early infancy that was invariably fatal and that had a distinctive histology of myocyte hyperplasia with marked proliferative activity.

2. Patients and methods

Five cases of this rare form of neonatal dilated cardiomyopathy with familial occurrence were identified from autopsies performed at the Division of Pathology at The Hospital for Sick Children in Toronto, Canada, in accordance with institutional guidelines.

The case histories are as follows:

2.1. Patient 1

This 42-day-old female infant presented with a 2- to 3-day history of poor feeding and lethargy. She was taken to hospital because of vomiting and a "blue spell." Initial examination revealed skin pallor and an elevated white cell count of 19 000. The infant did not have a fever. The clinical diagnosis was viral myocarditis. Eight hours after admission, she suffered a cardiac arrest and could not be resuscitated. This infant was born by cesarean delivery at term with a birth weight of 3.1 kg and was in good health. The histologic findings were appreciated to be unique, and the condition was designated *mitogenic cardiomyopathy*.

2.2. Patient 2a

This 67-day-old female infant presented with a 3-day history of poor feeding, vomiting, and fever. The infant stopped breathing suddenly while at home and was rushed to hospital, where she could not be resuscitated. This infant was born at term. The parents are first cousins. Other than physiologic jaundice after birth, she was in good health.

2.3. Patient 2b

This 60-day-old female infant is the sibling of patient 2a who was born 10 years later. She presented with poor feeding, lethargy, and difficulty breathing. On admission to the emergency department, she was found to be hypotensive and had significant metabolic acidosis, hyponatremia, hyperkalemia, and a high leukocyte count of 40 600. Antibiotics were administered, but the condition of the infant deteriorated, and she died 5 hours after admission. This infant was born at term after a normal pregnancy and was in good health.

2.4. Patient 3a

This 22-day-old female infant presented with decreased feeding and cyanosis while breast feeding. On admission to the emergency department, she was found to be febrile with a temperature of 40°C and poor peripheral perfusion. The

Table 1 Clinical findings

	Age	Sex	Presentation	Birth history	Family history	Original autopsy diagnosis
1	42 d	Female	2- to 3-d history of poor feeding, lethargy, and vomiting	Term cesarean delivery	No parental consanguinity	Mitogenic/hyperplastic cardiomyopathy
2a	67 d	Female	3-d history of poor feeding, vomiting, and fever	Term normal vaginal delivery	Siblings; parents are first cousins	Myocarditis
2b	60 d	Female	Poor feeding, lethargy, and difficulty breathing	Term normal vaginal delivery		Dilated cardiomyopathy with myocyte hyperplasia
3a	22 d	Female	Poor feeding and fever	Term normal vaginal delivery	Siblings; no parental consanguinity; one other sibling who is well	Cardiomyopathy with interstitial fibrosis
3b	38 d	Female	1-d history of poor feeding and difficulty breathing	Term cesarean delivery for maternal fever		Mitogenic/hyperplastic cardiomyopathy

infant died 2 hours after admission. Investigations for sepsis were negative. This infant was born at term and was in good health. The parents have a 20-month-old son in good health. The autopsy diagnosis of restrictive cardiomyopathy prompted genetic testing for mutations of genes encoding myosin-binding protein C, cardiac troponin T2, and cardiac troponin I, the results of which were negative.

2.5. Patient 3b

This 38-day-old female infant is the sibling of patient 3a and was born one and a half years later. She presented with a 1-day history of poor feeding and respiratory distress. There was no fever. She was found to be in shock on admission to the emergency department and died 5 hours later. This infant was born by cesarean delivery because of maternal fever, and the postdelivery clinical course of this infant was unremarkable. A cytochrome oxidase histochemical stain was performed that showed a normal positive result. A cardiomyopathy metabolic screen was performed, the results of which were negative.

