Cardiac Sarcoidosis with Twelve-year Survival

Tadashi KOIDE, M.D., Shinji ITOYAMA, M.D.,
Kazuaki KATO, M.D., Akihito KATO, M.D.,
and Satoru MURAO, M.D.

SUMMARY

A case of cardiac sarcoidosis survived 12 years after development of overt heart failure, which was the longest record hitherto reported. The survival after major cardiac involvement was probably much longer, since he had an attack of syncope 7 years before heart failure. He died of ventricular fibrillation at age 59. Progression of myocardial sarcoid involvement may be slower in some patients than has previously been believed.

Additional Indexing Words:

Angina pectoris Coronary artery disease Aortic regurgitation

CARDIAC sarcoidosis is known with its grave prognosis. Most of the patients die within a few years after development of major cardiac symptoms^{1),2)} and the longest record of survival hitherto reported is 9 years.³⁾ Clinical manifestation of cardiac sarcoidosis is variable, but heart failure, ventricular arrhythmia and heart block are common. Chest pain or ECG changes simulating myocardial infarction have also been reported on several occasions.^{2),4)} However, angina pectoris has not been considered as a manifestation of sarcoidosis. Direct involvement of cardiac valves is also rare.^{3),4)}

The case presented in this article was unique in his long survival and in his having chest pain simulating angina, diffuse coronary artery disease, and aortic valve disease, as well as common manifestations of cardiac sarcoidosis. Clinical and autopsy findings were described below.

CASE RECORDS

A 47-year-old city clerk was admitted to our hospital because of dyspnea and recurrent retrosternal tightness on effort on June 3, 1964. The history

From the Second Department of Internal Medicine and the Department of Pathology, Faculty of Medicine, University of Tokyo, Tokyo.

Address for reprint: Tadashi Koide, M.D., Second Department of Internal Medicine, University of Tokyo Hospital, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan.

Received for publication April 22, 1981.

of his heart disease could be traced back to 1957, when he had an attack of syncope lasting longer than several minutes. He recovered from the attack spontaneously without neurological sequelae. In the following year, he recognized palpitation with irregular arterial pulse on several occasions. On March 1964, retrosternal tightness developed while walking in an early morning. Similar attacks recurred every morning thereafter, constantly after walking about 10 min, and subsided with several minutes of rest. On May 17, he had rhinorrhea and productive cough, which heralded paroxysmal nocturnal dyspnea on the next day. Examination by a physician revealed evidences of cardiomegaly and heart failure. Cardiothoracic ratio was 60% and pulmonary veins were engorged on a chest X-ray. On ECG, frequent ventricular premature beats, complete right bundle branch block, left axis deviation of -60 degree and evidences of left ventricular hypertrophy were seen. Although dyspnea was alleviated with digitalis and diuretics, he was referred to us for further examination.

In his previous history, he had acute renal disease at age 6 and malaria at age 22. Tuberculin skin reaction was found to be positive at 22 years of age. He had been a heavy drinker consuming 900 ml of Japanese sake (about 125 ml of alcohol) and a smoker of 10–15 cigarettes daily, but abstained from alcohol following the development of heart failure and thereafter until death. Family history was non-contributory and without cardiac death.

On admission, he was already free from dyspnea. He was 157 cm tall and body weight was 47 Kg. He was afebrile, heart rate was 70 beats/min and blood pressure was 132/60 mmHg. There was no evidence of cardiomegaly on physical examination. On auscultation, S_2 was split, and there was a grade II/VI apical systolic murmur, which became pansystolic on methoxamine infusion. Liver, spleen and lymphnode were not palpable and ocular fundi were normal.

On hematology, eosinophilia (1,040/cmm) was seen repeatedly, while total white cell count was normal. Parasite ova were negative. Erythrocyte sedimentation rate was accelerated to 30 mm/h and both the latex fixation and bentonite tests were 1+ positive. STS and tests for ASO, C-reactive protein, LE factor and cold hemagglutinin were negative or normal. Tuberculin skin tests, done twice, were borderline positive. Urinalysis and serum chemistry were normal, including serum cholesterol level of 206 mg/100 ml. Chest X-ray revealed slight cardiomegaly with a cardiothoracic ratio of 51%, without pulmonary congestion or hilar lymphnode swelling. ECG findings were essentially similar to those on May 19, but subsequent follow-up records revealed junctional and multifocal ventricular premature beats and PQ prolongation occasionally. Exercise stress testing was negative in ischemic change

and in induction of arrhythmia. Slight elevation of left ventricular end-diastolic pressure (15 mmHg) was the sole hemodynamic abnormality on cardiac catheterization. Angiocardiography was not the routine at that time. The patient was diagnosed as having cardiomyopathy of obscure origin. The positive serological reactions turned to negative following the use of aspirin, 4.8 Gm/day at maximum. He was discharged on July 3 without cardiac medication.

