AN EXTENSIVE PRIMARY MYOCARDIAL FIBROSIS
IN PROGRESSIVE SYSTEMIC SCLEROSIS
—A Case Report with Autopsy Findings—

KAZUHIDE YAMAOKI, M.D., YOSHIO YAZAKI, M.D., HIROSHI MATSUNAGA, M.D.
TERUNAO ASHIDA, M.D., RYOZO NAGAI, M.D., YASUYOSHI OHUCHI, M.D.
SEIGO UEDA, M.D., YUZO MIYAKAWA, M.D., AND KINORI KOSAKA, M.D.

An extensive myocardial fibrosis due to progressive systemic sclerosis (PSS) was described in a 36-year-old normotensive woman without pulmonary hypertension. An electrocardiogram showed low voltage and a pseudo-infarctional pattern in leads V₁ through V₃. Right ventricular dilatation and generalized left ventricular hypokinesis were present, but her pulmonary artery pressure was normal. Serum creatine kinase (CK) was elevated to 2305 U/L and CK-MB isoenzyme was as high as 7.1%. Simultaneously performed isoenzyme analysis of CK from the homogenate of the skeletal muscle of the patient showed a similar pattern, thus confirming that serum CK originated mainly from the skeletal muscle lesions. Autopsy findings demonstrated diffuse myocardial fibrosis and relatively unremarkable changes in the lungs and the kidneys. Our case serves as a warning that primary myocardial fibrosis could be, in some cases, so extensive that it might lead to a rapidly aggravated myocardial dysfunction and eventual death.

PROGRESSIVE systemic sclerosis (PSS) is a systemic disorder, occasionally involving the heart. Heart failure in PSS generally predicts an ominous clinical course and is commonly caused by cor pulmonale due to pulmonary fibrosis resulting in pulmonary hypertension.

As compared with other connective tissue diseases such as systemic lupus erythematosus in which pericarditis and pericardial effusion are the most common manifestations of cardiac involvement, PSS characteristically causes myocardial lesions not infrequently as well as pericardial and rarely endocardial ones.

In this paper we describe a patient with PSS and heart failure, in whom an extensive primary myocardial fibrosis proved to be the cause of her cardiac dysfunction and premature death.

Case Report

A 36-year-old woman was admitted to the Tokyo University Hospital on May 18, 1979, because of progressive exertional dyspnea. Her mother and sister were suffering from rheumatoid arthritis, and the patient's son from bronchial asthma.

She had been well until 4 months earlier, when she began to feel stiffness in her fingers. One month before admission, she noted Ray-

Key Words:
Progressive systemic sclerosis
Myocardial fibrosis
Catheterization study
Creatine kinase MB isoenzyme

(Received December 12, 1981; accepted May 24, 1982)
The Third Department of Internal Medicine, University of Tokyo, Tokyo, Japan
Address for correspondence: Kazuhide Yamaoki, M.D., The Third Department of Internal Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

Japanese Circulation Journal Vol. 46, November 1982 1159
nau'd's phenomena in her hands, progressive exertional dyspnea and peripheral edema.

There was no history of fever, arthritis, dysphagia or angina pectoris.

On admission, her blood pressure was 94/76 mmHg; her pulse rate was 90 per min and regular. Scleroderma was noted in the distal upper extremities and the face. Examinations of the chest revealed no rales. Cardiac examination showed a cardiomegaly. The second heart sound was widely split with a slight respiratory variation. A pulmonary component of the second heart sound was normal in intensity. No gallop sound was present. There was a 3/6 ejection murmur along the left lower sternal border. The liver was enlarged 6 cm below the right costal margin. There was moderate pitting edema of both lower legs and feet. Neurological examination disclosed muscular weakness in her upper and lower extremities. No subcutaneous calcification was noted.

The hematocrit was 36.2%, and the white cell count was 5300/mm³ with a normal differential count. The erythrocyte sedimentation rate at one hour was 24 mm.

The urinalysis was normal.

Blood chemistries were as follows: a urea nitrogen of 7 mg per 100 ml, a GOT of 122 U/L, a GPT of 96 U/L, a LDH of 900 U/L. Isoenzyme analysis of LDH showed elevations of types II and III. Serum creatine kinase (CK) was 2305 U/L (normal range: 24 to 170 U/L). CK-MB isoenzymes of the serum and the extract of the specimen of the skeletal muscle biopsy were 7.1 and 6.9%, respectively. Serum aldolase was 6.4 mU/ml (normal range: 0.5 to 3.0 mU/ml).

