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Isolated Noncompaction of the Ventricular Myocardium: Clinical and Molecular Aspects of a Rare Cardiomyopathy

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Isolated noncompaction of the ventricular myocardium (INVM) is a rare congenital heart disease that results from an abnormal arrest in endomyocardial embryogenesis. It is characterized by the presence of prominent ventricular myocardial trabeculations and deep intertrabecular recesses, in the absence of other structural heart defects. INVM was initially described in the pediatric population (Chin et al, 1990), but it has also been recognized more recently in adults (Oechslin et al, 2000; Ritter et al, 1997). We present a case of a 35-year-old woman with clinical and echocardiographic features of INVM who underwent cardiac transplantation in our institution. The literature on cardiac embryogenesis and development, with an emphasis on the different genetic factors that lead to noncompaction of the ventricular myocardium, is also reviewed.

Case Presentation

Clinical History

A 35-year-old woman of Hispanic descent was evaluated at our institution for progressive signs and symptoms of heart failure. The patient was asymptomatic until age 23 years, when she began to experience intermittent episodes of shortness of breath, chest pain, and syncope. Her past medical history was negative for illegal drugs, alcohol, or tobacco consumption, systemic hypertension, or diabetes mellitus. Family history was negative for congenital heart diseases, with none of the patient's parents or 22 siblings, including a nonidentical twin sister, presenting a similar clinical picture. The patient also has a 16-year-old son, who has no manifestations of cardiac disease.

Both transthoracic and transesophageal echocardiograms performed 2 weeks before surgery revealed a severe reduction in the patient's left ventricular systolic function with an asymmetric pattern of hypertrophy of the left ventricular myocardium, localized to the anterior and anterolateral segments. Prominent trabeculations with deep intertrabecular recesses were also identified in these regions of hypertrophy (Fig. 1). The patient's congestive heart failure progressed despite pharmacotherapy, and the patient underwent orthotopic heart transplantation 12 years after the onset of symptoms. Recovery after transplantation has been uneventful.

Gross and Microscopic Findings

The explanted heart weighed 420 g. It had been transected at the level of the atria, the aorta, and the pulmonary artery as part of the transplantation surgical procedure. The epicardial surface was grossly unremarkable. The coronary arteries and the remaining segments of the great vessels had a normal anatomic distribution. The tricuspid, pulmonary, mitral, and aortic valve circumferences measured 15, 8, 10, and 7 cm, respectively. Serial sectioning from the apex toward the base of the ventricles revealed a thickened left ventricular wall, measuring 25 mm in greatest thickness. The left ventricular myocardium showed prominent trabeculations, with intertrabecular recesses invaginating deeply into the outer one-third of the myocardium (Fig. 2A). The right ventricular wall and the interventricular septum measured 15 mm and 20 mm, respectively. Multiple histologic sections were taken and stained with hematoxylin/eosin, Klatskin's trichrome, and elastin stains. Marked interstitial fibrosis with compensatory hypertrophy of the myocytes was present in the left ventricular myocardium. The endocardium was thickened by fibrous tissue, but no

