Pulmonary Capillary Hemangiomatosis With Severe Pulmonary Hypertension

Koji Ito, MD; Toshihiro Ichiki, MD; Keiji Ohi, MD; Kensuke Egashira, MD; Mituhiko Ohta, MD; Kenichi Taguchi, MD*; Akira Takeshita, MD

Pulmonary capillary hemangiomatosis (PCH) is a rare idiopathic lung disorder that occurs in young patients and leads to pulmonary hypertension (PH). It is difficult to diagnosis in the early stage and is often mistaken for primary PH; in almost all cases of PCH, the correct diagnosis is not made until autopsy. In the present case of PCH, the patient had severe pulmonary hypertension and died of respiratory failure. Pathologically, PCH is characterized by proliferation of benign thin-walled capillary sized blood vessels in the lung parenchyma. (*Circ J* 2003; 67: 793–795)

Key Words: Epoprostenol; Pulmonary capillary hemangiomatosis; Pulmonary hypertension

A 25-year-old man presented in 1998 with the complaint of progressive dyspnea on exertion and was admitted to hospital in August 1999. Cardiac catheterization revealed moderate pulmonary hypertension (PH; pulmonary artery pressure 61/33 mmHg). Congenital heart disease and left-sided heart failure were excluded by echocardiography. Collagen disease and liver disease were ruled out by negative results for the autoantibody test and liver function test. Furthermore, a perfusion lung scan did not show any perfusion defects, which excluded pulmonary thromboembolism as a cause of PH!

An acute challenge test with O₂ inhalation or continuous infusion of epoprostenol (PGI₂) under right heart catheterization showed a moderate decrease in pulmonary artery pressure. The patient then had a catheter implanted in superior vena cava and continuous infusion of epoprostenol was initiated, as well as home O₂ therapy and an anticoagulation regimen with warfarin.

Later, after the patient had been discharged, serial Doppler echocardiography revealed an increase in pulmonary pressure despite an increase in the dose of infused epoprostenol (maximum dose: 10 ng·kg⁻¹·min⁻¹). The patient was readmitted in February 2000 because of exacerbation of the dyspnea on exertion. Physical examination showed an accentuated pulmonary component of the second heart sound and right ventricular heave. There was a prominent V wave of the jugular vein and hepatojugular reflux was observed. Marked hepatomegaly was also present, but without overt edema of the lower limbs. An electrocardiogram showed right ventricular hypertrophy with right heart strain and tachycardia. Right axis deviation and right ventricular hypertrophy had progressed between the initial and current admission (Fig 1).

Echocardiography showed an increase in pulmonary artery pressure and enlargement of both the right atrium and right ventricle with severe tricuspid regurgitation; left ventricular function was preserved. Measurement of arterial blood gases with inhalation of 15 L/min of O₂ showed a pH of 7.437, CO₂ tension of 24.4 mmHg and O₂ tension of

Fig 1. Electrocardiogram showing right ventricular hypertrophy with right heart strain and right axis deviation. (A) Initial admission in August 1999: heart rate 71 beats/min and (B) current admission in February 2000: heart rate 128 beats/min.

(Received December 21, 2001; revised manuscript received April 8, 2002; accepted April 11, 2002)

Departments of Cardiovascular Medicine and *Anatomical Pathology, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Mailing address: Toshihiro Ichiki, MD, Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Science, 3-1-1 Maidashi, Higashi-ku, 812-8582 Fukuoka, Japan. E-mail: ichiki@cardiol.med.kyushu-u.ac.jp

Fig 2. (A) Chest X-ray shows enlargement of the main pulmonary artery and a reticulonodular shadow in both lower lung fields. (B) High-resolution computed tomographic scan demonstrates multiple centrilobular nodules.

Fig 3. Low magnification (A) and high magnification (B) views of lung histology show proliferation of thin-walled capillaries involving the alveolar septa and secondary vascular changes with severe thickening of small arteries (hematoxylin–eosin). Low magnification (C) and high magnification (D) views of immunohistochemistry with an anti-CD31 antibody that recognizes vascular endothelium show proliferation of capillary sized vessels.

67.2 mmHg. Chest radiography showed substantial enlargement of the main pulmonary artery and a coarse reticulonodular shadow in both lower lung fields (Fig 2A).

Computed tomography demonstrated multiple, small, ill-defined nodules (Fig 2B), which together with the radiography results suggested that the cause of the PH was pulmonary capillary hemangiomatosis rather than primary PH. Pulmonary pressure measured with a Swan-Ganz catheter was 79/49 mmHg under inhalation of 15 L/min of O₂ and infusion of epoprostenol.

The respiratory failure progressed despite maximal doses of epoprostenol. The patient underwent nitric oxide inhalation, which reduced the pulmonary artery pressure in the challenge test of his initial admission. However, the patient's condition gradually exacerbated and he died in May 2000 from respiratory failure.

