☐ Case Report ☐

Progression of Hypertrophic Cardiomyopathy to Dilated Cardiomyopathy
—A Case Reports and Review of the Literatures—

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Left ventricular systolic function in hypertrophic cardiomyopathy (HCMP) does not usually deteriorate even in the end stage of the disease. However, occasionally cases of HCMP progress to a similar form of dilated cardiomyopathy (DCMP) with a decreased systolic function and dilated left ventricle. We report two cases of HCMP which progressed to DCMP during follow-up. Our cases have been documented by serial M-mode echocardiography which shows a prominent decrease in the left ventricular systolic function and a chamber enlargement of the left ventricle. There are various explanations of the pathogenesis of the functional and morphological myocardial deterioration of HCMP progressing to DCMP, and more cases should be studied to determine the pathogenesis and prevention of this end-stage feature of HCMP.

Key Words: Hypertrophic cardiomyopathy, dilated cardiomyopathy, progression

Hypertrophic cardiomyopathy (HCMP) is a disease characterized by marked left ventricular hypertrophy, not due to other cardiovascular or systemic diseases, accompanied by a decreased left ventricular systolic cavity dimension and a nondilated chamber (Goodwin *et al.* 1960; Braunwald *et al.* 1964). The course of HCMP is extremely variable and patients who are asymptomatic initially tend to remain so, while those who are more disabled generally deteriorate or die suddenly. Accordingly, it is very rare that a patient with HCMP dies as a result of congestive heart failure, characterized by cardiac enlargement similar to that of dilated cardiomyopathy (DCMP)(Spirito *et al.* 1987; Hina *et al.*

1993). HCMP and DCMP are presumed to be different disease entities and also have different etiologies. In most patients with HCMP, left ventricular systolic function is normal or supernormal. However, in a few patients, HCMP has been reported to progress to a state that is characterized by systolic dysfunction with left ventricular dilation that resembles DCMP (Fujiwara *et al.* 1984; Horita *et al.* 1990; Miura *et al.* 1992).

Echocardiography has been the mainstay for the diagnosis of HCMP with distinct morphological and functional descriptions. However, HCMP progressing to left ventricular dilatation over a long period of time has not been documented until now by echocardiographic examination. This paper reports on two patients with HCMP who progressed to DCMP-like features diagnosed by M-mode echocardiography findings before and after a follow-up period of more than 15 years.

CASE REPORT

Case 1

The patient was a 17-year-old male when he was

first hospitalized as a result of exertional dyspnea. He received echocardiography examination and cardiac catheterization and was diagnosed concentric nonobstructive hypertrophic cardiomyopathy. The patient was re-hospitalized 16 years later for 2 months as a result of aggravation of dyspnea on exertion. Echocardiographic findings were normal in both parents and three brothers, and none of the family members had hypertension or any other organic heart diseases. The pulse rate was 103/min, respiratory rate was 20/min and blood pressure was 110/70 mmHg. The general appearance was acutely-ill looking and the mental state was alert. The conjunctiva showed no signs of anemia or jaundice and the jugular vein was mildly dilated. Fine crackles were audible in both lower lobes of the lung. The point of maximal intensity of the heart was palpated in the fifth intercostal space of the left mid-clavicular line. At the first admission, a grade III/VI harsh systolic murmur was heard at the lower-left sternal border, but no murmur was heard on the second admission after 16 years when the patient progressed to dilated cardiomyopathy. There were no other abnormal physical findings. Laboratory features were hemoglobin 14.2 gm/dl, hematocrit 42%, and white blood cell count 6,800/mm^3. The urinalysis was normal. The biochemical laboratory