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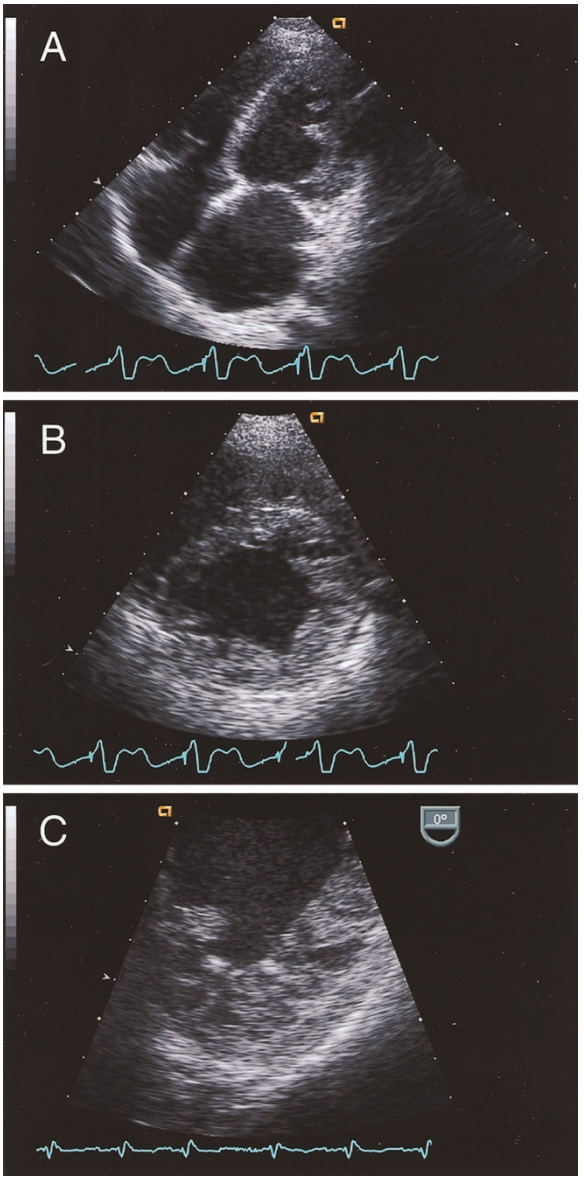

Figure 1.
Transthoracic echocardiogram. A, Apical four chamber, and B, parasternal short axis views demonstrating the prominent trabeculations and deep intertrabecular recesses localized to the regions of hypertrophy in the mid and apical anterior and anterolateral segments. Transesophageal echocardiogram. C, Short axis view further depicting the trabeculations and intertrabecular recesses in the anterior and anterolateral segments.

fibroelastosis was identified. The right ventricle showed moderate myocardial hypertrophy. Prominent myocardial trabeculations with deep intertrabecular recesses, and overlying endocardium thickened by fibrous tissue were also evident microscopically (Fig. 2, B–D).

Review of the Literature

Isolated Noncompaction of the Ventricular Myocardium

INVM, also designated "spongy myocardium" or "persistent embryonic myocardium," results from an arrest in the normal process of myocardial compaction, with persistence of multiple prominent ventricular trabeculations and deep intertrabecular recesses. INVM typically involves the left ventricular myocardium. However, in less than one-half of patients, right ventricular noncompaction may also be present (Hook et al, 1996; Ritter et al, 1997).

The clinical manifestations are not specific and may include heart failure resulting from systolic and diastolic ventricular dysfunction, conduction abnormalities, and cardioembolic events from thrombus formation within intertrabecular recesses (Ritter et al, 1997). Cardiac manifestations may range from complete absence of symptoms to severe cardiac disability leading to heart transplantation or death (Agmon et al, 1999; Ichida et al, 1999).

Currently, echocardiography is the diagnostic modality of choice for INVM (Agmon et al, 1999). Echocardiographic criteria for INVM, in the absence of significant heart lesions, include a thin, compacted epicardial and an extremely thickened endocardial layer with prominent trabeculations and deep recesses (Oechslin et al, 2000). Although INVM is a congenital myocardial disorder, the onset of symptoms is commonly delayed until adulthood, possibly secondary to progressive ventricular dysfunction. The mechanism of systolic dysfunction is not entirely clear, but it is most likely due to chronic ischemia caused by a mismatch of blood demand and supply to the multiple prominent myocardial trabeculae (Agmon et al, 1999; Junga et al, 1999). Similarly, the causes and electrophysiologic mechanisms of arrhythmias are still unknown. However, grossly irregular branching and connection of myocardial fascicles, isometric contractions with increased wall stress, and localized coronary perfusion impairment can all induce disorganized or delayed activation, and have been implicated as potential causes for arrhythmias in cases of INVM (Buonanno et al, 2000).

