An Autopsy Case of Hypertrophic Cardiomyopathy with Pathological Findings Suggesting Chronic Myocarditis

Hiroaki KAWANO, M.D., Sachio KAWAI, M.D.,
Takashi NISHIJO, M.D.,* Toshikazu SHIRAI, M.D.,**
Yoshiaki INAGAKI, M.D.,***
and Ryoza OKADA, M.D.

SUMMARY

Myocardial fibrosis in patients with hypertrophic cardiomyopathy (HCM) may play an important role in the function and/or dimensions of the left ventricle. We present an autopsied case of HCM followed for 10 years. A 68-year-old woman with HCM underwent trans-aortic myectomy of the interventricular septum in 1979. A significant amount of round cell infiltration, myocardial fibrosis and disarray were observed in the resected specimen. She experienced repeated admissions due to diabetes mellitus and congestive heart failure, and died of renal failure in 1989. An autopsy revealed extensive myocardial fibrosis and significant cell infiltration in the ventricular myocardium. The infiltrating cells were almost all lymphocytes, and the ratio of CD4 to CD8 was 3.8. This ratio was different from that of typical viral myocarditis. This case suggests that there may be an undefined inflammatory process causing fibrosis in HCM, in addition to the ischemia due to intramural small coronary artery stenosis. (*Jpn Heart J* 35: 95–105, 1994)

Key words: Hypertrophic cardiomyopathy Myocarditis Lymphocyte subsets

ALTHOUGH lymphocytic infiltration and inflammation are considered to be among the potential causative factors for dilated cardiomyopathy, focal collection of mononuclear cells in the myocardium of patients with hypertrophic cardiomyopathy (HCM) is recognized as a non-pathognomonic and incidental finding.¹⁾

Myocardial fibrosis in HCM^{2,3)} could play an important role in the development of dilatation of the ventricle.⁴⁻¹¹⁾ Among several hypotheses⁴⁻¹³⁾ concerning

From Research Laboratory for Cardiovascular Pathology, *Division of Cardiology, Department of Internal Medicine, **Department of Pathology, Juntendo University School of Medicine, Tokyo, and ***Third Department of Internal Medicine, University of Chiba, Chiba, Japan

Address for correspondence: Hiroaki Kawano, M.D., Research Laboratory for Cardiovascular Pathology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113, Japan.

Received for publication October 8, 1993.

Accepted December 2, 1993.

the etiology of myocardial fibrosis in HCM, intramural coronary artery sclerosis has become widely accepted.^{12,13)} However, other possible factors causing fibrosis were not extensively studied.

We treated a case of HCM which showed cell infiltration in a surgical biopsy specimen 10 years earlier, and broad myocardial fibrosis and cell infiltration at autopsy.

CASE REPORT

A 68-year-old Japanese female without personal or family history of any cardiac disease began to notice dyspnea and pretibial edema at the age of 39 years (1961). She experienced dyspnea on exertion, and consulted a family doctor in 1970. Subsequently, cardiomegaly and diabetes mellitus were diagnosed. She underwent medication and her condition ameliorated. Symptoms of congestive heart failure recurred, but she stopped taking medication. In 1976, she experienced severe orthopnea and was admitted to Chiba University Hospital. Chest X-ray showed marked cardiomegaly (Figure 1A). Echocardiogram demonstrated asymmetrical septal hypertrophy and systolic anterior movement of the anterior leaflet of the mitral valve (Figure 2). She was diagnosed as having HCM with obstruction, and was treated with spironolactone and furosemide. She felt faintness in spite of medication, and was transferred to our hospital for surgery.

On admission her body temperature was 35.6°C and pulse rate was 75/min. Blood pressure was 122/68 mmHg. On physiological examination, her height was 147.2 cm and her weight was 72.5 kg. Heart sounds were regular; a Grade 4 systolic murmur was maximal at the left upper sternal border; an S₄ was present. Inspiratory crackles were heard at both lung bases. The liver was felt 2 cm in width. There was pretibial edema.

