Primary Pulmonary Hypertension: A Case Report with Discussion on Its Pathogenesis

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The reports of primary pulmonary hypertension has increased since the introduction of cardiac catheterization technique. However this condition is thought to be rare in frequency. Several decades of cases were reported with the use of catheterization between 1950 and 1957. In Japan more than 10 cases have been reported. The etiology of this condition is still obscure. We have experienced a case of pulmonary hypertension which suggests some possible relationship between this condition and pregnancy.

CASE REPORT

A 29-year-old housewife had been completely healthy until June 1965, when she developed pressure sensation on the chest, dyspnea, puffy face and edema of legs. She was admitted three months later to the Hospital of Kyoto Prefectural University of Medicine. The patient was married at 26 years of age and delivered of two children, one at 27 years of age and the other at 29, with full term (2 gravida and 2 para). There were no complications during pregnancies. Two months after the last delivery, however, she felt oppressive on the chest, when she walked up a flight of stairs or a slope, and noticed puffy face and swelling of the lower legs and ankles. Until the admission she had been treated by her family doctor without benefit. The patient’s father died of cancer of the liver and mother of pleurisy. Six siblings were all living and well.

On physical examination she was a well developed, poorly nourished small woman of chronic illness. Blood pressure was 100/60 mmHg and pulse rate 118 per minute and regular.

She was slightly dyspneic and cyanotic, but there was no clubbed fingers. The neck veins were slightly distended and breath sounds were rough but no rales were audible over the lung fields. The apex beat was located in the fifth intercostal space on the left mid-clavicular line. There was no precordial lift, nor deformity of the chest. On auscultation a faint (grade 1, Levine) early systolic ejection murmur was audible at the pulmonic area, associated with wide splitting of the second sound and marked accentuation of pulmonic component. The interval of the splitting was changed with respiration. The liver was palpable 1 cm below the right costal margin and firm, smooth and tender. The abdomen was soft and flat. There was no sign of ascites. Edema of the feet and ankles was noticed.

Laboratory studies: The urinalysis was normal except for occasional protein trace. ESR was 1 mm/hr. Hematology showed that RBC was $459 \times 10^4$; Hb, 14.4 g/dl; hematocrit, 45 % and WBC, 6200 with normal differentials. Serum urea nitrogen was 14 mg/dl. Serum sodium, potassium and chloride were 144 mEq/L, 5.1 mEq/L and 115 mEq/L, respectively. Serum protein was 5.4g/dl, with

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64% of albumin, 3.2% of $\alpha_1$-globulin, 9.6% of $\alpha_2$-globulin, 11.2% of $\beta$-globulin and 12.0% of $\gamma$-globulin, and albumin/globulin ratio, 1.8. Bilirubin; direct was 0.23 mg/dl and indirect, 0.77 mg/dl. Thymol turbidity and zinc sulfate turbidity were normal. Total cholesterol was 194 mg/dl. Alkaline phosphatase was 27 Bessy-Lowry units. Bromsulphalein retention test was prolonged, probably owing to the congestion. SGOT and SGPT were 59 and 43 units respectively. PSP was 32% in 15 minutes and 64% in 120 minutes. Serology for syphilis was negative. CRP and ASLO were both negative. Venous pressure was 280 mm H$_2$O. The electrocardiogram (Fig. 1) showed marked right auricular and ventricular hypertrophy. The plain X-ray films of the chest (Fig. 2) and selective angiograms showed enlargement of the heart to the left and inferiorly with the roundish apex, prominence of the pulmonic artery component and enlarged hilar marking with clear lung fields. These clinical and laboratory findings led us to the diagnosis of EISENMENGER'S complex.

A right cardiac catheterization performed on October 11, showed an increased of both right auricular and ventricular pressures (Table 1). It was impossible to insert the catheter into the pulmonary arteries despite of several trials. The presence of left to right shunt was not noticed from the oxygen saturation of blood samples.

