Clin. Cardiol. 26, 536–539 (2003)

Autopsy Findings in Siblings with Hypertrophic Cardiomyopathy Caused by Arg92Trp Mutation in the Cardiac Troponin T Gene Showing Dilated Cardiomyopathy-Like Features

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Summary

Background: Hypertrophic cardiomyopathy (HCM) is caused by mutations in the genes that encode sarcomeric proteins. Although some patients with HCM have shown dilated cardiomyopathy (DCM)-like features, the relationship between genotype and histologic findings is not well known.

Hypothesis: Family members with the same gene mutation may show the same histopathologic changes and clinical manifestations.

Methods: Siblings with HCM caused by an Arg92Trp mutation in the cardiac troponin T gene, showing DCM-like features, were examined.

Results: The patients were a 69-year-old woman and her 57-year-old brother who both died from congestive heart failure. Their autopsies revealed the same histopathologic findings in the heart. The anterior walls and interventricular septa of their hearts were replaced with extensive fibrosis and showed thinning. Myocyte hypertrophy, disarray, and thickened medial walls of the intramural coronary arteries were found. On electron microscopy, the number of mitochondria was seen to be increased and they formed many clusters.

Conclusions: Patients with HCM caused by an Arg92Trp mutation in the cardiac troponin T gene may have the same histopathologic findings, which may result in DCM-like features.

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Received: September 19, 2002
Accepted with revision: December 24, 2002

Key words: hypertrophic cardiomyopathy, cardiac troponin T, gene mutation

Introduction

Recent advances in molecular genetics have demonstrated that hypertrophic cardiomyopathy (HCM) is caused by mutations in the genes that encode sarcomeric proteins.[1] Differences in gene mutations may affect different sarcomeric proteins and consequently result in different histopathologic changes. However, the relationship between genotype and histologic findings is not well known. We previously reported familial HCM caused by an Arg92Trp mutation in the cardiac troponin T (cTnT) gene that showed a progression to dilated cardiomyopathy (DCM).[2] We report here the autopsy findings in two siblings who showed DCM-like features and died of severe heart failure.

Methods

Subjects

A 69-year-old woman (Case No. 1) died of congestive heart failure. She had experienced back pain and exertional dyspnea from 20 years of age and was diagnosed with HCM at 49 years of age. In spite of medical treatment, her symptoms gradually deteriorated from 59 years of age, and she was implanted with a permanent pacemaker because of trifascicular block. Her brother (Case No. 2) also died of congestive heart failure at 57 years of age. He had experienced atrial fibrillation at age 35, and was implanted with a permanent pacemaker because of bradycardia at age 45. Dilated cardiomyopathy-like features were already present at age 50; left ventricular (LV) end-diastolic dimension was 60 mm, LV end-systolic dimension was 52 mm, and % fractional shortening of LV was 13% on echocardiogram. Consequently, he had been diagnosed with DCM. Unfortunately, it was unknown whether clinical features of HCM, such as septal hypertrophy, were found in him before 50 years of age.

Their familial survey revealed that some family members had HCM associated with a cTnT gene mutation (Arg92Trp) and that they were carriers of this mutation (Fig. 1). The details of the clinical and genetic analyses have been reported previously.[2]