The hematocrit was 11.1% and the white-cell count was 6800/mm³. The erythrocyte sedimentation rate was 14 mm per hour. The blood urea nitrogen was 20 mg/dl, creatinine 1.5 mg/dl, creatine phosphokinase 53 IU, glutamate oxaloacetate aminotransferase 28 IU/l, glutamate pyruvate aminotransferase 8 IU/l, lactate dehydrogenase 480 IU/l, glucose 99 mg/dl, total cholesterol 227 mg/dl, and triglycerides 109 mg/dl. The sodium was 149 mEq/l, potassium 3.6 mEq/l, and chloride 108 mEq/l.

Electrocardiogram (ECG) showed left ventricular hypertrophy. Right-sided and left-sided cardiac catheterization revealed a right atrial mean pressure of 12 mmHg, and a right ventricular pressure of 70/10 mmHg; the pulmonary arterial pressure was 50/34 mmHg, with a mean pressure of 44 mmHg; the pulmonary-capillary wedge pressure was 24 mmHg; the left ventricular pressure was 232/20 at the apex and 135/20 mmHg at the outflow, and the aortic pressure was 130/

Figure 1. Chest X-ray film (A) and left ventriculogram (B) in 1976. A: Chest X-ray film showed marked cardiomegaly. B: Left ventriculogram showed cavity obstruction at the end-systolic phase.

Figure 2. Echocardiogram (parasternal long axis view; M-mode and B-mode). Systolic anterior movement of the anterior mitral leaflet and asymmetrical septal hypertrophy were demonstrated.

90 mmHg, with a mean pressure of 105 mmHg. The cardiac index was 2.3 l/min/m². Coronary angiogram revealed no obstructive lesions. Left ventriculogram showed obliteration of the left ventricular cavity in the end-systolic phase (Figure 1B).

On April 16, 1979, trans-aortic myectomy of the interventricular septum

Figure 3. Electrocardiogram before operation (left) and after operation (right). Left electrocardiogram showed left ventricular hypertrophy, left atrial overload, and ST segment depression in I, aVL, V₃, and V₆ leads. Right electrocardiogram demonstrated left atrial overload and ST segment depression in I, aVL, V₃ and V₆ leads.

was performed. In a postoperative ECG, left axis deviation was present and voltages in V₅ and V₆ were decreased compared to the pre-operative ECG (Figure 3). The left ventriculogram demonstrated a slight decrease in the left ventricular cavity (Figure 4A and 4B).

Postoperative catheterization revealed reduction of the interventricular pressure gradient from 98 mmHg to 50 mmHg. A coronary angiographic examination two years after surgery showed normal coronary arteries (Figure 4C and 4D).

After more than ten admissions because of congestive heart failure and

Figure 4. Left ventriculogram [A; end-diastolic phase, B; end-systolic phase and coronary angiogram (C and D)] 2 years after operation. A, B: Left ventricular function slightly improved. C: Left coronary artery was normal. D: Right coronary artery was normal.

Figure 5. Pathological findings of the resected myocardium. A: Intramural small coronary arteries showed only mild medial thickening (Pentachrome $\times 100$). B: Moderate myocardial disarray and interstitial cell infiltration were seen (H-E $\times 200$). C: Interstitial fibrosis and cell infiltration were seen (H-E $\times 400$).

Figure 6. Gross findings of heart (A: anterior view, B: mitral valve, C: left ventricular inflow, D: left ventricular outflow, E: transverse section of ventricle at the middle portion). A: Epicardium was adherent to the heart due to operation. B: Commissure site (...) of posterior mitral leaflet (post) bulged toward the left atrium and anterior mitral leaflet (ant) did not. C: Left mitral leaflet thickened at coaptation. A small mural thrombus was seen near the left appendage (lt app). D: Fibrous thickening was seen at the surgical site in the base of the left ventricular outflow. E: Left ventricle showed marked hypertrophy.

diabetes mellitus the patient died of renal failure in October, 1989.

Pathological findings of the myocardium resected in 1979: Myocardial histology revealed marked endocardial fibroelastic thickening and slight fibrosis in the subendocardial layer. Intramural small coronary arteries did not show sclerotic changes except for mild medial thickening (Figure 5A). Myocardial disarray and a mild amount of cell infiltrations were recognized (Figure 5B and C).