With administration of digitalis and thiazide the edema diminished and cardiac silhouette was decreased in size, but sense of precordial oppression was present. Since her general condition improved, she was discharged on December 13, 1965. After her discharge she was treated by her family doctor and became able to walk within short distance. In the middle of June, however, edema and dyspnea became conspicuous again and was re-admitted to our clinic on June 24, 1965. She developed cough at night for a few days prior to the admission.
A CASE OF PRIMARY PULMONARY HYPERTENSION

Fig. 2. X-ray films of the chest and angiogram. A: Right anterior oblique view. B: Posteroanterior view and C: Left anterior oblique view. D: Serial angiograms showed dilatation of the pulmonary artery. There were no findings of pulmonary stenosis. Contrast substance was injected with a catheter into the right ventricle.

<table>
<thead>
<tr>
<th>Site</th>
<th>Pressures (mmHg)</th>
<th>O₂ Saturation (%)</th>
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<tr>
<td>IVC</td>
<td></td>
<td>48</td>
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<tr>
<td>SVC</td>
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<td>RA</td>
<td>16/8(12)</td>
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<tr>
<td>RV</td>
<td>100/0</td>
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On physical examination the patient was orthopneic and debilitated. Her lips were cyanotic. Blood pressure was 118/80 mmHg and pulse rate, 120 per minute. Jugular vein was distended. Breath sounds were rough but no rales were audible in lung fields. Heart sounds were unchanged except for high-pitched diastolic murmur audible at the pulmonic area (Fig. 3). The liver was palpable 2 cm below the costal margin, and firm and tender. There was no sign of ascites. Moderate pitting edema of legs was noticed.

Laboratory studies were as follows: Urinalysis showed positive protein with 3 positive red cells in sediment. Erythrocyte sedimentation rate was 10 mm/hr. Serum urea nitrogen was 78 mg/dl. Serum sodium was 137 mEq/L. Serum total protein was 6.2 g/dl, with 1.2 of albumin-globulin ratio. Venous pressure was 290 mmHg. Arm-to-lung circulation time was 15 seconds and arm-to-tongue 21 seconds.

The patient was on the back rest and administrated with digitalis and diuretics. On the 5th admission day jaundice and arrhythmia was noticed. Liver function tests showed as follows: Serum bilirubin, direct and indirect increased to 2.69 mg/dl and to 1.27 mg/dl respectively. Thymol turbidity was 3.6 units and zinc sulphate turbidity, 1.2 units. Alkaline phospha-

Fig. 3. Phonocardiogram revealed accentuated pulmonary second sound, the atrial sound and ejection sound.

Fig. 4. Electrocardiogram on the second admission. Sinus rhythm converted into atrial fibrillation two days prior to her death.

tase was 3.1 Bessy-Lowry units. The electrocardiogram showed atrial fibrillation (Fig. 4). The patient developed nausea and abdominal pain and on the following day she suddenly died.

Gynecological history: There was no men-

sturation from second pregnancy to December, 1965. After that time menstruation reappeared with 20 day interval during 3 months. From March 1966 genital bleeding was noticed. It was small in amount and fresh red in color. Endometrial biopsy showed proliferative phase.

At necropsy 270 cc of straw-colored clear fluid was found in the pericardial cavity, but the pericardial lining was smooth. The heart weighed 420 g. Both the right atrium and ventricle were markedly dilated. The muscle of the right ventricle was hypertrophied (0.8 cm in thickness), whereas that of the left one was normal (1.0 cm in thickness). In the endocardium of the right ventricle some whitish patches were noticed. Valves were all normal. There was no defect in the septum. The foramen ovale was completely closed. The mitral circumference was 9.0 cm, the tricuspid 11.0 cm, the aortic 6.0 cm and the pulmonic 7.5 cm. The pulmonary artery was dilated both in the trunk and branches, and yellowish atheromatous plaques were noticed, while the lumen of the aorta showed no such finding. Macroscopic examination did not detect any thrombus or embolus in the pulmonary arteries. The ductus arteriosus was closed. The lungs were dark and reddish in color. The liver weighed 1,150 g and showed a nutmeg appearance. The spleen and kidneys were normal except for congestion. Histologically, alveoli showed no evidence of fibrosis. Bronchus and bronchial branches were normal. In pulmonary arteries thickening of the intima was observed (Fig. 5). The small vessels of the lungs showed narrowing of the lumen and obstruction (Fig. 6). In some sections fibrin-like substances were deposited in the lumen. Careful microscopic examination disclosed granulation tissues in the wall of narrowed vessels (Fig. 7). There were hematoxylin-stained amorphous or fine reticular substances (Fig. 8a), some times with peripheral eosinophilic zone (Fig. 8b), in the alveolar capil-