2.6. Methods

Autopsy examination of the heart in each case involved measurement of the weight and of valvular circumferences of the tricuspid, pulmonary, mitral, and aortic valves, and myocardial wall thicknesses of the right and left ventricles. Sections of the heart were obtained in accordance to local protocol that included obtaining 2 sections of the right heart (inflow and outflow tracts), 2 sections of the left heart (including anterior and posterior papillary muscles), and 1 section of the interventricular septum. Histologic sections of the hearts of all 5 cases were stained with hematoxylin and eosin and with a combined elastic-trichrome stain. Immunohistochemical staining for Ki67 and CD117 (c-kit) was performed on 4-μm–thick paraffin sections with the standard streptavidin-biotin complex method with 3,3-diaminobenzidine as the chromogen. The Ki67 antibody (clone Mib1, Dako Carpinteria, CA, USA) was applied at 1:30 dilution after heat-induced epitope retrieval. The CD117 antibody (Dako) was applied at 1:80 dilution; no antigen retrieval was necessary.

Table 2 Autopsy findings

	Infant weight	Infant length	Heart weight	Cardiac phenotype	Endocardial fibroelastosis	Myocardial mitotic counts	Myocardial proliferative indices
1	4490 g	57 cm (51.9 ± 4.5 cm)	39.7 g (21 ± 5 g)	Dilated cardiomyopathy in all 5 cases	Present in atria and ventricles	+++ in RA, RV, LA, LV, and Sep of all 5 cases	10%-20% in RA, RV, LA, LV and Sep of all 5 cases
2a	4940 g	59.5 cm (54.0 ± 3.7 cm)	35.9 g (26 ± 6 g)		Present in ventricles		
2b	5300 g	57 cm (54.0 ± 3.7 cm)	35.9 g (26 ± 6 g)		Present in atria and ventricles		
3a	3190 g	50.5 cm (51.9 ± 4.5 cm)	22.4 g (21 ± 5 g)		Present in left atrium		
3b	4770 g	55 cm (51.9 ± 4.5 cm)	36 g (21 ± 5 g)		Present in left atrium and ventricle		

NOTE. Mitotic counts are scored semiquantitatively, as follows: 0, none to 1 mitosis per 10 high-power fields; +, 1 to 5 mitoses per 10 high-power fields; ++, 5 to 10 mitoses per 10 high-power fields; +++, more than 10 mitoses per 10 high-power fields. Reference ranges are included in parenthesis: Those for infant length are obtained from Schulz DM, Giordano DA, Schulz DH, *Arch Pathol* 1962;74: 244. Those for heart weight are obtained from Schulz DM, Giordano DA, *Arch Pathol* 1962;74: 464-471.

Abbreviations: RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; Sep, interventricular septum.

3. Results

The 5 affected infants were all female and included 2 pairs of siblings. Death occurred in early infancy (range, 22-67 days; mean, 42 days). Clinical presentation was with general lethargy, decreased feeding, respiratory distress, and cyanosis. Two infants had fever. The clinical and autopsy findings are summarized in Tables 1 and 2, respectively. Autopsy revealed findings of congestive cardiac failure in all 5 infants with serous pericardial, pleural, and peritoneal effusions. The hearts were enlarged, and 4 of the 5 hearts were heavy in comparison to age-specific reference values. Chamber dilatation was present in all 5 cases, with ventricular dilatation more pronounced than atrial dilatation (Fig. 1A). Valvular dimensions of the tricuspid and mitral valves were increased, consistent with a dilated phenotype. Endocardial fibroelastosis was present in all cases (Fig. 1B).