Gross findings of the heart autopsied in 1989: The heart was enlarged and weighed 660 g. Focal fibrosis of the pericardium due to cardiac surgery was seen on the epicardial adiposis (Figure 6A). The posterior mitral leaflet, near the posterior commissure site, bulged toward the left atrium (Figure 6B). The anterior mitral leaflet was thickened at the coaptation site of the valve (Figure 6C). Focal endocardial fibrous thickening was seen at the operated site of the septum in the base of the left ventricular outflow tract (Figure 6D). In the ventricular transverse section, the left ventricle showed concentric hypertrophy (Figure 6E). The thickness of the interventricular septum was 20–24 mm, and that of the left ventricular

Figure 7. Microscopic findings of heart (A, B and C: lateral wall, D: myectomy site). A: Disarray and fibrosis at the subepicardial site were seen (Azan $\times 4$). B: Fibrosis and slight cell infiltration were seen at the subepicardial site (Epi) (H-E $\times 100$). C: Disarray and mild cell infiltration were seen (H-E $\times 125$). D: Fibrosis and mild intramural coronary artery stenosis were seen at the left ventricular septum (LV sept) (H-E $\times 2$).

Figure 8. Pathologic finding of transverse section of left ventricle (Azan). Fibrosis was seen mainly in the lateral and posterior wall.

Figure 9. Lymphocyte subsets (A: hematoxylin, B: CD3 and CD5b, C: CD4, D: CD8). A: Cell infiltration was seen ($\times 200$). B: CD3 positive and CD5b positive cells were seen in the interstitium ($\times 200$). C: Many CD4 positive cells were seen ($\times 400$). D: Fewer CD8 positive cells were seen than CD4 positive cells ($\times 200$).

posterior wall was 18 mm. Fibrosis was seen mostly in the internal layer of the left ventricle, but patchy irregular fibrosis was seen in the middle and outer layers of the posterolateral wall.

There was subtotal stenosis of the left anterior descending branch of the left coronary artery, and 50–75% stenosis in the left circumflex branch of the left coronary artery and the right coronary artery, respectively. Fibrosis was more severe in the lateral and posterior wall than in the anterior wall (Figure 7).

Microscopic findings of the heart: In the outer and middle layers of the lateral wall of the left ventricle, a moderate degree of myocyte disarray was recognized. The outer layer of the ventricular wall showed interstitial fibrosis and partial depletion of myocytes (Figure 8A and 8B). Diffuse small round cell infiltrations were also observed in the myocardium of the left ventricle (Figure 8C). The intramural small arteries ending in the myocardial fibrosis showed medial thickening, but the lumens were patent (Figure 8D).

Lymphocyte subsets (Figure 9): The lymphocyte subsets of the infiltrating cells of the frozen section of the right ventricle were investigated by the ABC (avidin biotin complex) method. Lymphocytes were stained as follows; Leu-4+Leu-5b (CD2+CD5) for pan T cells, Leu-16 (CD20) for B cells, Leu-3a (CD4) for helper/

inducer T cells, and Leu-2a (CD8) for suppressor/cytotoxic T cells. The positive cells for every stain were counted in 20 field areas microscopically (magnification, $\times 200$) and their means were calculated. Mean numbers of these positive lymphocytes per field were 16.3 for pan T cells, 2.4 for B cells, 9.2 for helper/inducer T cells, and 2.4 for suppressor/inducer T cells, respectively. CD4-positive lymphocytes were greater in number than the CD8-positive lymphocytes, and the ratio of CD4 to CD8 was 3.8. Fifty-six percent of the T cells were CD4-positive.

DISCUSSION

This case had shown interstitial cell infiltration in a biopsy specimen 10 years before death. However, myocardial histology revealed slight fibrosis in the subendocardial layer and the intramural small coronary arteries did not show sclerotic changes except for mild medial thickening. At autopsy, cell infiltration remained and fibrosis was seen in the middle and outer layers of the posterolateral wall. Myocardial fibrosis was seen not only in the subendocardium, but also in the subepicardium. The fibrosis was not consistent with coronary stenosis, since the anterior interventricular coronary artery had subtotal stenosis, but fibrosis was seen in the posterolateral wall, which was supplied by the right coronary artery and left circumflex artery. Although a part of the fibrosis was caused by coronary artery stenosis, it could not be explained merely by ischemia, because fibrosis was seen not only in the subendocardium, but also in the subepicardium.