The prognosis of INVM is variable and may range from a prolonged asymptomatic course to a fulminant course of progressive heart failure leading to heart transplantation or death (Agmon et al, 1999; Ritter et al, 1997). Only seven cases of INVM treated by heart transplantation have been previously reported in the literature (Conraads et al, 2001).

Cardiac Embryogenesis and Development

Cardiac embryogenesis and development involve precisely regulated molecular and embryogenetic events, triggered by specific signaling molecules and mediated by tissue-specific transcription factors. Cardiomyocytes originate in the anterior lateral mesoderm soon after gastrulation, in response to protein factors secreted from the adjacent endoderm. These cardiogenic signals, which include cerberus and bone morphogenetic proteins, activate the expression of the homeobox gene *tinman* in flies and the related gene *Nkx2.5* in vertebrates. These factors cooperate with zinc-finger transcription factors of the GATA family to activate cardiac gene expression, including the *Mef2* gene, which encodes a transcription factor that con-

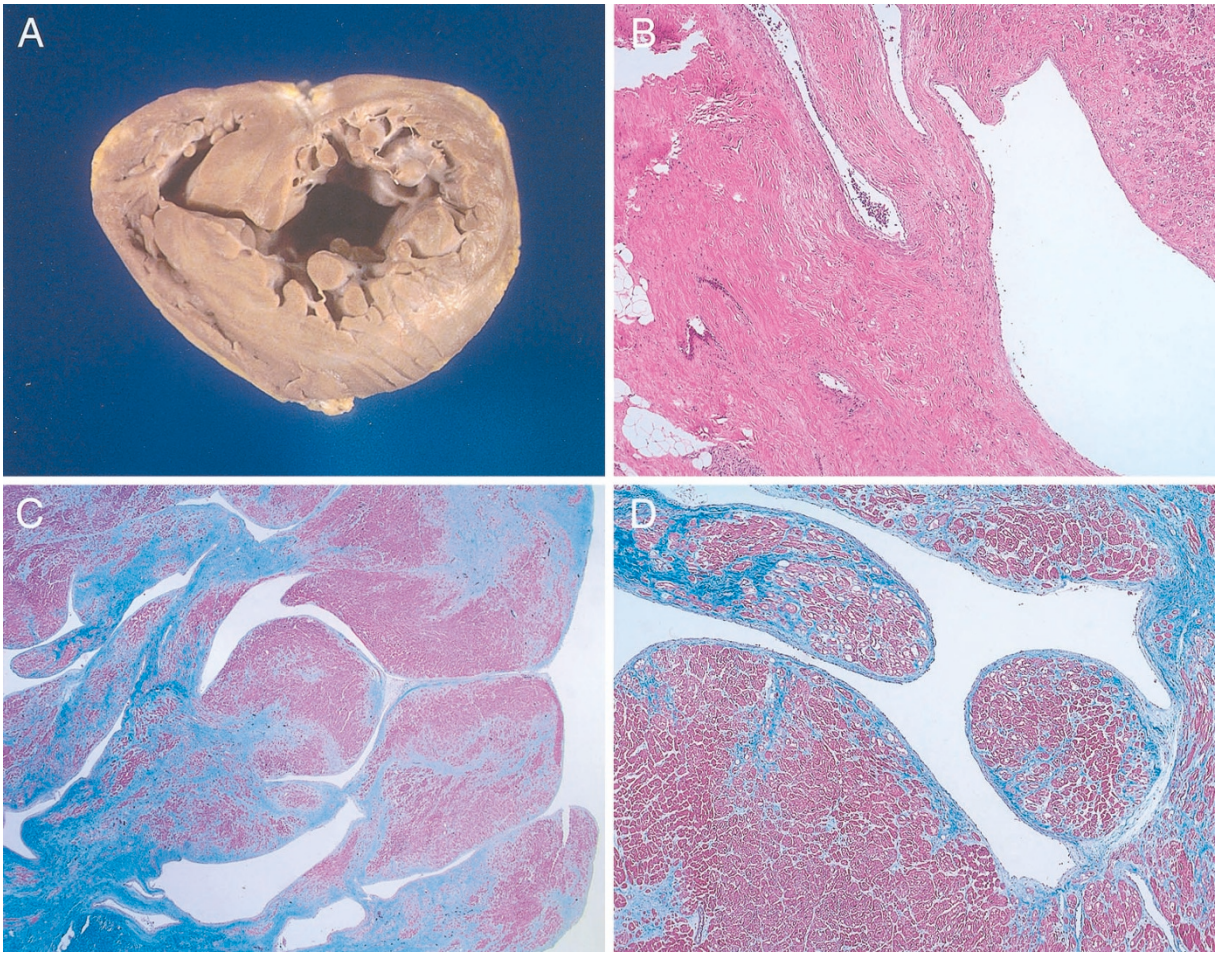

Figure 2.

A, Gross photograph of the explanted heart showing prominent myocardial trabeculations and deep recesses in the left ventricular wall. Multifocal areas of fibrosis are also evident. A section has been taken from the interventricular septum. B, Low-power view of histologic section showing a deep myocardial recess in close proximity to the epicardial adipose tissue (hematoxylin and eosin stain; Original magnification, ×40). C, Low-power view of histologic section showing multiple trabeculations and myocardial projections, with extensive fibrosis (Klatskin trichrome stain; original magnification, ×10). D, Low-power view of histologic section showing a thickened endocardium overlying the myocardial recesses, with areas of patchy fibrosis (Klatskin stain; original magnification, ×40).

trols cardiac muscle cell differentiation. The Mef2 transcription factor activates the expression of genes encoding cardiac muscle-specific proteins (such as cardiac actin, atrial natriuretic factor, and the alpha myosin heavy chain) (Gilbert, 2000; Srivastava and Olson, 2000).

