Maternally Inherited Familial Hypertrophic Cardiomyopathy Manifested by Pregnancy Related Early Progression and Sudden Cardiac Death

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ABSTRACT

Although hypertrophic cardiomyopathy (HCM) may cause heart failure, HCM and dilated cardiomyopathy (DCM) are generally recognized as separate diseases. This report describes two cases of maternally inherited familial HCM, which, after pregnancy, rapidly deteriorated to heart failure and cardiac chamber dilatation, resembling DCM. Some members of this family also suffered sudden cardiac death (SCD). (Korean Circulation J 2004;34(1):112-117)

KEY WORDS: Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Pregnancy; Sudden cardiac death.

Introduction

HCM is a disease characterized by marked left ventricular hypertrophy accompanied by decreased left ventricular systolic dimension and a non-dilated chamber, which are not caused by any other cardiovascular or systemic disease. DCM is a primary myocardial disease that causes slow dilatation of the cardiac chamber and systolic and diastolic heart failure. HCM and DCM are different diseases with different causes. Although, in some cases, HCM may progress to systolic heart failure after a long time, the systolic function is normal or supernormal in most cases of HCM.1-3) Recently, a report suggested that a number of mitochondrial point mutations are associated to familial HCM with systolic heart failure.4-5) However, detailed clinical characteristics and inheritance patterns remain to be clarified. We experienced a maternally inherited familial HCM with rapidly deteriorating systolic function and cardiac chamber dilatation resembling DCM after pregnancy. Some members of this family also expressed sudden cardiac death (SCD).

Case

Case 1

A 26-year-old female was admitted for NYHA class III dyspnea. She had been diagnosed with HCM 8 years before. In 1995, during her first pregnancy, she had experienced shortness of breath, which aggravated after delivery. Electrocardiography showed a right bundle-branch block pattern with left atrial enlargement (Figure 1A). The ejection fraction (EF) was about 55% and the dimensions of septum and free wall were 19.0 mm and 11.5 mm, respectively. Obstructive-type HCM was diagnosed at the time (Figure 2A) (Table 1). Her symptoms ameliorated through medical therapy. In 1996, she delivered her second baby without any heart problems. Echocardiography showed asymmetric septal hypertrophy with an EF of 65%. However, the ratio of septum to posterior wall decreased compared to that of the year before (Table 1). She had her third pregnancy...
against the doctor’s advice in 2001. She began feeling mild dyspnea from the 8th week of pregnancy. It intensified at the 38th week of pregnancy, and she was hospitalized due to NYHA class IV dyspnea, malaise, chilling, and febrile sensation. The echocardiographic findings changed remarkably, showing a dilated left ventricle, thinning septum and free wall (9.9 mm/9.9 mm), and systolic dysfunction (EF 30%), which suggested dilated cardiomyopathy (Figure 2B) (Table 1).

After stabilization, endomyocardial biopsy was performed to differentiate peripartum cardiomyopathy and acute myocarditis. The biopsy showed no prominent myofibrillar disarray, but the markedly increased fibrosis suggested healed inflammation, observed in chronic myocarditis, or dilated cardiomyopathy (Figure 3A, B). The symptoms improved through medical treatment. However, for several years, the patient complained of NYHA class I to II exertional dyspnea, which intensified whenever paroxysmal atrial flutter or fibrillation attacks occurred (Figure 1B).


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<th>Two-dimensional Echocardiogram</th>
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<td>1995–07–08</td>
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VS: ventricular septum, LVWT: left ventricular wall thickness, LVEDD: left ventricular end-systolic dimension, LVESD: left ventricular end-systolic dimension, LA: left atrium, EF: ejection fraction.

Figure 1. Electrocardiography of case 1. A: ECG at the time of the first visit. This ECG shows left axis deviation and right bundle branch block pattern. B: after eight years, the patient suffered from paroxysmal atrial flutter and fibrillation. This ECG shows atrial flutter with variable atrioventricular conduction. ECG: electrocardiogram.