![Fig. 5. Thickening of the intima of a larger pulmonary artery. The upper two thirds of the photograph is occupied by the thickened intima. × 100.](image)

![Fig. 6 (a). Occlusion of a branch of pulmonary artery. × 100.](image)

![Fig. 6 (b). Stenosis of a small branch of the pulmonary artery by fibrous tissue. × 200.](image)

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lary lumen. These substances seem to be remnants of some kind of cells. Other organ such as the liver, the spleen and kidneys showed also congestion.

**DISCUSSION**

Pulmonary hypertension is divided into two categories: Primary pulmonary hypertension and secondary pulmonary hypertension. The secondary pulmonary hypertension is commonly encountered in cardiological laboratories. DEXTER divided the diseases associated with the secondary pulmonary hypertension into four major categories; diffuse parenchymal diseases, certain types of congenital heart disease, mitral stenosis and left ventricular failure of any etiology and diffuse pulmonary vascular disease.

Primary pulmonary hypertension, in which any obvious cause to produce pulmonary hypertension is not found clinically and pathologically, is rather rare. Criteria made by McGuire et al. to confirm the existence of the primary pulmonary hypertension are as follows; 1) the demonstration of right ventricular hypertrophy in the absence of any other cardiac abnormality, 2) the demonstration, by cardiac catheterization of an elevated pulmonary artery pressure and of a normal pulmonary wedge pressure, and 3) absence at necropsy of occlusive lesions in the pulmonary vascular trees unless such lesions are so sparse that they could not possibly account for the hypertension in this circuit. In this case, while the patient was alive, secondary pulmonary hypertension
due to congenital defect was suspected. However, postmortem autopsy excluded congenital and acquired heart diseases. Although an elevated pulmonary pressure was not demonstrated clinically owing to failure to insert a catheter into the pulmonary artery, it was demonstrated in the autopsy that the pulmonary arteries had atheromatous changes; an evidence of the pulmonary hypertension. Furthermore there were no other gross findings of the parenchymal disease in the lungs. Thus, it was concluded that the patient had so-called primary pulmonary hypertension.

Etiology of the primary pulmonary hypertension has been discussed by many authors. Some authors suspected changes in the pulmonary arteries. For example, Evans et al.\textsuperscript{18} attributed the disease to congenital abnormality of pulmonary vessels, and Heath and Edwards\textsuperscript{14} to maintenance of the fatal pattern of pulmonary vessels. Collagen disease, arthritis\textsuperscript{15} and Raynaud's disease\textsuperscript{15,16} may be related to this condition. As a factor to cause pulmonary hypertension Farrar\textsuperscript{17} considered immunological reaction, referring to Grove's experiment in which pulmonary vasoconstriction was observed in rabbit. Rawson and Worske\textsuperscript{15} reported a case of pulmonary hypertension associated with finding of Hashimoto's disease. These findings suggest that the third criterion of McGuire et al. is not reasonable.