After their specification, myocytes migrate along the ventral midline of the embryo. As they migrate, the cells begin to express N-cadherin and differentiate into an epithelium. A small population of these cells then down-regulates N-cadherin and dissociate from the epithelium to form the endocardium. The epithelial cells, in turn, will form the myocardium. The myocardium and endocardium eventually fuse together into a single beating cardiac tube, at 3 weeks of human gestational life (Gilbert, 2000). The linear heart tube undergoes segmentation along the anterior-posterior axis into precursors of the aortic sac, conotroncus, ventricles, and atria, with different patterns of gene expression in each of these chambers. In addition, a subset of ventricular cardiomyocytes surrounding the developing coronary arteries differentiates into cells that form the conduction system of the heart, in response to endothelin-1 (ET-1) (Srivastava and Olson, 2000).

At this stage, before the development of the coronary circulation, the human embryonic myocardium consists of a "spongy" meshwork of interwoven myocardial fibers forming trabeculae with deep intertrabecular recesses (Dusek et al, 1975). The intertrabecular recesses communicate with the left ventricular cavity, and blood is supplied to the myocardium through the intertrabecular spaces. Neuregulin growth factors secreted from the endocardium, and the local expression of the myocardial receptors ErbB2 and ErbB4, are required for the development of these trabeculae. Other angiogenic factors expressed in the endocardium, such as vascular endothelial growth factor and angiopoietin-1, may also play a role in the process of ventricular trabeculation (Srivastava and Olson, 2000).

After this, during weeks 5 to 8 of human fetal life, the ventricular myocardium undergoes gradual compaction, with transformation of the relatively large intertrabecular spaces into capillaries, and the large spaces

within the trabecular meshwork flatten or disappear. The process of compaction of the ventricular myocardium normally progresses from epicardium to endocardium and from the base of the heart toward the apex. At the same time, while the process of ventricular myocardium compaction occurs, the coronary vessels are formed and the coronary circulation is established (Agmon et al, 1999).