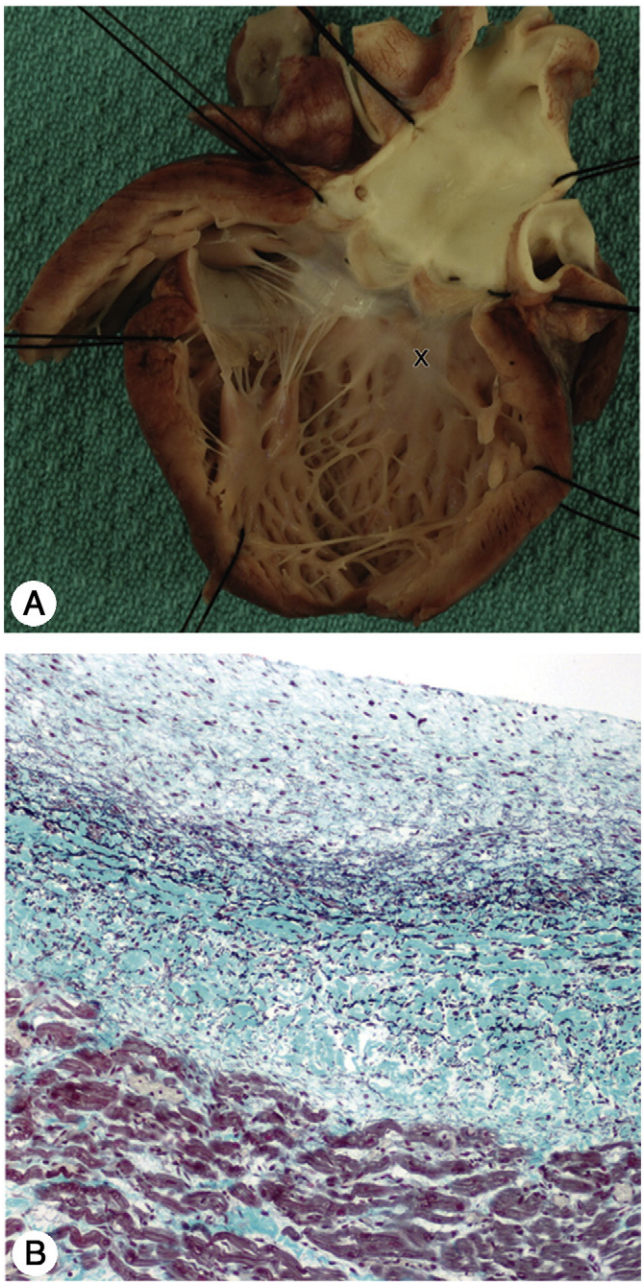

Fig. 1 A, Gross photograph of heart showing left ventricular outflow tract with ventricular dilatation and endocardial fibroelastosis (x). B, Photomicrograph of left ventricular endocardium showing endocardial fibroelastosis (elastic trichrome stain, ×100).

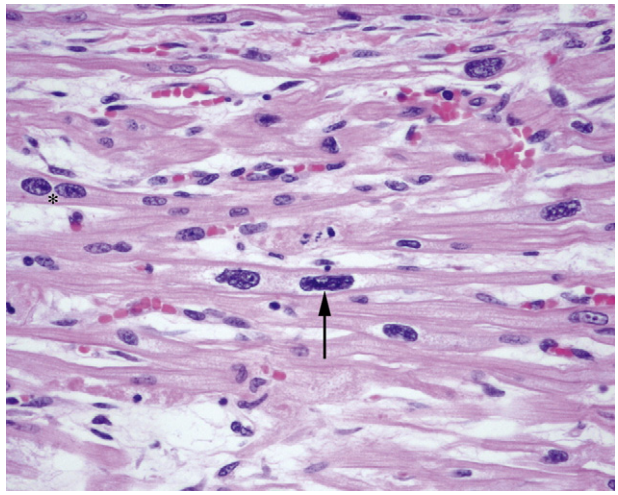

Fig. 2 Photomicrograph of myocardium showing myocyte nuclear hypertrophy. A caterpillar nucleus is present (arrow). A binucleate myocyte is present (∗) (hematoxylin and eosin, ×400).