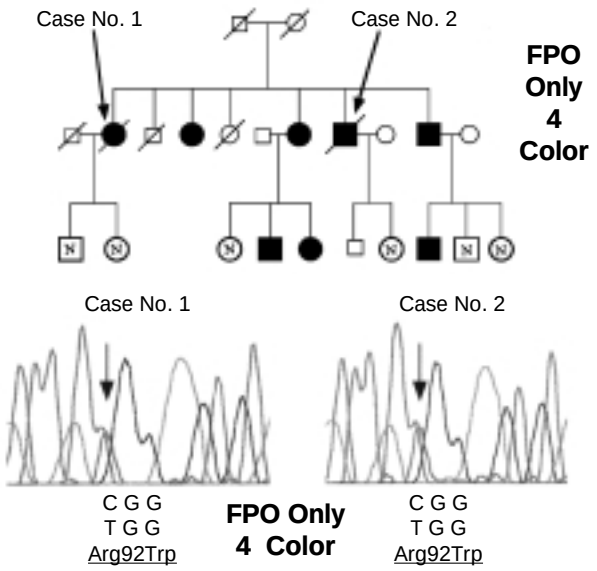

FIG. 1 Pedigrees and the results of nucleotide sequence of exon 9 of the cardiac troponin T gene. Solid large symbols indicate carriers; open large symbols with N indicate noncarriers; open small symbols indicate undetermined individuals; slashed symbols indicate deceased individuals; square symbols indicate males; circle symbols indicate females. Sequence analysis shows a mutation from arginine to tryptophane at codon 92 (normal allele is CGG and that of the mutant allele is TGG).

Histopathologic Examinations

Tissue was fixed in 10% buffered formalin. Some sections were stained with hematoxylin and eosin, and others with Mallory-Azan. For electron microscopy, the LV muscle was immediately removed from the heart and cut into small blocks. They were fixed in cacodylate-buffered 2.5% glutaraldehyde, postfixed in phosphate-buffered 1.2% osmium tetroxide, dehydrated in a graded series of ethanols, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate.

Results

Macroscopic Findings

The heart weights of Case No. 1 and Case No. 2 were 550 and 610 g, respectively. The left ventricles in both cases were markedly dilated, and thinning and massive fibrosis of the interventricular septa and LV anterior walls were found (Figs. 2A and 3A). No stenotic lesions were found in epicardial coronary arteries in either case.

Microscopic Findings

Histological examination of the LV posterior wall in Case No. 1 revealed myocyte hypertrophy and great disarray (Fig. 2B). Histologic examination of the LV lateral wall in Case No.

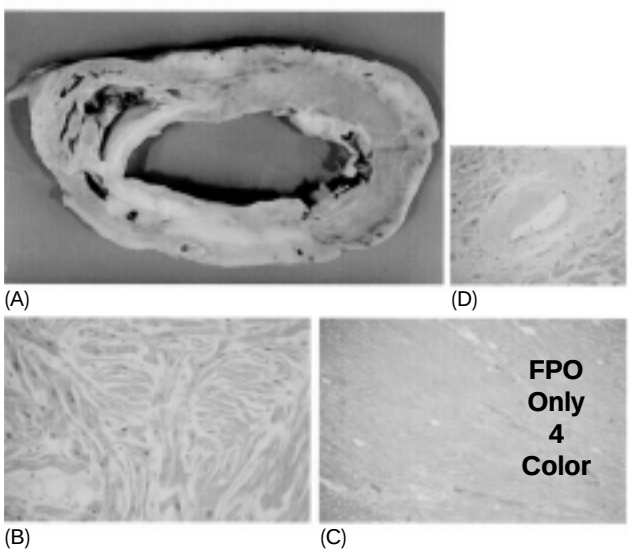

FIG. 2 Macroscopic and microscopic findings in Case No. 1. (A) Gross photograph of the heart, (B) myocyte disarray in the posterior wall (hematoxylin and eosin), (C) massive fibrosis in the anterior wall (Mallory-Azan), (D) intramural coronary artery (hematoxylin and eosin).