Figure 2. The echocardiography of case 1. Asymmetric septal hypertrophy in 1995 (A) disappeared in 2003 (B). Systolic anterior movement (SAM) of anterior mitral leaflet was not observed.
Post-partum Progression of Familial Hypertrophic Cardiomyopathy

The patient has a special family history of SCD and HCM (Figure 4). Her mother (A) died suddenly one month after delivery of her fifth child at the age of 32, and her cousin (B) also died suddenly after the birth of her first child at the age of 27. Both family members complained of dyspnea at the time of SCD. Her younger sister (Case 2, Figure 4) also had HCM diagnosed by an echocardiogram. However, her HCM changed to systolic heart failure with wall thinning after delivery, and she experienced aborted SCDs twice. Her brother (C) and son (D) have also been diagnosed with HCM through echocardiography (Figure 4).

At the time of this study, the patient was hospitalized due to aggravated heart failure symptoms accompanying atrial flutter (Figure 1B). The patient appeared ill and cyanotic. Although the vital signs were within normal limits, her heart rate was 95 beats per minute. Jugular venous engorgement and hepatomegaly were observed. The auscultation findings identified S3 gallop sounds and basal crackles due to pulmonary congestion.

**Figure 3.** Pathologic findings of case 1 (A and B) and 2 (C and D). The myocardium shows slightly hypertrophied muscle fibers and interstitial fibrosis (A and C, Hematoxylin-Eosin stain ×200). Masson’s trichrome stain reveals marked fibrosis, suggesting healed inflammation (B and D, ×200). However, there is no prominent myofibrillar disarray.

**Figure 4.** Pedigree of two cases. Three out of four female patients passed away due to SCD or experienced aborted SCD after delivery. The remaining patient (case 1) also suffered from atrial arrhythmia. SCD: sudden cardiac death.
Pitting edema was observed at the lower extremities. Electrocardiography showed atrial flutter and complete blockage of the right bundle branch (Figure 1B). Echocardiography showed more thinning of the interventricular septum (7.6 mm) and systolic dysfunction as compared to one year before (Table 1). After changing the dosages of diuretics and angiotensin-converting enzyme inhibitors, the symptoms and signs of heart failure improved markedly. The atrial flutter was converted to the sinus rhythm spontaneously. To evaluate exercise capacity, the predischarge treadmill exercise test was performed. She tolerated the test for more than 6 minutes with modified Bruce protocol despite dyspnea and dizziness.

Case 2

This female patient is a sister of the patient of case 1 and was diagnosed with HCM in a family screening program at the age of 15 (1995). Electrocardiogram showed complete blockage of the right bundle branch at the time (Figure 5A). Echocardiography showed asymmetric septal hypertrophy (septum 19 mm, posterior wall 11 mm) and 65% EF, which were within the echocardiographic criteria of HCM (Figure 6A) (Table 1). However, there was no sign of outflow tract obstruction. She has a peculiar history of HCM, rapidly aggravating heart failure, and aborted SCD as described above. She has felt mild to moderate exertional dyspnea since childhood and experienced a few episodes of syncope after 17. She was admitted to evaluate the syncope when she was 20 years old (2000). Although the programmed electrical stimulation of the ventricle and head up tilting test were carried out, there was no inducible ventricular arrhythmia or neurocardiogenic syncope. She was followed-up with beta-adrenoceptor blockade prescription. She delivered a male baby by