Her chest roentgenogram showed a cardiothoracic ratio of 63%. Lung fields were clear (Fig. 1).

Arterial blood gas values were normal. Pulmonary function testing demonstrated a moderate restrictive ventilatory abnormality: the forced vital capacity was 71% of the predicted normal value. The diffusion capacity was 74% of that predicted.

A skin biopsy showed atrophy of the epidermis and increased collagen in the dermis which was compatible with scleroderma.

Findings of a skeletal muscle biopsy of the left upper arm include atrophy and degeneration of the muscle fibers compatible with polymyositis.

An electrocardiogram showed a low QRS voltage in both the limb and chest leads, right

![Fig.1. Chest roentgenogram at the first admission. The cardiothoracic ratio is 63%. The lung fields are clear.](image)

![Fig.2. Electrocardiogram. Marked low QRS voltage, right axis deviation and small q waves in V₁₋₃ are shown.](image)
Fig. 3. M-mode echocardiograms. Left: Mitral valve (MV) echogram shows reduced amplitudes and interruptions of mitral closure (B-B’ shoulder). Right: Right ventricular enlargement, paradoxical motion of the interventricular septum (IVS) and hypokinesis of the left ventricular posterior wall (LVPW) were noted. RVAW = right ventricular anterior wall

A two-dimensional and a M-mode echocardiogram revealed an enlarged right ventricle (Figs. 3 and 4). The interventricular septum had a normal thickness and showed a paradoxical motion. The left ventricular wall was normal in thickness, but showed a generalized hypokinesis. No pericardial effusion was noted. Pulmonary valve echogram showed an “a” dip of normal depth (5 mm) and the e-f slope was also normal (45 mm/sec).

Cardiac catheterization showed slightly elevated biventricular end-diastolic pressures (EDP) (Fig. 5) (right ventricular pressure 18/7 mmHg, RVEDP 9 mmHg; left ventricular pressure 82/9, LVEDP 12). Pulmonary artery pressure was 17/9 mmHg with a mean of 11 mmHg. Intra-

end-diastole

end-systole

Fig. 4. Two-dimensional echocardiograms. (A), (B): Long axis view of the left ventricle (LV). (C), (D): Short axis view of the LV. The right ventricle (RV) is dilated. The arrows in (B) and (C) show the paradoxically moving interventricular septum (IVS). Ao = aorta; AML = anterior mitral leaflet; PML = posterior mitral leaflet; A = anterior; P = posterior; I = inferior; S = superior

Japanese Circulation Journal Vol. 46, November 1982
Cardiac blood sampling revealed no significant shunting of the flow.

A right ventriculogram showed a markedly dilated right ventricle and decreased contractility (Fig. 6). A left ventriculogram revealed a slightly dilated left ventricle with a generalized hypokinesis (Fig. 7). The left ventricular ejection fraction was 0.39. The cardiac index was 2.0 L/min/m².

The patient was treated with furosemide, digoxin and prednisolone (beginning with a daily dose of 50 mg, then tapering off to 35 mg daily), with a subsequent improvement in her physical capacity. The serum CK decreased gradually to 395 U/L, when she was discharged in August, 1979.

Two months later the patient was readmitted with increasing dyspnea and abdominal distension.

On the second admission on October 11, 1979, her blood pressure was 98/64 mmHg and her pulse rate was 100 per min. Moderate ascites was present. Chest X-ray film showed a cardiothoracic ratio of 65%. No pericardial effusion
was noted on repeated echocardiograms.

Laboratory data was as follows: a GOT of 61 U/L, a GPT of 86 U/L, a LDH of 508 U/L and a CPK of 79 U/L.

She was given oxygen, furosemide, dopamine and prednisolone but with no improvement. She became progressively oliguric and died on the 12th hospital day (October 23, 1979).

Autopsy Findings: At autopsy the heart weighed 350g. Both ventricles were markedly dilated. Sections of the myocardium revealed numerous patches of fibrosis, evenly distributed in both ventricles. Microscopically, the myocardial fibrosis extended into the epicardium and subendocardium (Fig. 8). In the interventricular septum, fibers of the cardiac conduction system were also involved randomly in various locations. The myocardial degeneration and necrosis were not prominent. Scattered muscle fibers persisted within the fibrotic scars. The interstitium was edematous and highly vascular with capillaries engorged with blood.