findings were AST 21 IU/L, ALT 33 IU/L, total bilirubin 1.0 mg/dl, alkaline phosphatase 79 IU/L, LDH 120 IU/L, and CK-MB 4 IU/L. At the first admission, chest x-rays revealed left ventricular hypertrophy, but pulmonary vascular markings were normal without pulmonary congestion. After 16 years when the patient progressed to DCMP, CT ratio was inverted compared with the chest PA taken 16 years previously, left ventricular hypertrophy was even more progressed with a round-shaped heart and pulmonary congestion was prominent. At the first admission, the EKG showed a normal sinus rhythm with normal QRS axis and normal p-waves. All leads showed an extremely high QRS voltage ($V_1S+V_5R=236$ mm), but after progressing to DCMP, the QRS axis changed to right superior axis deviation with prominent p-waves and the QRS voltage was decreased compared to the EKG taken 16 years before ($V_1S+V_5R=72$ mm). Non-significant Q waves were newly observed in II, III and aVF. At the first admission, M-mode echocardiogram demonstrated that there was a severe concentric hypertrophy, but systolic anterior motion was not observed. The left ventricular ejection fraction was approximately 70%, and after progressing to DCMP, the ejection fraction decreased to 17% with ventricular wall thinning (Fig. 1). The patient remained clinically unchanged
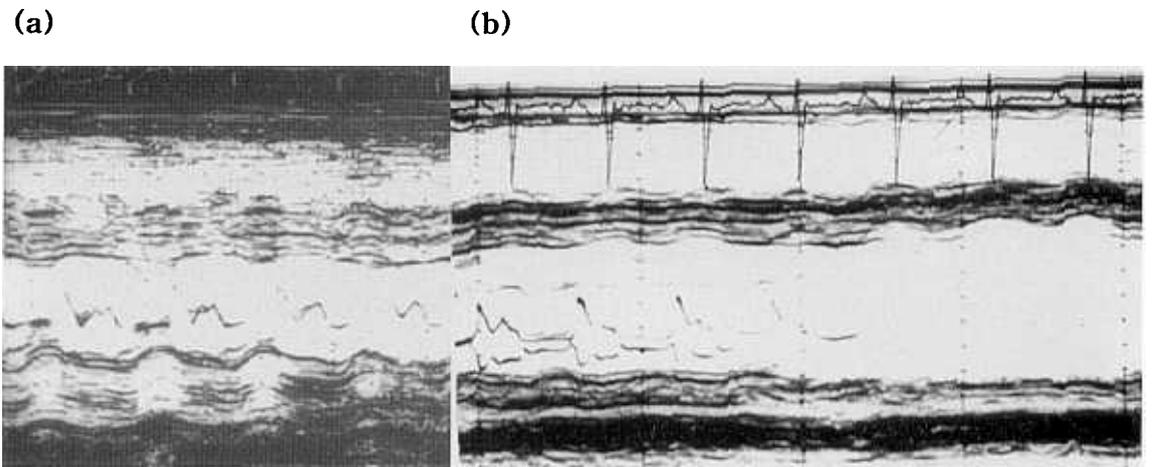
(a)   (b)

Fig. 1. M-mode echocardiography showing transition of hypertrophic cardiomyopathy to end-stage heart failure (case 1). (a) March 1980: Thickness of interventricular septum and posterior wall of left ventricle is 2.0 cm and 3.2 cm respectively. (b) August 1996: Thickness of interventricular septum and posterior wall of left ventricle has decreased to 1.6 cm and 2.0 cm respectively. Ejection fraction decreased from 70% to 17%.

with no specific treatment until the recent aggravation of exertional dyspnea. This symptom was relieved after conservative treatment with intravenous dobutamine infusion, diuretics, and angiotensin-converting-enzyme inhibitors. The patient was discharged uneventfully and is now in follow-up on an outpatient basis.

Case 2

The patient was a 31-year-old male hospitalized at Yonsei University Severance Hospital for exertional dyspnea. He had been diagnosed 15 years before as idiopathic hypertrophic subaortic stenosis (IHSS) by cardiac echocardiography and catheterization, but he was not followed up until exertional dyspnea was recently aggravated. The patient's father died of heart disease and his sister was also diagnosed as HCMP. On physical examination, the pulse rate was 87/min, respiratory rate was 22/min, blood pressure was 110/70 mmHg. The general appearance was chronically-ill looking and the mental state was alert. The conjunctiva was slightly pale and the jugular vein was not distended. Lung sounds were clear and the point of maximal intensity of the heart was palpated in the fourth intercostal space of the left mid-clavicular line. At the first admission,