In another point of view, the pattern of distribution of sex and age in the primary pulmonary hypertension is very interesting. Most of cases are females; all of 3 cases by Dresdale\textsuperscript{19}, all of 3 cases by East\textsuperscript{19}, all of 3 cases by James\textsuperscript{20}, all of 4 cases by Kuida et al.\textsuperscript{21}, all of 3 cases by Parry and Verel\textsuperscript{22}, all of 4 cases by Rawson\textsuperscript{15}, 1 case by Rosen et al.\textsuperscript{23}, 9 of 10 cases by Shepherd et al.\textsuperscript{24}, and all of 5 cases by Yu\textsuperscript{1}. The majority of reported cases were distributed between ages of 20 and 40. This condition seems to occur in the reproducing period of female in almost all cases. Therefore, it is likely that the primary pulmonary hypertension is related to menstrual cycle, venous thrombosis during pregnancy\textsuperscript{25} and amniotic embolism\textsuperscript{24}. In our case the history that symptoms appeared two months after the delivery seems to suggest this possibility. As well known, masses of trophoblastic tissue and even of villi are often broken off and swept into the maternal blood stream, finding lodging most often in the lungs. This deportation of villi is a perfectly normal process, constituting a physiologic type of embolism, but it may in some instances be abnormal, if for example abnormally large amount of deportation of villi occurs. Here again, the so-called primary pulmonary hypertension seems to be attributed to the pathology of the pulmonary arteries.

Naeve\textsuperscript{26} reported 6 cases of pulmonary hypertension associated with portal hypertension and stated that a possible origin of pulmonary emboli was portal thrombi and that the pulmonary arterial lesion in his cases from intravascular thrombosis within the lesser circulation itself. It is therefore, possible that some cases reported as primary pulmonary hypertension were induced by wide spread embolization\textsuperscript{15,16} due to silent manifestation of thrombophlebitis\textsuperscript{11}, pelvic lesion, abnormal absorption of amniotic fluid and organized thrombi\textsuperscript{15}. The experimental studies that pulmonary hypertension was made with intravenous injection of blood clots into rabbits\textsuperscript{27,28} and of Lycopodium spores into dogs\textsuperscript{29} sustain these deductions. Heard\textsuperscript{27} demonstrated that worm clots were converted into fibrous tissue in the pulmonary arteries of rabbits within a month or six weeks.

Although there were no marked gross findings in the lung parenchyma in our case except for the atheromatous plaques on the intima of the pulmonary arteries, histological examination revealed proliferation of the intima, and stenotic and occlusive lesions in small arteries and arterioles of the lungs. The concentric intimal thickening with atheromatosis may be interpreted as an effect of prolonged pulmonary hypertension. However, eccentric narrowing of the lumen due to granulation tissue represents organized thrombi or emboli. There were hematoxylin-stained bodies in the lumen of alveolar capillaries. Some of the hematoxylin-stained bodies have eosinophilic peripheral zone, which seems to be degenerated cytoplasm. As a whole, therefore, bodies in the vessels might represent a part of villi, especially trophoblastic tissue. The question what a role

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the hematoxylin-stained bodies in the vessels played in our case remains unanswered. However, it is not unlikely that they might be a remnant of emboli originating in absorption of placental tissue, or amniotic fluid and that they could be the cause of granulation tissue in pulmonary vessels.

Although etiology and pathogenesis of primary pulmonary hypertension is not yet understood, many observations mentioned above, especially the pattern of distribution of sex and age, and high probability of deportation of villi into the maternal blood stream even during the normal pregnancy strongly suggest embolism or thrombosis in the pulmonary circuit as a cause of primary pulmonary hypertension. The findings on the case presented here also support this point of view. These observations can also explain the reason why so-called primary pulmonary hypertension occurs so frequently in the female reproducing period.

SUMMARY

A case of primary pulmonary hypertension of a 30-year-old female was reported. The onset of symptoms was noticed 2 months after the second delivery. The patient died one year later thereafter. Autopsy findings did not reveal any definite gross anatomical evidence to cause pulmonary hypertension. Histological examination demonstrated concentric and eccentric thickening of the intima of pulmonary arteries and arterioles, stenosis and obliterative lesions in smaller arteries and arterioles, and hematoxylin-stained bodies in these vessels. The etiology of primary pulmonary hypertension was discussed, especially in regard to the role of the reproducing period of female.

REFERENCE