[Case Report]

Two Cases of Familial Primary Pulmonary Hypertension

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Abstract: Case 1, a 28-year-old woman (third daughter of Case 2) delivered her first child in September 2000, but leg edema and dyspnea on exertion appeared the following January. At the time of our first examination of the patient in May 2001, a chest X-ray showed cardiomegaly and pulmonary artery enlargement. Echocardiography demonstrated enlargement of the right ventricle and small left ventricular dimensions, and an electrocardiogram revealed right ventricle hypertrophy. After perfusion-ventilation lung scintigraphy and cardiac catheterization, she was diagnosed as having primary pulmonary hypertension (PPH). Although she was discharged with prescriptions for a diuretic, warfarin and beraprost sodium, she died of a pulmonary hypertensive crisis twenty days after readmission. Case 2, a 60-year-old woman (mother of Case 1) developed the same symptoms as those in Case 1, in May 2001, but recovered after medication. PPH is a rare disease and only a few familial cases are reported. In this family, the eldest daughter of Case 2 had also died of pulmonary hypertension ten years ago, several months after her first delivery. In contrast to the daughters, the mother's symptoms developed gradually.

Key words: primary pulmonary hypertension, familial primary pulmonary hypertension, beraprost sodium.

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Introduction

Primary pulmonary hypertension (PPH) is a rare disease, occurring with the incidence of 2 ~ 3/100,000 and is associated with poor prognosis. Familial PPH (FPPH) accounts for at least 6% of PPH cases. Here we report two cases of FPPH from the same family. A young woman died two months after her diagnosis of PPH, and her mother is being cared for as an outpatient. The eldest daughter of Case 2 also died of pulmonary hypertension ten years ago, in a manner similar to the third daughter.

Case Report

Case 1

A healthy 28-year-old woman gave birth to her first child on September 9, 2000. In January 2001 she consulted a primary physician with complaints of shortness of breath, leg edema, general fatigue and abdominal fullness. Since a blood test indicated low albuminemia, and cardiomegaly was recognized on a chest X-ray, she was admitted to our hospital for further examinations and medical treatment on May 9, 2001.

On admission, her blood pressure was 102/64 mmHg, and jugular venous distension was present. Cardiac auscultation revealed a loud pulmonic S2 and grade 3/6 systolic murmur over the left upper sternal border. The abdomen was distended and leg edema was present. Immunological test for antinuclear antibodies, anti-DNA antibodies, and anti-cardiolipin antibodies were negative. Factors for coagulation and fibrinolysis were all within the normal range. In arterial blood gas analysis, PaO₂ was 56 mmHg and SaO₂ was 91.0%. A perfusion-ventilation lung scintigraphy showed a normal perfusion and ventilation pattern in both lungs. Abdominal echography showed hepatomegaly, ascites and no splenomegaly. Hemodynamic data in the right cardiac catheterization inspection are shown in Table 1. Cardiomegaly, enlargement of the main pulmonary artery, and right pleural effusion were seen on the chest X-ray (Fig. 1A). Echocardiograms (Fig. 1B) showed a dilated right ventricle with small left ventricular dimensions and tricuspid regurgitation in which systolic pulmonary artery pressure was estimated as 90 mmHg by measuring tricuspid pressure gradient. The 12-leads

Table 1. Right cardiac catheterization

	Case 1	Case 2
mPCWP(mmHg)	10	7
mPAP(mmHg)	59	45
RVP(mmHg)	80/8	80/4
mRAP(mmHg)	17	4
C.O.(ℓ/min)	2.79	2.05
C.I.(ℓ/min/m ²)	1.86	1.60
PVR(dynes·sec·cm ⁻⁵)	1428	1483

mPCWP: mean pulmonary capillary wedge pressure, mPAP: mean right atrium pressure, RVP: right ventricle pressure, mRAP: mean right atrial pressure, C.O.: cardiac output, C.I.: cardiac index (calculated Fick), PVR: pulmonary vascular resistance

Fig. 1. Chest X-ray(A), echocardiogram(B), 12-leads ECG(C) and pulmonary angiogram(D) in Case 1. RV indicates right ventricle; LV, left ventricle.

ECG revealed right ventricle hypertrophy (Fig. 1C).