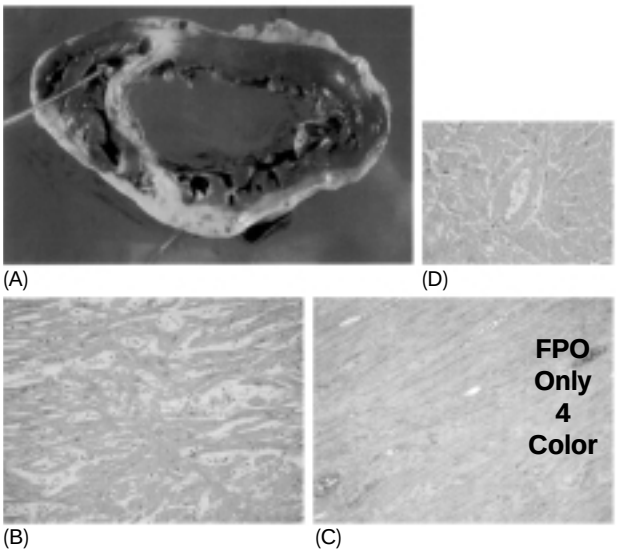

FIG. 3 Macroscopic and microscopic findings in Case No. 2. (A) Gross photograph of the heart, (B) myocyte disarray in the lateral wall (hematoxylin and eosin), (C) massive fibrosis in the interventricular septum (Mallory-Azan), (D) intramural coronary artery (hematoxylin and eosin).

TABLE I Histopathologic findings of the heart associated with cardiac troponin T gene mutations

Species	Mutation	Reference	Hypertrophy	Disarray	Fibrosis	Other findings	Ultrastructural findings
Mouse	Truncation	5		Mild	Mild	Pleomorphic nuclei	
Mouse	Arg92Gln	6		Variable	Twofold		
Mouse	Arg92Gln	7	Mild	Massive	Massive	Pleomorphic nuclei Myocyte necrosis	Myofibrillar disarray
Rat	del ex16	8		Mild [a]			
Feline	Arg92Gln	9					Intact sarcomere structure
Human	Arg92Trp	2	Mild	Minimal	Mild		
Human	Arg92Trp Arg92Leu Arg94Leu Ile79Asn Intrl5G1→A Pro77Leu Ser69Phe	4		Greater	Less		

[a] After exercise.

2 revealed myocyte hypertrophy, but disarray was milder than that seen in Case No. 1 (Fig. 3B). The interventricular septa and anterior walls in both cases were replaced with extensive fibrosis (Figs. 2C and 3C), and thickened medial walls of the intramural small coronary arteries were found in both cases (Figs. 2D and 3D).

Electron Microscopy Findings

The number of mitochondria in Case No. 1 was increased and formed many clusters. Myofibrils varied from hypertrophic to atrophic. Lipofuscin was increased. Electron microscopy of tissue from Case No. 2 was not performed.

Discussion

It has been reported that almost 10% of patients with HCM showed DCM-like features.[3] It is very interesting that the siblings in the present study showed the same morphologic and pathologic characteristics. Histopathologic findings of the heart associated with cardiac troponin T gene mutations in previous reports[2, 4-9] are summarized in Table I. Until now, there have been only a few reports on histopathologic changes of the human heart associated with cTnT gene mutations.[2, 4] It has been shown that myocyte disarray in HCM hearts caused by cTnT gene mutations is greater than that in those without cTnT gene mutations.[4] In Case No. 1, typical myocyte disarray was found in addition to myocyte hypertrophy. In contrast, only mild myocyte disarray was found in Case No. 2, while myocyte hypertrophy and wall thickening of intramural coronary arteries were found. This may be because myocyte disarray is found predominantly in the septum of the HCM heart,[10] and the septum in Case No. 2 was replaced by massive fibrosis.

Fibrosis has been reported to be less in the HCM heart associated with a cTnT gene mutation.[4] In contrast, fibrosis in our patients was quite severe. In animal models of HCM associated with cTnT gene mutations, mild to massive fibrosis in the heart has been reported.[5–7] One reason for the difference may be aging. The patients reported by Varnava *et al.*[4] experienced sudden death and were younger (6–37 years) than our patients. In the heart with a cTnT gene mutation, mild myocyte hypertrophy and disarray may occur at an early stage. In the later stages, myocyte cell death and replacement by fibrosis may progress. The mechanism of how cTnT gene mutation leads to myocyte cell death and replacement with fibrosis is unknown. Further investigations are necessary in the future.