Genetics of INVM

INVM results from an arrest in the normal process of myocardial compaction, with persistence of multiple prominent ventricular trabeculations. It is a distinctive clinical entity with a heterogeneous genetic background. Both sporadic and familial forms of INVM have been described (Agmon et al, 1999; Bleyl et al, 1997a; Chin et al, 1990; Kurosaki et al, 1999; Matsuda et al, 1999). Although male predominance is the rule in familial cases of INVM, both sexes are affected in the sporadic forms of the disease. Nevertheless, whereas the genes responsible for some familial forms have been identified (Bleyl et al, 1997b; Ichida et al, 2001) those for the sporadic forms of INVM have not yet been characterized.

Genetic linkage analysis has revealed that mutations in the gene *G4.5* on the Xq28 chromosomal region are responsible for some familial cases of INVM (Bleyl et al, 1997a; Ichida et al, 2001). These cases of X-linked INVM are allelic with Barth syndrome (MIM 302060) (Bleyl et al, 1997b), which is characterized by dilated cardiomyopathy, short stature, skeletal myopathy, neutropenia, and abnormal mitochondria. Interestingly, molecular studies have linked together what were formerly considered different conditions and have shown that the *G4.5* gene is also responsible for X-linked endocardial fibroelastosis (MIM 305300), and severe X-linked cardiomyopathy (MIM 300069) (D'Adamo et al, 1997). In addition, this locus is in proximity to other genes associated with systemic myopathies that are commonly accompanied by various cardiomyopathies and arrhythmias, such as Emery-Dreifuss muscular dystrophy (MIM 310300) and myotubular myopathy (MIM 31040) (Bleyl et al, 1997a). The function of the *G4.5* gene protein products, called tafazzins, is currently unknown (Bione et al, 1996; Cantlay et al, 1999). However, gene sequencing has revealed nucleotide homology to a highly conserved superclass of acyltransferases. It is therefore predicted that a glycerophospholipid is most likely the missing end product (Barth et al, 1999).

Some cases of INVM have been found to be associated with certain genetic syndromes (Mandel et al, 2001; Wong and Bofinger, 1997). Other forms of nonventricular myocardial compaction associated with additional types of congenital heart diseases have also been described. Recently, a transition C→T mutation was identified in the *α-dystrobrevin* gene in one family with such type of congenital heart disease (Ichida et al, 2001). The *α-dystrobrevin* gene has been localized to chromosome 18q12 (Sadoulet-Puccio et al, 1997). It encodes for an intracellular protein that interacts with dystrophin and other proteins that intervene in muscular contraction and in maintaining the structural integrity of tissues (Mizuno et al, 2001). In addition, a distal 5q deletion, del(5)(q35.1-q35.5), was described in a girl with a complex heart malformation including ventricular myocardial noncompaction. This deletion includes the locus for the cardiac-specific homeobox gene *CSX*, suggesting that in some instances ventricular myocardial noncompaction can be caused by haploinsufficiency of *CSX* (Pauli et al, 1999). Figure 3 summarizes the different factors that intervene in cardiac embryogenesis, and the process of ventricular myocardial trabeculation and compaction.

Given that most familial cases of INVM are X-linked and that no relatives in the patient's extensive family present a similar clinical picture, the case under discussion most likely represents a sporadic form of the disease. As previously stated, no genes responsible for the sporadic forms of INVM have yet been identified.

Conclusion

In the past few years, our understanding of the molecular factors involved in the embryogenesis and development of the human heart has increased remarkably. As a result of this, abnormalities of specific genes and their products are now known to be responsible for different types of congenital heart diseases once thought to have multifactorial etiologies (Chin, 1998; London, 1998; Seidman et al, 1998; and Table 1). On many occasions, these developmental cardiopathies result from single gene point mutations that disrupt their normal function in cardiac specification and morphogenesis. The consequences of these mutations vary widely, not only because of the specific