a grade II/VI ejection systolic murmur was heard at the apex, but no murmur was heard when the patient's left ventricular wall motion progressed to become globally hypokinetic. There were no other abnormal physical findings. Laboratory features were hemoglobin 11.0 gm/dl, hematocrit 34.1%, and white blood cell count 8,090/mm^3. The biochemical laboratory findings were AST 29 IU/L, ALT 14 IU/L, total bilirubin 0.6 mg/dl, alkaline phosphatase 79 IU/L, LDH 67 IU/L, and CK- MB 5 IU/L. At the first admission, chest x-rays revealed left ventricular hypertrophy, but after 15 years when the heart progressed to dilated cardiomyopathy, the heart showed marked cardiomegaly with mild pulmonary congestion. At the first admission, EKG showed left ventricular hypertrophy with strain pattern and typical WPW syndrome. The patient underwent electrophysiological study and later had radiofrequency ablation for atrio-ventricular re-entrant tachycardia. After the radiofrequency ablation when the heart progressed to become hypokinetic, the EKG showed left atrial enlargement and left ventricular hypertrophy with QRS widening and right bundle-branch block. At the first admission, M-mode echocardiography demonstrated marked hypertrophy of the septum and posterior wall, and systolic anterior motion of the anterior mitral leaflet.
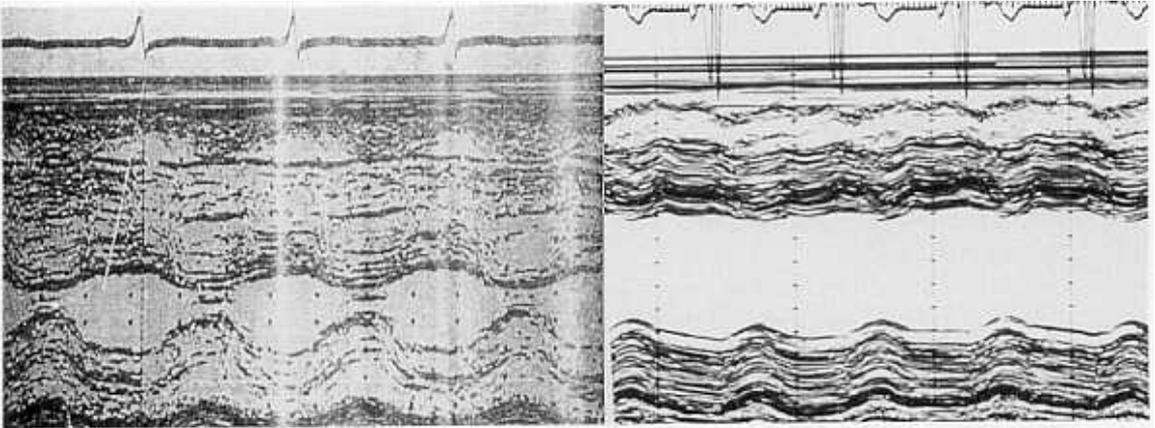
(a) (b)

Fig. 2. M-mode echocardiography showing transition of hypertrophic cardiomyopathy to end-stage heart failure (case 2). (a) April 1981: Marked hypertrophy of inverventricular septum and posterior wall. (b) May 1996: Size of left ventricular cavity has increased and the ejection fraction decreased to 31% with global hypokinesia.

Cardiac catheterization revealed left ventricular ejection fraction of 90% and no systolic left ventricular pressure gradient between aorta and left ventricular cavity. After progressing to DCMP, M-mode echocardiography showed a markedly decreased left ventricular ejection fraction of 31% compared to that of 15 years before. Severe global hypokinesia of the left ventricle was observed and minimal pericardial effusion was also detected (Fig. 2). The symptom of the patient was relieved after conservative treatment with intravenous dobutamine infusion, diuretics and angiotensin-converting enzyme inhibitors. The patient is in follow-up on an outpatient basis with tolerable exertional dyspnea.

DISCUSSION

The first case that we experienced in 1979, diagnosed by echocardiography and cardiac catheterization, had hypertrophied ventricular walls in a concentric feature (Cho et al. 1980). This is known to have an incidence of only 10% (Braunwald, 1989), which is different from the usual asymmetric septal hypertrophy feature. This case did not show systolic anterior motion, left ventricular outflow tract obstruction, or left ventricular pressure gradient. Electrocardiography showed extremely high QRS voltage (S wave in lead V_1 136mm and R wave in V_5 100 mm) in all leads, and giant negative T waves ($8 \sim 12$ mm) in $V_{4 \sim 6}$. This case is very similar to the hypertrophic nonobstructive cardiomyopathy with giant negative T waves, called the "apical hypertrophy", described by Yamaguchi (Yamaguchi et al. 1979), but the voltage of QRS was even higher in this case. Such a specific type of HCMP progressing to DCMP has not been reported in Korea until now, but reports of such cases have recently been increasing worldwide.

