Case Report

Familial Primary Pulmonary Hypertension —Report of Two Siblings—

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Familial primary pulmonary hypertension was found in two siblings (sister and brother). The woman noted exertional dyspnea at the age of 28 yr. The younger brother noticed exertional dyspnea, cough with bloody sputum and pretibial edema at the age of 38 yr. We diagnosed them as primary pulmonary hypertension as based on hemodynamic and histopathological findings. Regardless of the treatment, both patients died of right-sided heart failure with a short time course. We examined their family members, but there were no other members with primary pulmonary hypertension.

Key words: Genetic transmission, Right-sided heart failure

In Japan, the incidence of patients with primary pulmonary hypertension has been reported to be from 11 to 12 persons/yr (1). In addition, familial primary pulmonary hypertension seems to be less than 10% of all patients with primary pulmonary hypertension (2). To our knowledge, there have been 6 reports of adult familial primary pulmonary hypertension in Japan (3–8). We describe adult familial primary pulmonary hypertension in a sister and a brother.

CASE REPORTS

Case 1: The patient, a housekeeper, first noted dyspnea on exertion in March 1977 at the age of 28 yr, 8 months after the delivery of her second child. Thereafter, exertional dyspnea gradually progressed in severity, moreover palpitation and faintness developed. She was referred to Ehime University Hospital and admitted on May 8, 1978. Physical examination on admission revealed a right ventri-

cular enlargement and a narrow splitting of the second heart sound with an accentuated pulmonic component. The systemic arterial pressure was 128/70 mmHg with a regular pulse rate of 72/min. Examination of the lung was unremarkable, and there was no hepatomegaly, pretibial edema, clubbing of fingers or cyanosis. Hematological and biochemical studies were within normal limits except for iron deficiency anemia. Arterial blood gas analysis in the room air showed hypoxemia (PO_2 64.8 mmHg, PCO_2 35.8 mmHg).

Electrocardiogram demonstrated right-axis deviation and hypertrophy of the right ventricle and atrium (Fig. 1A). Chest X-ray film showed cardiomegaly (cardio-thoracic ratio of 57%) and enlargement of the pulmonary arteries at the hilar regions with marked tapering of the peripheral arteries (Fig. 2A). A two-dimensional echocardiogram showed that the left ventricle was oppressed by the markedly enlarged right ventricle (Fig. 3A), and on M-mode

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Fig. 1. Electrocardiograms of case 1(A) and case 2(B) show right-axis deviation and hypertrophy of the right ventricle and atrium.

Fig. 2. Chest roentgenograms of case 1(A) and case 2(B) demonstrate cardiomegaly and enlargement of the pulmonary arteries at the hilar regions with tapering of the peripheral arteries.

recording of the pulmonary valve, midsystolic notching, diminished A wave amplitude and a flat EF slope, which indicate pulmonary hypertension, were observed. Perfusion scanning of the lung demonstrated nonsegmental, heterogeneous and multiple defects.

Cardiac catheterization showed pulmonary hypertension with a normal pulmonary capillary wedge pressure and no evidence of intracardiac shunts (Table 1). By open lung biopsy performed on June 5, 1978, the lesions equivalent to grade 4 of the grading system for hypertensive pulmonary vascular disease by Heath and Edwards (9) were confirmed. Although phenoxybenzamine and anticoagulant was administered, she died of right-sided heart failure in July 1983 at the age of 34.

Fig. 3. Short axis two-dimensional echocardiograms of case 1 (A: end-diastole, A': end-systole) and case 2 (B: end-diastole, B': end-systole) show that the left ventricle (LV) is oppressed by markedly enlarged right ventricle (RV).

Case 2: This patient, the younger brother of the case 1, was a 38-year-old farmer. He had been able to work hard as a farmer until he noticed exertional dyspnea in January 1988. Moreover, cough with bloody sputum and generalized edema developed, thus he was admitted to Yoshida General Hospital on April 26, 1988. With the combined treatment with diuretics, digitalis and dietary sodium restriction, the above-mentioned symptoms improved. For the purpose of further investigation, he was admitted to Ehime University Hospital on May 10, 1988. On admission, the systemic arterial pressure was 114/78 mmHg and the pulse rate was 66/min with regularity. On auscultation, there was a grade 2/6 diastolic blowing murmur along the lower left sternal border, and the pulmonic component of the second heart sound was accentuated. The liver was palpable two finger-breadths along the right midclavicular line below the costal margin. There was no pretibial edema, jugular venous dilatation or cyanosis. On hematological and biochemical studies, values of alkaline phosphatase (ALP), γ -glutamyl transpeptidase (γ -GTP) and leucine aminopeptidase (LAP) exceeded the normal range. These abnormalities were thought to be due to the congestion of the liver. An arterial blood gas analysis in the room air showed hypoxemia (PO_2 66.1 mmHg, PCO_2 35.1 mmHg).