When he returned to his job, chest tightness on effort recurred, progressed gradually into attacks of flank pain, and continued to occur thereafter until shortly before death. Propranolol (30–120 mg/day) and sublingual nitroglycerin were given, and remained to be effective throughout the course. From the end of 1973 on, sinus bradycardia, second degree atrioventricular block of both Wenckebach type and Mobitz type II, left anterior hemiblock and left posterior hemiblock appeared and disappeared frequently, and complete heart block was seen occasionally. On June 26, 1975, he was admitted again for electrophysiological study, which revealed a prolonged H-V conduction time of 80 msec. Pacemaker implantation was recommended, but was refused by the patient. Eosinophilic leukocyte was increased occasionally (210–610/cmm), but all the other laboratory tests were normal. Treadmill exercise testing was again negative in ischemic change, and was limited by dyspnea.

After discharge, frequency of chest pain decreased gradually, but exertional dyspnea became prominent. The final admission on January 20, 1976, was because of severe dyspnea and pretibial edema. He was treated with furosemide, to which the heart failure responded promptly. However, ventricular premature beats increased in frequency, and he died of ventricular fibrillation on February 11. During the admission, slight eosinophilia (460/cmm) and I+C-reactive protein were seen again. Another notable finding was the development of grade I/VI short diastolic murmur following the aortic component of S₂ at the left sternal border, which had not been recorded on the previous phonocardiograms.

On autopsy, heart weight was 540 Gm. All the cardiac chambers, especially the left ventricle, were dilated. A region of 1 cm in diameter was yellowish on the epicardial surface of the anterobasal left ventricular wall, where the wall was thin and the outer half was replaced with fat. The pericardium was normal. All the aortic valve cusps were thick and there was a slight fibrous adhesion between the left coronary and the non-coronary cusps. Other valves were normal. The lumen of all the epicardial coronary arteries was relatively narrow diffusely, but no localized stenosis was seen, when sectioned at 3–5 mm intervals extensively. The aorta and its major branches

(a)

(b)

(c)

(d)

Fig. 1. Giant cell granuloma. (a) Numerous multinucleated giant cells were seen in non-caseating epithelioid cell granuloma in the hilar lymphnodes (hematoxyline-eosin). (b) A few giant cells in the lymphnodes had asteroid body (hematoxyline-eosin). Similar giant cells were seen also in the left ventricular myocardium (c, hematoxyline-eosin) and in the ileopsoas muscle (d, hematoxyline-eosin) in foci of small round cell infiltration. Muscle cells were degenerated in these areas. The bar in each panel shows 100 μ .

were otherwise normal. Hilar and other lymphnodes were apparently normal. There was slight congestion in the abdominal organs.

On histological examinations, non-caseating granulomatous inflammation with multinucleated giant cells was seen in the bilateral hilar lymphnodes, left ventricular myocardium, and ileopsoas muscle (Fig. 1). In the left ventricle, the area with giant cells was limited to the posterobasal wall, but foci of small round cell infiltration and perivascular fibrosis were seen diffusely. Myocardial fibrosis was especially marked around the fatty infiltration in the anterobasal left ventricular wall and in the upper interventricular septum. In the latter, distal part of the His bundle was interrupted on examination with serial section. The atrioventricular node was preserved, although there was slight round cell infiltration. The atria and the sinus node were normal. In the epicardial coronary arteries, intimal hyperplasia was seen diffusely (Fig. 2). The degree of stenosis was less than 70% in luminal area. Many intramyocardial coronary arteries were also stenotic with intimal hyperplasia and medial hypertrophy. The change in small coronary artery tended to be prominent in the vicinity of myocardial fibrosis, but was seen also in areas of apparently normal myocardium. The arterial wall was degenerated and infiltrated with round cell occasionally in areas with active myocarditis (Fig. 2).

(a)

(b)

(c)

(d)

Fig. 2. Coronary artery changes. Areas with intimal hyperplasia were seen in all the coronary artery trunks, either in the proximal or in the distal region. In the figure, the left anterior descending artery at 1 cm from the origin (a, hematoxyline-eosin), left circumflex artery at 0.8 cm from the origin (b, Weigert-van Gieson), and right coronary artery at 1 cm from its ostium (c, Weigert-van Gieson) were shown. Many intramyocardial small coronary arteries were also stenotic, especially in the vicinity of myocardial scar or fatty infiltration. The wall of the artery shown in (d) was infiltrated with small number of round cells and degenerated (hematoxyline-eosin). The bar in each panel shows either 1 mm (a, b, c) or 100 μ (d).