At autopsy, the heart weighed 530 g and had marked right ventricular enlargement and hypertrophy. Both lung were slightly congested (right lung 810 g; left lung 640 g) with multiple small gray nodules in the parenchyma. Microscopic examination showed irregular nodular proliferation

of small capillary sized vessels filled with red blood cells (Fig 3A,B). Immunohistochemical examination of the lung with anti-CD31 antibody that recognizes platelet/endothelial cell adhesion molecule confirmed proliferation of capillary sized vessels (Fig 3C,D). The endothelium did not show cytologic atypia. No venous occlusion was observed. Pulmonary arterioles showed substantial medial hypertrophy, indicative of PH. These histological and immunohistochemical findings were considered compatible with a diagnosis of pulmonary capillary hemangiomatosis (PCH).

Discussion

PCH is a rare cause of pulmonary hypertension and was first reported by Wagenvoort et al in 1978.² Most of the patients are 20–40 years of age, as was the present case, and the earliest symptom is a gradual onset of shortness of breath on exertion.³ Because patients with primary PH also frequently complain of the same symptom, PCH is often misdiagnosed. Although hemoptysis is a symptom of PCH, it is observed in only 30% of the patients and is non-specific.

ic.³ Therefore, careful follow-up by chest radiography has been recommended because PCH typically has a characteristic radiographic feature of a diffuse coarse reticulonodular pattern. Computed tomography usually shows a mosaic pattern of attenuation of pulmonary parenchyma and lobular ground-glass opacification in the area of increased pulmonary perfusion.^{4,5} We observed both these radiographic features of PCH in the present patient.

The typical clinical course of PCH is rapid deterioration because of the progressive increase in pulmonary artery pressure, which leads to right ventricular failure and death. Although a case of successful treatment of PCH with interferon has been reported,⁶ the best treatment for PCH is bilateral lung transplantation.³

Although it is difficult, diagnosis in the early stage is -2a important. In the present case, an acute challenge test of epoprostenol decreased the pulmonary artery pressure and therefore continuous infusion of epoprostenol was instituted; however, both the dyspnea on exertion and the pulmonary artery pressure gradually worsened. The same clinical course was reported by Lippert et al.³ It is reported that epoprostenol may cause pulmonary edema in patients with pulmonary occlusive diseases such as PCH and pulmonary veno-occlusive disease,^{7,8} but we did not observe pulmonary edema in this case, which suggests that epoprostenol may have been effective in the early stage of PCH.

The histopathological examination at autopsy showed proliferation of capillary sized vessels³ and immunostaining with an antibody against CD31 confirmed it. Havlik et al.⁹ found incidental PCH-like foci in 5.7% of autopsy cases without any symptoms of PH; the distribution of the foci was local and the patients were old men, so that may be a different entity from PCH, which affects young adults of both sexes and has diffuse histopathological changes. Umezu et al.¹⁰ reported an autopsy case of PCH without any evidence of PH in which proliferation of capillaries was observed in the alveolar and bronchial walls, but not in the vascular walls; however, most patients with PCH, includ-

ing the present case, have PH and related symptoms because of the diffuse proliferation of capillaries. Because PCH is a rare disorder, it is not clear at this point whether PCH without PH represents an early stage of PCH or is a different class of PCH.

The definitive diagnosis of PCH is based on histopathological findings, but lung biopsy is usually impossible because of the critical respiratory condition of PCH patients at the time of presentation. Special attention should be given to the radiographic findings in patients with PH and lung or heart-lung transplantation should be considered when the diagnosis of PCH is made in the early stage.

References

1. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet* 1998; **352**: 719–725.
2. Wagenvoort CA, Beetsma A, Spijker J. Capillary hemangiomatosis of the lung. *Histopathology* 1978; **2**: 401–406.
3. Lippert JL, White CS, Cameron EW, Sun CC, Liang X, Rubin LJ. Pulmonary capillary hemangiomatosis: Radiographic appearance. *J Thorac Imaging* 1998; **13**: 49–51.
4. Langleben D, Henegham JM, Batten AP, Wang NS, Fitch N, Schlesingen RD, et al. Familial pulmonary capillary hemangiomatosis resulting in primary pulmonary hypertension. *Ann Intern Med* 1988; **109**: 106–109.
5. Masur Y, Remberger K. Pulmonary capillary hemangiomatosis as a rare cause of pulmonary hypertension. *Pathol Res Pract* 1996; **192**: 290–295.
6. White CW, Sondheimer HM, Crouch EC, Wilson H, Fan LL. Treatment of pulmonary hemangiomatosis with recombinant interferon alfa-2a. *N Engl J Med* 1989; **320**: 1197–1200.
7. Humbert M, Maitre S, Capron F, Rabin H, Musset D, Simonneau G. Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. *Am J Respir Crit Care Med* 1998; **157**: 1681–1685.
8. Veeraraghavan S, Koss MN, Sharma OP. Pulmonary veno-occlusive disease. *Curr Opin Pulm Med* 1999; **5**: 310–313.
9. Havik DM, Massie LW, Williams WL, Crooks LA. capillary hemangiomatosis-like foci An autopsy study of 8 cases. *Am J Clin Pathol* 2000; **113**: 655–662.
10. Umezu H, Naito M, Yagisawa K, Hattori A, Aizawa Y. An autopsy case of pulmonary capillary hemangiomatosis without evidence of pulmonary hypertension. *Virchows Arch* 2001; **439**: 586–592.