Table 1. Cardiac catheterization data

	Case 1				Case 2			
	Pressure (mmHg)			SaO ₂ (%)	Pressure (mmHg)			SaO ₂ (%)
	syst	dias	mean		syst	dias	mean	
PCW			7				12	
PA	101	44	62	75.0	103	44	63	66.7
RV	102	5			107	7		66.7
RA			4	79.4			5	65.2
SVC				78.7				69.8
IVC				81.4				69.8
LV	98	7						
Ao	98	40	60	95.6	103	77	85	91.9
CI		2.93 l/min/m ²				2.26 l/min/m ²		
SI		40.7 ml/beat/m ²				34.2 ml/beat/m ²		

PCW, pulmonary capillary wedge; PA, pulmonary artery; RV, right ventricle; RA, right atrium; SVC, superior vena cava; IVC, inferior vena cava; LV, left ventricle; Ao, aorta; syst, systole; dias, diastole; CI, cardiac index; SI, stroke volume index; SaO₂, O₂ saturation

An electrocardiogram demonstrated right-axis deviation and hypertrophy of the right ventricle and atrium (Fig. 1B). Chest X-ray film showed enlargement of the pulmonary arteries at the hilar regions with tapering of the peripheral arteries; the cardiothoracic ratio was 52% (Fig. 2B). A two-dimensional echocardiogram showed that the left ventricle was oppressed by the markedly enlarged right ventricle (Fig. 3B). On M-mode recording of the pulmonary valve, a diminished A wave, midsystolic notching and a flat EF slope, which indicate the presence of pulmonary hypertension, were observed. Perfusion scanning of the lung demonstrated nonsegmental, heterogeneous and multiple defects. Cardiac catheterization showed pulmonary hypertension with a normal pulmonary capillary wedge pressure, low cardiac output and no evidence of intracardiac shunts (Table 1).

He was discharged on June 16, 1988, and was treated with diuretics, digitalis, calcium channel blockade (diltiazem) and anticoagulant. His symptoms and signs became worse after he had a cold in January, 1989 and he died on February 4, 1989. At autopsy, histological findings of the lung were compatible with grade 4–5 in Heath-Edwards classification (9) as shown in Fig. 4.

Fig. 4. Case 2, A: pulmonary artery with severe laminar concentric intimal fibrosis (Elastica-van Gieson stain, $\times 50$), B: pulmonary artery with plexiform lesion (hematoxylin and eosin stain, $\times 100$).

DISCUSSION

The pathogenesis of primary pulmonary hypertension is unknown. However, the most prevalent theory has focused on vasoconstriction. The findings of increased pulmonary vascular reactivity and pulmonary vasoconstriction in patients with primary pulmonary hypertension suggest that a marked vasospastic or constrictive tendency underlies the development of this disease (10, 11). Calcium channel blockades often have beneficial effect on primary pulmonary hypertension (11–14). This finding may also support the vasospastic theory in the pathogenesis of primary pulmonary hypertension.

Clarke et al (15) first reported that primary pulmonary hypertension might be affected by genetic transmission. Evidence of genetic transmission is provided by the appearance of the same disease in successive generations. In the literature, there were several families with primary pulmonary hypertension in two generations, for example, mother and child. Melmon and Braunwald (16) reported a kindred in which 5 members of three generations had primary pulmonary hypertension. This is the only one report of familial primary pulmonary hypertension in three generations. They suggested that the genetic transmission appeared to

be by a mendelian-dominant gene with variable penetrance, and genetic anticipation was observed. Table 2 summarizes the records of familial primary pulmonary hypertension reported in Japan. The study of the sporadic form of primary pulmonary hypertension in Japan indicates that 67% of patients are female, and the age of onset of the disease is observed most frequently in the twenties. The mean age at diagnosis of familial primary pulmonary hypertension was 30 ± 8 yr. Comparison of the age at the diagnosis between familial primary pulmonary hypertension and sporadic form of primary pulmonary hypertension shows no significant difference. Preference of female patients in familial primary pulmonary hypertension seems to be lower than that in the sporadic form. However, the number of familial primary pulmonary hypertension cases is too small to compare with the sporadic form. To define the true mode of inheritance, the accumulation of more cases with familial primary pulmonary hypertension is necessary.

The most frequently encountered mode of death in primary pulmonary hypertension is right-sided heart failure (17). Late in the course of the disease, patients may not respond to drugs. For the appropriate treatment of the heart, it is very important to estimate the right ventricular dysfunction associated with pulmonary hypertension. However, it is very

Table 2. Familial primary pulmonary hypertension in Japan

Reference	Age	Sex	Relationship	Diagnosis
Sato et al (1971)	22	M	brothers	Cath
	20	M		Cath
Shinagawa et al (1973)	44	M	father & daughter	Necropsy
	32	F		Necropsy
Okita et al (1978)	48	M	brothers	Cath
	34	M		Cath
Haneda et al (1980)	25	F	sisters	Necropsy
	23	F		Cath
Kanemoto et al (1983)	24 (died)	M	brother & sister	Cath
	26	F		Cath
Kunieda et al (1986)	29	F	twin sisters	Cath
	29	F		Necropsy

Cath, catheterization

difficult to noninvasively estimate the right ventricular function. We have reported that in patients with right ventricular dysfunction, left ventricular function appeared to be impaired due to the reduced volume of the left ventricle associated with the enlargement of the right ventricle (18, 19). In primary pulmonary hypertension, left ventricular function estimated by echocardiography and systolic time intervals could be indicative of the severity of the disease (18, 19). Therefore, early treatment for primary pulmonary hypertension should be performed based on the noninvasive estimation of left ventricular function.

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