At the time of hospitalization, the patient was diagnosed with right heart failure. We considered diseases that cause pulmonary hypertension such as congenital heart diseases or pulmonary artery thromboembolism. Lung ventilation-perfusion scintigraphy was normal and pulmonary artery resistance was markedly elevated in the cardiac catheterization, but we did not recognize any congenital heart diseases. Although dilatation of the main truncus of the pulmonary artery and narrowing of the peripheral pulmonary artery were seen, pulmonary angiography (Fig. 1D) showed no macro-thromboembolism. The patient was therefore diagnosed as having PPH. The patient's pulmonary hypertension was considered to develop after delivery of her child, because 12-leads ECG did not show any right ventricular hypertrophy and right atrial hypertrophy just before delivery (Fig. 2). After a definite diagnosis, administration of warfarin and beraprost sodium (BPS) was started. Her brain natriuretic peptide (BNP) and uric acid (UA) levels were 630 pg/ml and 8.1 mg/dl, respectively, and the walking distance in 6 minutes was 190 m after medical treatment. She was discharged on June 19.

Two weeks after leaving the hospital, the patient experienced a reduction of urine volume,

Fig. 2. Case 1, 12-leads ECG before delivery (2000.8.30).
ECG shows left axis deviation and clockwise rotation.

Fig. 3. Chest X-ray (A), echocardiogram (B), 12-leads ECG (C) and pulmonary angiogram (D) in Case 2. RV indicates right ventricle; LV, left ventricle.

abdominal distention, appetite loss, severe cough and leg edema. Since her condition did not improve even after increasing diuretics, she was re-hospitalized on July 9. On the morning of July 25, she complained of general fatigue and her blood pressure had fallen. Continuous blood filtration dialysis was started due to advanced metabolic acidosis. However, blood pressure and heart rate suddenly dropped immediately after the procedure, and she died on July 27.

Case 2

A 60-year-old woman complained of anasarca. She became aware of leg edema at the end of May 2001 and edema of the upper limbs and face appeared in June. Pulmonary hypertension was suspected, and she was admitted to our hospital on June 27.

At the time of hospitalization, her weight was 52 kg and her blood pressure was 120/90 mmHg. Cardiac auscultation revealed a loud pulmonic S2 and grade 3/6 systolic murmur over the left upper sternal border. The abdomen was distended and edema was observed in both legs. The chest X-ray, the echocardiography and the ECG (Fig. 3A, 3B and 3C) had almost the same appearance as those in Case 1. In the peripheral blood analysis, polycythemia and liver dysfunction were present. The blood gas measurements revealed the following: pH 7.453, PaO₂ 60 mmHg, PaCO₂ 33.6 mmHg, HCO₃⁻ 23.8 mEq/ℓ, and SaO₂ 92.2%. Pulmonary function tests were normal, and lung ventilation perfusion scintigraphy also had almost normal appearance. Since anasarca was recognized at the time of hospitalization, a diuretic was prescribed and her weight decreased to 42 kg. From the family history, PPH was strongly suspected and medication of warfarin and BPS was started. In a right cardiac catheter inspection performed on August 16, the pulmonary artery pressure was 78/24 mmHg (a mean of 45 mmHg). Hemodynamic data on cardiac catheterization is shown in Table 1. Pulmonary angiography (Fig. 3D) showed no thrombus. At this time she was diagnosed as having PPH. Home oxygen treatment was introduced and she left the hospital on September 25. At that time, her BNP and UA levels were 167 pg/ml and 4.3 mg/dl, respectively, and the walking distance in 6 minutes was 240 m just before discharge. She is now being treated as an outpatient.

Discussion

We encountered two cases of FPPH, a mother and her third daughter. The eldest daughter may also have had FPPH since she developed a respiratory condition worsening after delivering a child, and died of pulmonary hypertension. However, because she died about ten years ago, it is unclear whether she definitely suffered from PPH.

As was true for Case 1, PPH is often discovered in women of child-bearing age during pregnancy and delivery. Weiss and others[1] reviewed published reports to evaluate the outcome of pregnancy and delivery in women with pulmonary vascular disease, and reported

that about 30% of 27 women with PPH died less than 1 month after giving birth. The physiological changes that occur in pregnancy and delivery can potentially activate the disease and result in death of the mother and/or the child. Even in a healthy person, pregnancy increases in cardiac output from 30 to 50%, in blood volume from 40 to 50%, and in oxygen consumption 20%. Delivery then brings a change in the pulmonary blood vessel tone due to the reduction of blood volume, a low oxygen state, increase of catecholamine, or microthromboembolism, resulting in worsening of the pulmonary vascular disease [2].