The myocardial histologic features were distinctive and identical in all 5 cases. There were prominent hypertrophic changes of the myofibers (Fig. 2), featuring elongated, enlarged, and hyperchromatic nuclei with coarsely clumped chromatin. Occasional nuclei had condensed chromatin forming a serrated thread running in the long axis, an appearance which has been termed *caterpillar nuclei* [16]. Mitotic activity was markedly increased in all sections of right and left atrial and ventricular and interventricular septal

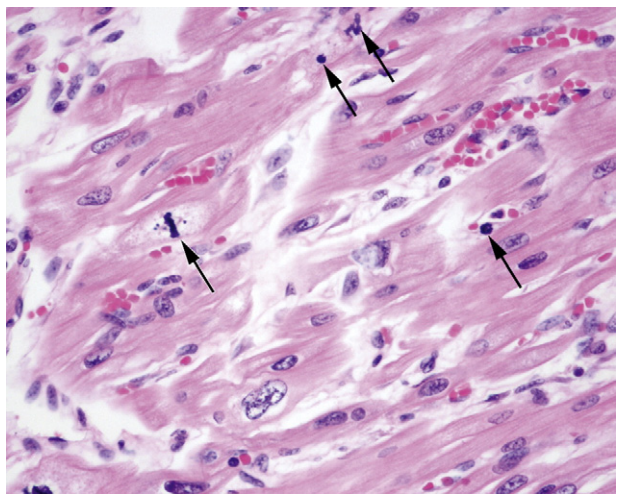

Fig. 3 Photomicrograph of myocardium showing myocyte nuclear hypertrophy and numerous mitoses (arrows) (hematoxylin and eosin, ×400).

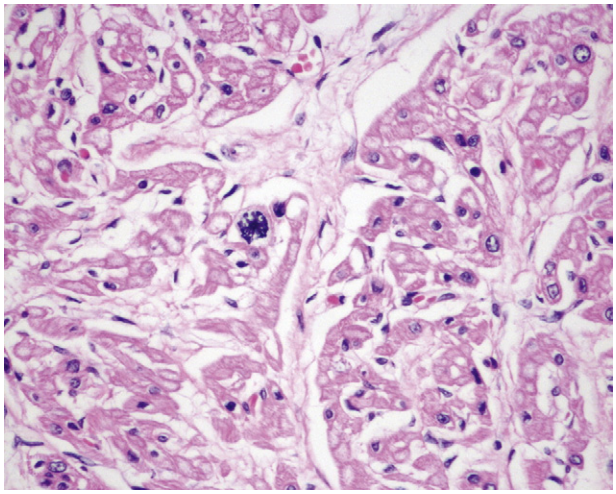

Fig. 4 Photomicrograph of myocardium showing an abnormal multipolar mitosis (hematoxylin and eosin, ×400).