The causes of myocardial fibrosis in HCM, and the transformation of HCM to DCM have been reported as follows: organic stenosis or functional spasm of the intramural small vessels,¹⁴⁾ the obstruction of main coronary arteries due to thrombus or spasm,¹⁴⁾ relative shortness of coronary flow associated with myocardial hypertrophy,¹⁴⁾ decreased vasodilator reserve,¹⁵⁾ myocarditis,⁸⁾ surgery,¹⁶⁾ and long-term administration of beta-blocker.¹⁷⁾

Cell infiltration in HCM was demonstrated to be for the purpose of phagocytosis of degenerating cardiac myocytes.¹⁾ Yutani et al suggested that cell infiltration may be related to fibrosis in HCM.¹⁸⁾ Moreover, it was reported that the heart of a patient with myocarditis in childhood showed gradually increasing left ventricular hypertrophy that was confused with HCM.¹⁹⁾ However, a precise study of infiltrated cells in HCM has not been reported.

Several investigations of cell infiltration and lymphocyte subsets in myocarditis and dilated cardiomyopathy from endomyocardial biopsy specimens have been reported.²⁰⁻²⁶⁾ These authors reported that CD8-positive T lymphocytes increased. The CD4/CD8 ratio was 0.3–0.6 and changed during the healing process in acute myocarditis. In dilated cardiomyopathy, 50% of infiltrating

cells consisted of macrophages, 30% were T lymphocytes, and about half of the T lymphocytes were CD8 positive. In this case, CD4/CD8 was 3.8 and 56% of the T cells were CD4-positive cells. These values were different from those seen in myocarditis and dilated cardiomyopathy. It was not clear whether or not this result was specific for infiltrating cells in HCM.

Considering that the main infiltrating T cells in the skin lesions of Kawasaki's disease are CD4, and those in the skin lesions of measles are CD8,²⁷⁾ the ratio of CD4/CD8 in this case does not imply viral infection. However, cell infiltration in HCM should be studied further.

REFERENCES

1. Silver MD: Cardiovascular Pathology. 2nd ed, Churchill Livingston, New York, p743, 1991
2. St John Sutton MG, Lie JT, Anderson KR, Frye RL: Histopathological specificity of hypertrophic obstructive cardiomyopathy; myocardial fibre disarray and myocardial fibrosis. *Br Heart J* **44**: 433, 1980
3. Tanaka M, Fujiwara H, Onodera T, Wu D-J, Hamashima Y, Kawai C: Quantitative analysis of myocardial fibrosis in normal, hypertensive hearts, and hypertrophic cardiomyopathy. *Br Heart J* **55**: 575, 1986
4. Waller BF, Maron BJ, Epstein SE, Roberts WC: Transmural myocardial infarction in hypertrophic cardiomyopathy; a case of conversion from left ventricular asymmetry to symmetry and from normal-sized to dilated left ventricular cavity. *Chest* **79**: 461, 1981
5. ten-Cate FJ, Roelandt J: Progression to left ventricular dilatation in patients with hypertrophic obstructive cardiomyopathy. *Am Heart J* **97**: 762, 1979
6. Beder SD, Gutgesell HP, Mullins CE, McNamara DC: Progression from hypertrophic obstructive cardiomyopathy to congestive cardiomyopathy in a child. *Am Heart J* **104**: 155, 1982
7. Fujiwara H, Onodera T, Tanaka M, Shirane H, Kato H, Yoshikawa J, Osakada G, Sasayama S, Kawai C: Progression from hypertrophic obstructive cardiomyopathy to typical dilated cardiomyopathy-like features in the end stage. *Jpn Circ J* **48**: 1210, 1984
8. Yutani C, Imakita M, Ishibashi-Ueda H, Hatanaka K, Nagata S, Sakakibara H, Nimura Y: Three autopsy cases of progression to left ventricular dilatation in patients with hypertrophic cardiomyopathy. *Am Heart J* **109**: 545, 1985
9. Funakoshi M, Imamura M, Sasaki J, Fujino M, Kawano T, Sasaki Y, Nakashima Y, Motooka T, Keisuke F, Imagawa M, Hiroki T, Arakawa K: Seven year follow-up of a patient with hypertrophic cardiomyopathy which progressed to dilated cardiomyopathy. *Jpn Heart J* **25**: 805, 1984
10. Onodera T, Fujiwara H, Tanaka M, Wu DJ, Hamashima Y, Kawai C: Familial hypertrophic cardiomyopathy mimicing typical dilated cardiomyopathy. *Jpn Circ J* **50**: 614, 1986
11. Hirota Y, Shimizu M, Sugihara N, Suematsu T, Shibayama S, Itoh H, Takeda R, Terada T: An autopsy case of hypertrophic cardiomyopathy showing dilated cardiomyopathy-like features by serial ventriculography. *Jpn J Med* **29**: 448, 1990
12. Becker AE, Anderson RH: Cardiac Pathology. Gower Medical Publishing, London, p3, 1982
13. Fujiwara H, Kawai C: Intramural coronary artery disease in hypertrophic cardiomyopathy. *in* Cardiomyopathy Update 2. Hypertrophic Cardiomyopathy. ed by Toshima H, Maron BJ, University of Tokyo Press, Tokyo, p 47, 1988
14. Maron BJ, Epstein SE, Roberts WC: Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. *Am J Cardiol* **43**: 1086, 1979
15. Cannon RO, Rosing DR, Maron BJ, Leon MB, Bonow RO, Watson RM, Epstein SE: Myocardial ischemia in patients with hypertrophic cardiomyopathy; contribution of inadequate vasodilator reserve and elevated left ventricular filling pressure. *Circulation* **71**: 234, 1985