The two cases that we have described had both progressed to enlarged left ventricles. The first case also had an enlarged left atrium, while the second case had a normal-sized left atrium. Perhaps it may be more discreet to define this end-stage heart as a "DCMP-like feature" rather than "DCMP".

The pathogenesis of how the left ventricular systolic function deteriorates and the ventricle size enlarges to progress to a DCMP-like feature from HCMP has been explained by many factors, such as the gross and microscopic morphology of the ventricle, the vascular structure and function, and the age at onset of HCMP.

The distribution of left ventricular wall thickness may influence the prognosis of HCMP as to whether it would progress to a dilated hypokinetic ventricle or not. HCMP with hypertrophy in the lower septal wall is named the "malignant type" or "S type" (Ogata et al. 1979) and is an atypical HCMP similar to the apical hypertrophic cardiomyopathy (Maron et al. 1982). This type of HCMP is known to progress to DCMP frequently. Another type of hypertrophy that frequently progresses to DCMP is associated with midventricular obstruction, which is rare. This obstruction to flow during systole might lead to compensatory apical hypertrophy, which by itself could make midventricular obstruction more severe. A stage is reached where the pressure overload in the apical chamber leads to myocardial dysfunction with dilatation of the apical chamber (Fighali et al. 1987). Symmetric- and concentric-type HCMP also have a tendency to frequently progress to DCMP (Yamaguchi et al. 1978) and the first case has a similar morphology with this type of HCMP.

The pathological aspect may be another influence in the progression from HCMP to DCMP. HCMP usually shows fibrosis in only a small area of the left ventricle in autopsy examinations (Anderson et al. 1979; Sutton et al. 1980), but in 3 autopsy cases which progressed to DCMP, diffuse myocardial disarray and fibrosis were observed in the entire left ventricle. The second case had undergone myocardial biopsy and multiple foci of marked replacement fibrosis were found in the right ventricular septum, but the biopsy was not available from the entire ventricle. Eighty-four percent of the myocardial disarray was found adjacent to the area of fibrosis (Yutani et al. 1985). This may be evidence that in HCMP progressing to DCMP, the myocardial disarray may be the cause of fibrosis which eventually dilates the ventricle. Pathological study of more cases may be necessary to reveal the pathogenesis of the functional and morphological change of the myocardium.

The mechanism of extensive fibrosis of the myocardium has been unclear until now, but a few pos-

sible explanations may include the structural or spastic stenosis of the intramural coronary arterioles, the thrombi of extramural coronary arteries, and the relative ischemia of the hypertrophied myocardium (Takuma *et al.* 1987; Yutani *et al.* 1987). Endomyocardial biopsy of the second case showed moderate vascular sclerosis of the intramural coronary arterioles. Myocardial fibrosis may also be related to ischemia by perfusion abnormality detected by the excercise stress thallium 201 myocardial scintigraphic study (O'Gara *et al.* 1987). Our cases had no evidence of myocardial ischemia symptomatically or in the electrocardiogram, but it may be necessary to identify any myocardial perfusion defects, as O'Gara has suggested.

The ages of the patients in our cases were 14 and 17 when the first exertional dyspnea had begun. These cases are compatible with the report that HCMP progresses to DCMP more frequently in patients whose onset of symptom is at a younger age (Toshima and Adachi, 1988).

In cases of HCMP that have progressed to DCMP, 7 out of 10 patients had a chronically increased serum level of LDH1 and CKMB (Nagata *et al.* 1985). This may represent a chronic insult and destruction of the myocardial cells. In our cases, there was no such increase in serum levels of these enzymes.

A study of isoproterenol stress echocardiography in HCMP patients showed that the group with myocardial contraction of 7% or less after isoproterenol infusion seemed to progress more frequently to DCMP than the group with myocardial contraction of more than 7%. This study is still the only way to predict the prognosis of HCMP (Kawano *et al.* 1995). It may be necessary in the future to routinely study patients of HCMP with isoproterenol stress echocardiography to establish a prognostic index of the probability of progression to a hypokinetic ventricle.

In conclusion, we are reporting 2 cases of HCMP progressing to DCMP after a follow-up period of more than 15 years with echocardiographic evidence. These cases are, to our knowledge, the first ones to be reported in Korea.

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