The extramural coronary arteries were normal. Some of the intramyocardial arteries in the fibrotic lesions showed a thickening of the walls with narrowed lumens. However, the majority of the small arteries and arterioles in the myocardium showed little evidence of intimal thickening and were widely patent.

Lymphocytes and mononuclear cells were encountered occasionally in a few foci.

The valves were normal. The pericardial cavity contained 50 ml of sanguinous fluid. There was no histological evidence of pericarditis. Moderate pulmonary fibrosis was present. Microscopically, moderate intimal thickening of the arteries and slight fibrosis of the alveolar walls were noted in the lungs.

The only renal change was a slight intimal thickening of the interlobular arteries.

In skeletal muscles slight myositic changes were noted.

DISCUSSION

Early in this century Matsui\(^1\) called attention to the fact that "scleroderma universalis" involves various internal organs including the heart. However, he ascribed the cause of myocardial changes to cor pulmonale accompanying pulmonary vasculitis and fibrosis. In the majority of cases, heart failure in PSS is due to pulmonary
hypertension or systemic hypertension with renal vasculitis. Recently Bulkley and others have reported a relatively high incidence of primary lesions in the myocardium (26 out of their 52 cases: 50%) and considered that they may lead to arrhythmias, heart failure, angina pectoris with normal coronary arteries and sudden death.

In our present case, electrocardiographic findings such as a marked low voltage and a pseudo-infarctional pattern suggested a possible myocardial involvement. As to the right ventricular enlargement disclosed by echocardiography, it was initially difficult to determine whether or not a right-sided heart failure in this patient was secondary to pulmonary hypertension. Smith et al. reported that pulmonary artery pressure was normal in 2 out of 7 cases with right ventricular dilatation revealed by echocardiography. In our case the catheterization and angiographic studies together with the autopsy confirmation demonstrated clearly that a primary myocardial fibrosis without pulmonary hypertension could be so extensive and severe that it might lead to a rapidly downhill course.

Regarding the pathogenesis of the myocardial fibrosis, the following possibilities are proposed:

1) Intimal thickening of intramyocardial small arteries and coronary arterioles
2) Vasospasm of small coronary vessels
3) Abnormal collagen proliferation and subsequent degeneration and necrosis of the myocardial fibers

As to the immune and other mechanisms underlying the above mentioned phenomena, it remains largely unknown.

In our case the degree of myocardial fibrosis exceeded that which could be ascribed to myocardial vascular changes noted in the histologic sections. Possibly various other factors including hypoxia and drugs such as steroids might have also contributed to the observed myocardial abnormalities.

Takatsu et al. reported a case of PSS with a normal pulmonary artery pressure. In that patient an endocardial biopsy demonstrated a severe myocardial fibrosis. However, other similar case reports are scanty in the literature and further studies must be done to know the exact frequency and clinical significance of a primary myocardial fibrosis in PSS.

A persistent elevation of serum CK with a high content of CK-MB isoenzymes was also remarkable in our case. The serum CK level remained high until corticosteroid administration.

Serum CK-MB isoenzymes are widely accepted as a highly specific marker for cardiac injury and, along with the total level of CK, are utilized in the diagnosis of acute myocardial infarction.

*Japanese Circulation Journal* Vol. 46, November 1982
On the other hand, high levels of serum CK-MB are also reported in noncardiac disorders such as polymyositis, dermatomyositis, muscular dystrophy, hypothyroidism and so on.

In our case content of CK-MB isoenzyme in the skeletal muscle taken by the biopsy procedure was just as high as in the serum (about 7%). Moreover, in order to explain its persistent elevation in the serum, continuous leakage of CK from tissues having a large enzyme content is necessary. High serum aldolase level and LDH isoenzyme analysis also support the idea that the elevated serum CK was originating mainly from the skeletal muscle lesions, and thus the presence of polymyositis in our case was indicated.

We must be cautious as to the differential diagnosis of the source of CK enzyme leakage, especially in the overlap syndromes such as PSS and polymyositis, in which cardiac involvement is reported to be frequent and tends to be severe.

REFERENCES

1. MATSUI S: Ueber die Pathologie und Pathogenese von Sclerodermia Universalis. Mitteilungen aus der medicinischen Fakultaet der Kaiserlichen Universitaet zu Tokyo 31: 55, 1924
5. JAMES T: Coronary arteries and conduction system in scleroderma heart disease. Circulation 50: 844, 1974