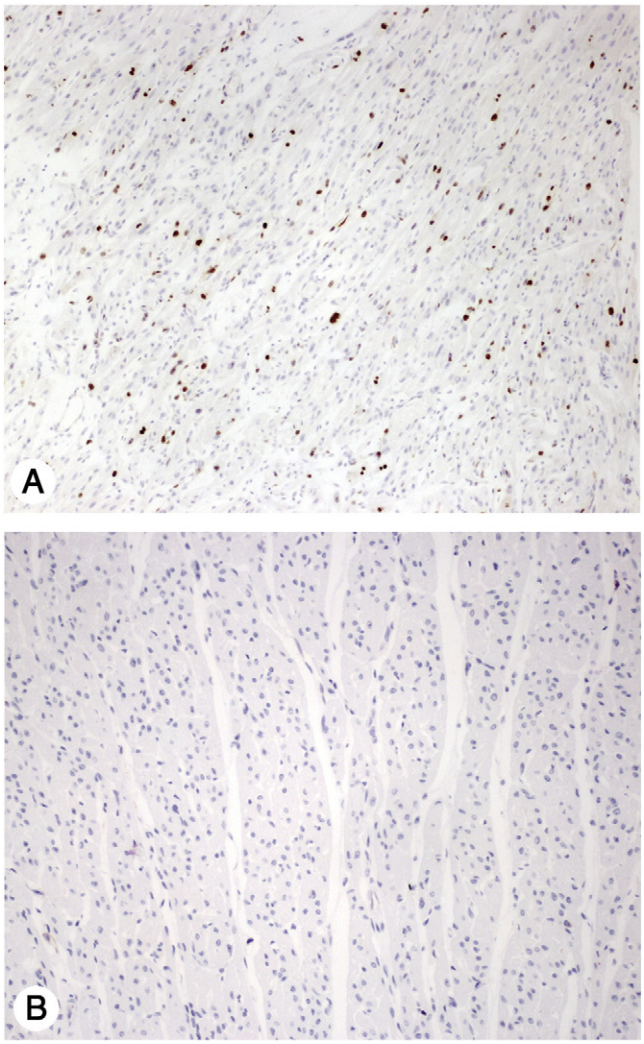

Fig. 5 Immunohistochemical staining for Ki67 (Mib1) showing (A) marked proliferative activity (×200) in contrast to (B) quiescent age-matched control myocardium (×100).

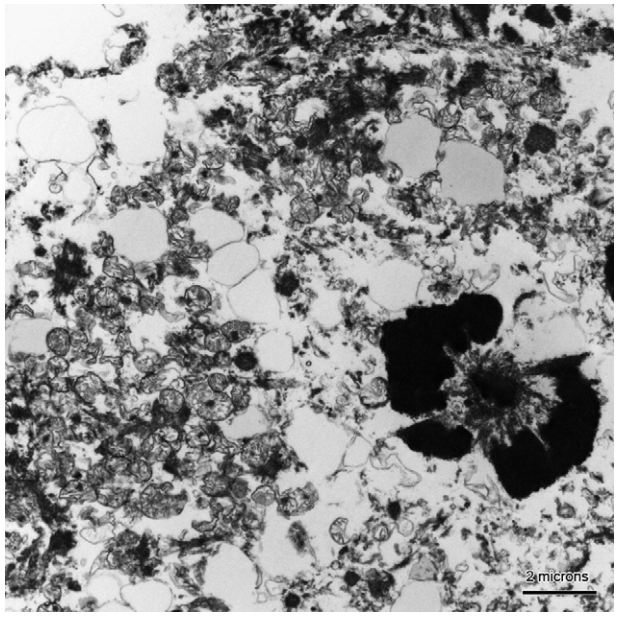

Fig. 6 Electron micrograph of cardiac myocyte undergoing mitosis (×8000).

myocardium, with mitoses numbering 2 to 3 per high-power field and numbering up to 4 per single high-power field (Fig. 3). Semiquantitative scoring of the mitotic counts in 10 high-power fields showed a score of +++ (more than 10 mitoses per 10 high-power fields) in different myocardial regions, namely, right and left atrial and ventricular and interventricular septal myocardium (Table 1). Scattered large atypical mitotic figures with multipolar configurations were also present (Fig. 4). There were no significant geographic variations in degrees of myocyte hyperplasia or mitotic activity in the right and left atria and ventricles and interventricular septum. These features contrasted with age-matched control myocardium in which myocyte nuclei were generally uniform in size and mitoses were rare or absent. Immunohistochemical staining for Ki67 (Mib1) showed a markedly increased proliferative index of between 10% and 20% in all regions of myocardium, namely, right and left atria and ventricles and interventricular septum. This contrasted with age-matched normal myocardium that had a proliferative index of less than 1% (Fig. 5A and B). Immunohistochemical staining with CD117 did not reveal any identifiable positively staining myocardial or stem cells. Electron micrographs showed cardiac myocytes with mild cytoplasmic lipid accumulation and dilated Golgi vesicles; at least one terminally differentiated cardiac myocyte undergoing mitosis was identified (Fig. 6). Ancillary clinical investigations did not reveal a known primary cause for the cardiomyopathy.