16. Turina J, Jenni R, Kraysenbuehl HP, Turina M, Rothlin M: Echocardiographic findings late after myectomy in hypertrophic obstructive cardiomyopathy. *Eur Heart J* **7**: 685, 1986
17. McKenna WJ, Borggrefe M, England D, Deanfield J, Oakley CM, Goodwin JF: The natural history of left ventricular hypertrophy in hypertrophic cardiomyopathy; an electrocardiographic study. *Circulation* **66**: 1233, 1982
18. Yutani C, Imakita M, Ishibashi-Ueda H, Nagata S, Sakakibara H, Nimura Y: Histopathological study of hypertrophic cardiomyopathy with progression to left ventricular dilatation. *Acta Pathol Jpn* **37**: 1041, 1987
19. Okuni M, Yamada T, Mochizuki S, Sakurai I: Studies on myocarditis in childhood, with special reference to the possible role of immunological process and thymus in the chronicity of the disease. *Jpn Circ J* **39**: 463, 1974
20. Kishimoto C, Tomioka N, Tamaki S, and Kawai C: A case of myocarditis with immunological identification of myocardial and peripheral lymphocyte subsets. *Jpn Circ J* **52**: 94, 1988
21. Cassling RS, Linder J, Sears TD, Waller BF, Rogler WC, Wilson JE, Kugler JD, Kay DH, Dillon JC, Slack JD, and McManus BM: Quantitative evaluation of inflammation in biopsy specimens from idiopathically failing or irritable hearts; experience in 80 pediatric and adult patients. *Am Heart J* **110**: 713, 1985
22. Zee-Chung CS, Tsai CC: High incidence of myocarditis by endomyocardial biopsy in patients with idiopathic congestive cardiomegaly. *J Am Coll Cardiol* **3**: 63, 1984
23. Marboe CC, Knowles DM: Characterization of the inflammatory infiltrate in human myocarditis: An endomyocardial biopsy study. *in* *Viral Heart Disease*, ed by Bolte HD, Springer, New York, p64, 1984
24. Kueul U, Toussaint M, Ulrich G, Wagner D, Wolff P, Schultheiss HP: Evaluation of immunohistological data for the diagnosis of myocarditis. *in* *New Concepts in Viral Heart Disease*, ed by Schultheiss HP, Springer, New York, p 325, 1988
25. Saito T, Shiokawa A, Inoue S: Lymphocytic subpopulations and their transition in myocardial tissue and peripheral blood of patients with biopsy proven myocarditis. *Jpn Circ J* **53**: 1, 1989
26. Hammond EH, Anderson JL: Cardiac immune complex and mononuclear cell subsets in myocarditis; an endomyocardial biopsy study. *Circulation* **68** (Suppl III): 27, 1983
27. Sugawara T, Hattori S, Hirose S, Furukawa S, Yabuta K, Shirai T: Immunopathology of the skin lesion of Kawasaki disease. *in* *Kawasaki Disease*, ed by Shulman ST, Alan R. Liss, Inc., New York, p 185, 1987