Figure 6. Echocardiographic findings of case 2. A: asymmetric septal hypertrophy is shown. B: left ventricular dilatation and systolic dysfunction are developed after eight years.
cesarean section without any problems (2001). However, occasionally, she experienced exertional shortness of breath after labor from time to time. One year after delivery, she was admitted due to aggravated dyspnea and epigastric pain. Physical examinations showed jugular venous distension and hepatomegaly. The S3 gallop sound and basal crackles were audible. Echocardiography showed severe systolic dysfunction (EF of 20%) and the left ventricular dimensions were dilated (Table 1). Electrocardiography showed frequent atrial premature beats, biatrial enlargement, and complete the right bundle branch block. An endomyocardial biopsy was performed and the pathologic findings were consistent with inflammatory cardiomyopathy (Figure 3C, D). Recently (2003), she experienced syncopal attacks at least three times. The duration of the last episode was a little longer than before, and she experienced transient left-side motor weakness. Brain magnetic resonance image showed small cerebral infarction on the right basal ganglia. Echocardiography showed diminished left ventricular systolic function (EF of 15%) and a thinning interventricular septum (Figure 6B) (Table 1). At least 4 episodes of non-sustained VT with palpitation were documented by telemetry (Figure 5B), and the patient will have a biventricular implantable cardioverter-defibrillator (ICD) implant.

Discussion

In this case report, we suggested a specific type of maternally inherited familial HCM, which rapidly deteriorated to DCM and SCD after pregnancy. HCM is a hereditary disease of autosomal-dominant fashion and is accompanied by diastolic dysfunction. About 10% of HCM patients may develop congestive heart failure over a long period of time, characterized by chamber enlargement similar to DCM. This appears to result, at least in part, from wall thinning and scar formation as a consequence of myocardial ischemia caused by small vessel coronary artery disease and an abnormal coronary vasodilator reserve. However, there was no evidence of ischemic heart disease or concomitant cardiovascular disease or anomaly in our cases. We took notice of the common features of the familial HCM cases: 1) they were maternally inherited, 2) they showed rapidly deteriorating systolic function after pregnancy without evidence of myocardial ischemia, 3) they resulted in sudden death, and 4) they caused inflammation and fibrosis without myofibrillar disarray.

Ten genes associated with HCM have been identified, with 9 of them encoding for cardiac sarcomeric proteins. These are the β-myosin heavy chain (MYH7), the myosin ventricular essential light chain 1 (MYL3), the myosin ventricular regulatory light chain 2 (MYL2), the cardiac α-actin (ACTC), α-tropomyosin (TPM1), the cardiac troponin T (TNNT2) and cardiac troponin I (TNNI3), the cardiac myosin binding protein C (MYBPC3), titin (TTN), and the gamma subunit of protein kinase A (PRKAG2). These genes code for sarcomeric proteins and exhibit the same phenotype, suggesting that HCM is a disease of the sarcomere. Recently a number of mitochondrial DNA point mutations associated with HCM were reported, and some of them had features of maternal inheritance similar to our cases.

Although the hemodynamic change of pregnancy can destabilize the underlying cardiovascular abnormalities, pregnancy does not increase the mortality of underlying HCM, and pregnancy with HCM usually shows good prognosis. Peripartum cardiomyopathy usually develops between the third trimester and 6 months after delivery. Acute myocarditis in the peripartum period is supposed to be the cause of peripartum cardiomyopathy, with evidence of endomyocardial inflammation and fibrosis. In our subjects’ family, only the female patients manifested systolic heart failure after the peripartum period, and the male patients maintained typical HCM with asymmetric septal hypertrophy.

SCD is one symptom of HCM. However, only the female patients with deteriorating systolic function died suddenly. Therefore, we cannot properly conclude
that SCD was due to HCM or heart failure. Other characteristics were complete right bundle-branch block pattern on electrocardiography in both cases and atrial flutter in case 1. Although we are planning to implant an ICD for case 2, a recent study was skeptical of the benefits of ICD on non-ischemic cardiomyopathy compared to amiodarone.25

Limitations

One limitation of this case report was that we did not perform the genetic clarification of this subtype of familial HCM.

Conclusion

We report a specific type of maternally inherited familial HCM, which rapidly deteriorated to DCM and SCD after pregnancy.

Acknowledgments

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REFERENCES

6) Cotran RS, Kumar V, Collins T. Pathologic basis of disease.