4. Discussion

Pediatric cardiomyopathies are a heterogenous group of conditions, of which dilated cardiomyopathy forms the most

common clinicomorphologic type [7]. Dilated cardiomyopathy is characterized by dilatation of the left ventricular chamber and systolic dysfunction resulting in congestive heart failure, and is the most common reason for cardiac transplantation in both adults and children [17,18]. The 2 most frequently identified causes of dilated cardiomyopathy are myocarditis and neuromuscular disease (Duchenne, Becker, and Emery-Dreifuss muscular dystrophies) [8]. Other known causes include mutations in genes for sarcomeric proteins [10], Z-band proteins, cytoskeletal proteins, and nuclear membrane proteins [19]. Dilated cardiomyopathies are also seen in inborn errors of metabolism such as mitochondrial disorders [20], Barth syndrome, and primary carnitine deficiency [21,22]. However, the underlying cause is not known in a majority of cases including the current series of cases [8]. A significant proportion of cases of dilated cardiomyopathy are familial with a majority having an autosomal dominant inheritance pattern [8], underlying the importance of accurate diagnosis for genetic counseling. The prognosis is grim in the majority of cases [8,15].

To our knowledge, only one similar case of this distinctive entity has been previously reported in the literature [23]. Zerbini et al describe an 8-day-old male infant with uneventful gestation and delivery who was well until a few hours before death, presenting with a short history of difficulty in breathing and then sudden death. The autopsy performed revealed unremarkable cardiac anatomy with no structural abnormalities. The right ventricle was slightly dilated, and there was endocardial fibroelastosis. Histologic sections of myocardium showed numerous mitoses and frequent enlarged myocardial nuclei with condensed chromatin forming a serrated thread running in the long axis that they termed *caterpillar nuclei*. They also describe "micronuclei" that in their illustrations likely represent apoptotic bodies. An abnormal DNA ploidy pattern is described in which multiple peaks (2N, 4N, and 6N) were obtained. The authors postulate that their findings of abnormal DNA ploidy associated with numerous mitotic figures and atypical chromatin patterns suggest "some derangement in the process of cellular division in the setting of a poorly defined stress situation" [23].

Traditional dogma has held that the heart is a postmitotic organ composed of terminally differentiated cardiomyocytes that are incapable of regeneration or replication [24]. This paradigm states that cardiac myocytes may undergo cellular hypertrophy but not cell division. However, recent studies have identified a subpopulation of cardiac stem cells with the emergence of a new paradigm that the heart has remarkable growth reserve and that cardiac myocyte formation is preserved during postnatal life through to adulthood and senescence [25]. The heart is now known to be an organ in which myocyte division and regeneration may occur throughout the organism's life span [26,27]. Many of these studies center on the adult human heart in relation to post–myocardial infarction myocyte regeneration as a means of myocardial repair and ventricular remodeling [28,29]. Nonetheless, this finding indicates the potential for myocardial myocytes to undergo mitosis in response to pathologic stimuli or unknown molecular aberrations.

The phenomenon of cardiac myocyte hypertrophy featuring enlargement of myocyte nuclei appears to bear some morphologic resemblance to islet cell nuclear enlargement in congenital hyperinsulinism [30]. The biologic significance of the large islet cell nuclei is unclear. An increase in nuclear size has been demonstrated in hyperfunctional endocrine cells [31]. Zerbini et al [23] used image analysis to evaluate DNA ploidy in their case report. This yielded an abnormal histogram with multiple polypoidal peaks of 2N, 4N, and 6N in contrast to control myocardium showing a uniform diploid population of cells.

In conclusion, we describe 5 cases of a rare form of dilated cardiomyopathy that is lethal in early infancy and characterized by distinctive histologic features of myocyte hyperplasia and marked mitotic activity. We propose naming this entity *mitogenic cardiomyopathy* to reflect its distinctive histologic appearance of marked mitotic activity, a feature that is not seen in recognized forms of cardiomyopathy. Its occurrence in 2 pairs of siblings suggests familial inheritance. It is important to recognize this distinctive entity at autopsy for purposes of genetic counseling. The pathogenesis is at present unknown, but requires further investigation to elucidate the underlying genetic defect. Identification of genetic mutational changes present may clarify the inheritance pattern of this condition and provide the basis for genetic counseling.

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