Conclusions

Siblings with HCM caused by an Arg92Trp mutation in the cardiac troponin T gene showed the same histopathologic findings. Patients with HCM caused by this mutation in the cardiac troponin T gene may show the same histopathologic changes, which may result in DCM-like features.

Acknowledgments

The authors thank Prof. Yuji Mizukami, School of Medicine, Kanazawa University, and Prof. Yoshimaro Ishikawa, Medical Research Institute, Kanazawa Medical University, for providing information regarding autopsy and electron microscopy findings.

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Clin. Cardiol. 26, 539 (2003)

Images in Cardiology: Focal Hypertrophic Cardiomyopathy Simulating a Mass

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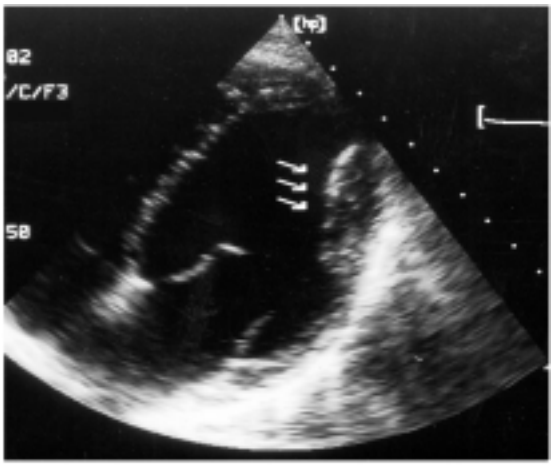

FIG. 1 Apical four-chamber-view echocardiogram. Distribution of hypertrophy is virtually confined to the middle and apical segments of lateral free wall (LFW) in the left ventricle (arrows). Note that the anterior ventricular septum and basal segment of LFW are of normal thickness.

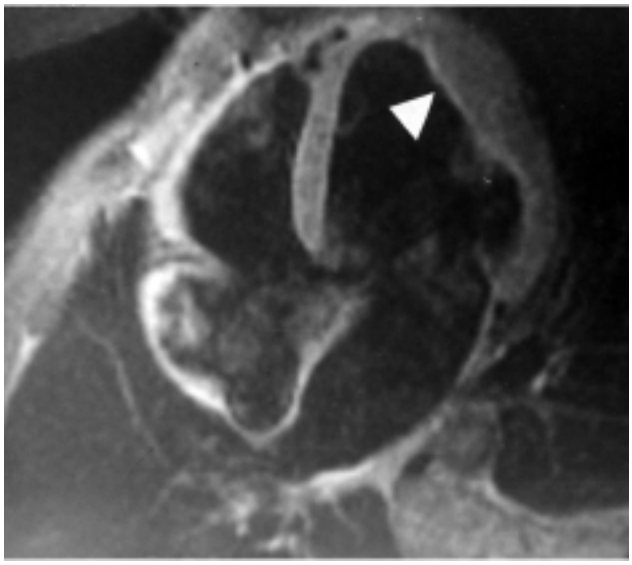

FIG. 2 Magnetic resonance image in the coronal orientation demonstrates a hypertrophic region in the LFW in the left ventricle (arrow), with normal myocardial segment shortening.

A 24-year-old man referred for preoperative cardiac evaluation related no cardiovascular symptoms. Family history included two hypertrophic cardiomyopathy-related sudden deaths at ages 35 and 48 years. Physical examination was normal. The 12-lead electrocardiogram showed T-wave inversion in precordial leads V_4 to V_6. Transthoracic echocardiogram demonstrated hypertrophy simulating a mass virtually confined to the lateral free wall (LFW) in the left ventricle (Fig. 1). No clinical suspicion of neoplasm existed. Magnetic resonance imaging with tagging technique was performed and confirmed a hypertrophic region in the LFW, isointense to adjacent myocardium, and normal myocardial segment shortening (Fig. 2).

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