DISCUSSION

The case presented in this article had multi-organ involvement with noncaseating epithelioid cell granuloma, which was compatible with the diagnosis of sarcoidosis.^{2),5)} The locus of the major involvement was the heart. Most of his presenting symptoms and signs including heart failure, tachyarrhythmia and conduction disturbances were common in cardiac sarcoidosis.^{2),4),5)} Eosinophilia and positive inflammatory reactions were also not rare in sarcoidosis.⁶⁾

The association of diffuse coronary artery disease and anginal chest pain with cardiac sarcoidosis in the present case may be incidental. In the literature, only 1 case report described sarcoid granuloma in an epicardial coronary artery causing luminal obstruction and myocardial infarction.⁷⁾ Although coronary arteritis has been advocated as a background of local spasm and angina,⁸⁾ inflammatory changes were limited to a few small intramyocardial arteries in our patient, and the change in the large coronary arteries was indistinguishable from ordinary atherosclerosis.

Aortic valve disease is a rare complication of sarcoidosis, and only 4 cases have been reported in the literatures.^{3),4),9),10)} In our patient, however, there

was no evidence of active inflammation in the aortic valve, and a possibility of incidental association of senile degenerative change could not be ruled out.

The long survival of 12 years after heart failure, or probably 19 years after syncope, is exceptional as cardiac sarcoidosis. The longest record of survival in the literature has been 9 years after development of syncope,³⁾ and average survival was 27 months in another report.¹⁾ Long-lasting remission of active sarcoid inflammation was likely to be the reason for long survival in the present case, since development of heart failure was always associated with positive inflammatory reactions. Initial use of aspirin might have had a beneficial effect in this concern. Possible association of alcoholic cardiomyopathy, which was known with marked reversibility of heart failure,¹¹⁾⁻¹³⁾ might be another reason.

REFERENCES

1. Iwai K, Tachibana T, Matsui Y, Shigematsu N, Izumi T: Statistical and pathological observations on the autopsied cases of sarcoidosis. *Jap J Thoracic Dis* **11**: 749, 1973 (in Japanese)
2. Roberts WC, McAllister HA, Ferrans VJ: Sarcoidosis of the heart. *Am J Med* **63**: 86, 1977
3. Simpkins S: Sarcoid with complete heart block. *JAMA* **146**: 794, 1951
4. Fleming HA: Sarcoid heart disease. *Brit Heart J* **36**: 54, 1974
5. Silverman KJ, Hutchins GM, Bulkley BH: Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* **58**: 1204, 1978
6. Mayock RL, Bertrand P, Morrison CE, Scott JH: Manifestations of sarcoidosis: analysis of 145 patients with a review of nine series selected from the literature. *Am J Med* **35**: 67, 1963
7. Tanaka R, Tanaka T, Ichinose S, Takagi M: A case of cardiac sarcoidosis with complex arrhythmias. *Shinzo* **6**: 223, 1974 (in Japanese)
8. Guermonprez JL, Guret P, Camilleri JP, Gurinon J, Deloche A, Maurice P: Angor de Prinzmetal. Etude histologique coronaire de prlvements per-opratoires: a propos de deux cas. *Arch Mal Coeur* **70**: 301, 1977
9. Laroche C, de Gennes JL, Hazard J, Samarzq P: Maladie de Besnier-Boeck-Schaumann avec manifestation polyarticulaires et localisations endomyo-pericardique mortelles. *Bull Mem Soc Hop Paris* **71**: 908, 1955 (Cited from Porter GH: Sarcoid heart disease. *New Engl J Med* **263**: 1350, 1960)
10. Ghosh P, Fleming HA, Gresham GA, Stovin PGI: Myocardial sarcoidosis. *Brit Heart J* **34**: 769, 1972
11. Demakis JG, Proskey A, Rahimtoola SH, Jamil M, Sutton GC, Rosen KM, Gunnar RM, Tobin JR: The natural course of alcoholic cardiomyopathy. *Ann Intern Med* **80**: 293, 1974
12. Koide T, Hayashi T, Ozeki K, Kono H: Hypertrophic cardiomyopathy in chronic alcoholism. *Proceedings of the International Medical Symposium on Alcohol and Drug Dependence*, p136, 1977
13. Koide T, Kato A, Takabatake Y, Iizuka M, Uchida Y, Ozeki K, Morooka S, Kakahana M, Serizawa T, Tanaka S, Ohya T, Momomura S, Murao S: Variable prognosis in congestive cardiomyopathy. *Jpn Heart J* **21**: 451, 1980