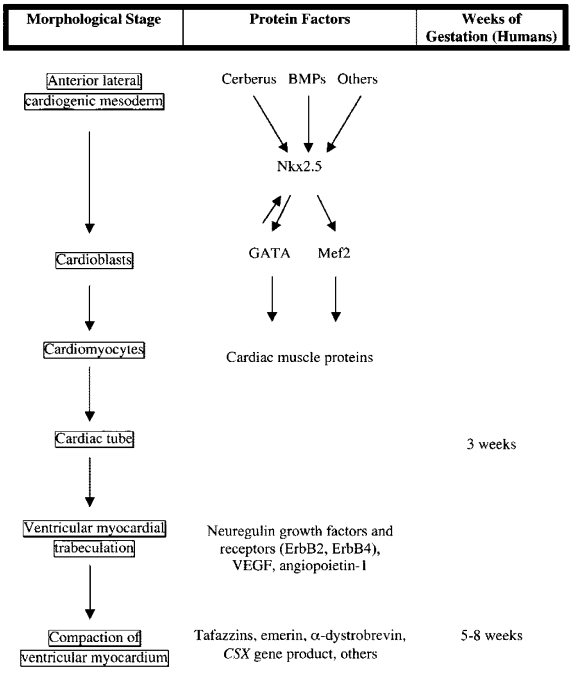

Figure 3.
Protein factors at different stages of cardiac development.

Table 1. Human Genes Implicated in Cardiac Defects

Gene	Locus	Protein type	Cardiac defect
NKX2.5	5q34	Transcription factor	Atrial septal defect, cardiac conduction abnormalities, tetralogy of Fallot
TBX5	12q24	Transcription factor	Atrial septal defect, ventricular septal defect, Holt-Oram syndrome
JAGGED-1	20p12	Signaling molecule	Pulmonary stenosis, tetralogy of Fallot, Alagille syndrome
TFAP2B	6p12	Transcription factor	Patent ductus arteriosus, Char syndrome
Elastin	7q11	Connective tissue	Supravalvular aortic stenosis, William's syndrome
Fibrillin	15q21	Connective tissue	Aortic aneurysm, Marfan's syndrome
Type III collagen	2q31	Connective tissue	Aortic aneurysm, Ehlers-Danlos syndrome type IV
Unknown	22q11	Multiple genes	DiGeorge syndrome, Tetralogy of Fallot, conotruncal and aortic arch defects
HERG	7q35–q36	Potassium channel	Long QT syndrome, Brugada syndrome
SCN5A	3p21	Sodium channel	Long QT syndrome
KVLQT1	11p15	Potassium channel	Long QT syndrome
KCNE2	21q22	Potassium channel	Long QT syndrome
Cardiac troponin T	1q32	Sarcomere protein	Hypertrophic cardiomyopathy
Cardiac myosin binding protein C	11q1	Sarcomere protein	Hypertrophic cardiomyopathy
Cardiac β-myosin heavy chain	14q1	Sarcomere protein	Hypertrophic cardiomyopathy
α-tropomyosin	15q2	Sarcomere protein	Hypertrophic cardiomyopathy
Unknown	7q3	Unknown	Hypertrophic cardiomyopathy, Wolf-Parkinson-White syndrome
G4.5	Xq28	Tafazzins (function unknown)	Barth syndrome, INVM, endocardial fibroelastosis, dilated cardiomyopathy
Emerin	Xq28	Emerin (function unknown)	Emery-Dreifuss syndrome, dilated cardiomyopathy
Dystrophin	Xp21	Membrane-cytoskeleton system in striated muscle	Duchenne syndrome, Becker syndrome, dilated cardiomyopathy
α-dystrobrevin	18q12	Membrane-cytoskeleton system in striated muscle	Noncompaction of ventricular myocardium
Others	1p1–1q1, 1q24, 3p25–p22, 9q13	Unknown	Dilated cardiomyopathies

genetic alteration they produce, but probably also because of the influence of modifier genes, environmental factors, and genetic polymorphisms that determine the severity, type, and age of onset of congenital heart disease. Unraveling the molecular factors that interplay in cardiac embryogenesis and development has important implications not only for understanding congenital heart diseases, but also for the potential of genetically reprogramming noncardiac cells to be used in cardiac regeneration or cell replacement.

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