PPH is defined as a progressive, intractable and often-fatal disease of unknown etiology. The small precapillary pulmonary arterioles in patients with PPH are characterized by medial hypertrophy, concentric laminar intimal fibrosis, plexiform lesions with obstruction of the arterial lumen, and proliferation of inter-connected channels [3, 4]. PPH occurs with a frequency of 2–3 persons/1 million people, a male to female ratio of 1 : 2, and a mean age at onset of 36 years old. FPPH is estimated to represent approximately 6% of all cases of PPH. Deng has reported the mutations in Bone Morphogenetic Protein Receptor-II (BMPR-II) gene on chromosome 2q31-32 in some cases of FPPH [5]. BMPR-II is a member of transforming growth factor-beta (TGF-beta) receptor, and mutant of BMPR-II, in which the 354th thiamine is replaced with guanine, may not inhibit the proliferation of smooth muscle cells in the pulmonary artery [6]. However, those who present PPH clinically in a career with the BMPR-II gene mutation are only 10–20% in FPPH. Other environmental factors, estrogen, or other gene mutations that are not known yet may participate in pulmonary hypertension [6, 7], and may explain why the clinical development was quite different between Case 1 or the eldest daughter of Case 2 and Case 2.

D'Alonzo and others reported that the one-, three- and five-year survival rate of PPH was 68, 48 and 34%, respectively, and that the prognosis was strongly influenced by the right heart function, measured by average right atrium pressure, average pulmonary artery pressure and the cardiac output index [8]. According to this report, one- and three-year survival rate of Case 1 was 55.5 and 29.4%, and that of Case 2 was 74.7 and 54.5%. On the other hand, Nagaya *et al.* recently reported that UA, BNP and the 6 minutes walk test are important factors for specifying a prognosis. Values of BNP over 180 pg/ml, values of UA over 8.9 mg/dl for a man or 6.4 mg/dl for a woman, and a distance walked in 6 minutes of less than 322 m suggest a poor prognosis [9–11]. According to these criteria, a poor prognosis also would have been expected for Case 1, but not for Case 2. Furthermore, in comparatively mild cases of PPH, the prognosis has been improved after administering BPS, an orally active prostacyclin analogue that strongly dilates blood vessels and inhibits platelet aggregation [10]. The oral prostacyclin we used for Case 2 has few side effects or complications as compared to continuous intravenous infusion of PGI₂. In a worsening case where internal medical treatment is not successful and the patient continues to worsen, it is necessary to take into consideration a lung transplantation or a heart and lungs simultaneous transplantation. Although the method of detecting the BMPR-II gene mutation has not been clinically estab-

lished yet, it may soon be possible to perform a gene diagnosis of the patient with a high risk of FPPH. In a patient with the genetic mutation, but no symptoms, it may become possible to diagnose the pulmonary hypertension at an early stage using Doppler echocardiography, and we may also be able to perform early detection and early treatment in the near future.

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家族性原発性肺動脈高血圧症の二症例

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要 旨: 症例一(症例二の三女, 28歳)は, 平成12年9月長男を出産, 翌年1月より下肢の浮腫, 労作時の呼吸苦が出現. 平成13年5月初診時, 心拡大・肺うっ血が認められ, 心電図上右室負荷, 心エコーにて, 右室の拡大, 左室の圧排を認めた. 肺換気血流シンチグラフィおよび心臓カテーテル検査の結果, 原発性肺高血圧症(PPH)と診断された. 利尿剤などの投与により, 改善を認め退院となったが, 1ヵ月後肺高血圧 crisis のため死亡した. 症例二(症例一の母, 60歳)は, 平成13年5月より, 症状が出現, 症例一と同様の所見を認め, 内服加療により症状軽快し経過観察中である. PPHは稀な疾患であり家族性の報告も少ない. 長女の場合も症例一と同様に, 第一子出産後, 肺高血圧症のため死亡した. 症例二は, 緩徐な経過で発症したと考えられる. 今回我々は, 家族性原発性肺高血圧症の二症例を経験したので報告する.

キーワード: 家族性原発性肺高血圧症, 肺高血圧症, ベラプロスト.

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