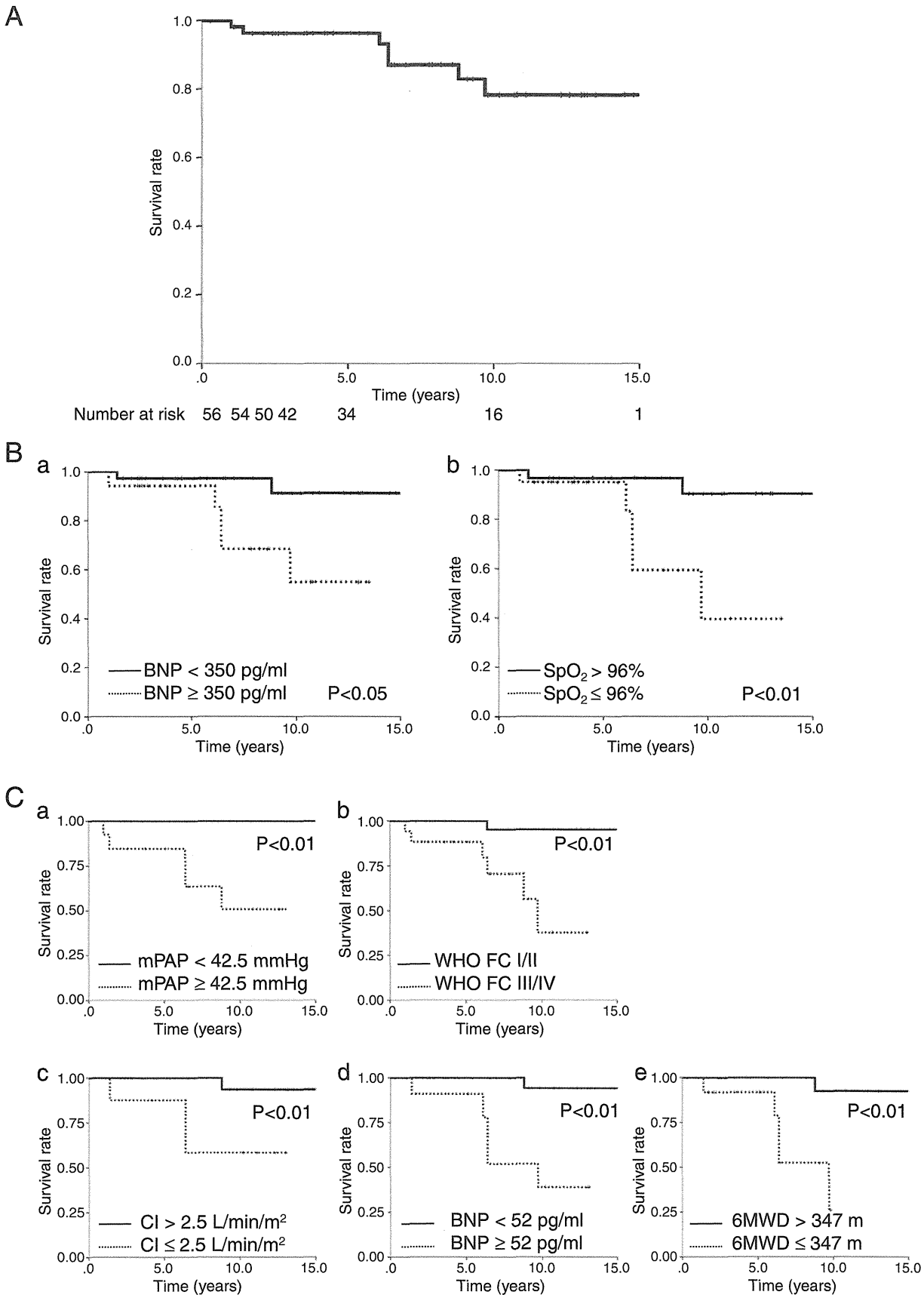

Fig. 1. (A) Mean survival time from the diagnosis was 14.9 ± 0.8 years (95% CI, 13.4–16.4 years), with 1-, 2-, 3-, 5- and 10-year survival rates of 98, 96, 96, 96 and 78%, respectively. (B) Survival rate of patients stratified by parameters at baseline. a: Survival rate of patients with BNP ≥350 pg/mL at baseline was significantly worse than patients with BNP <350 pg/mL ($P < 0.05$). b: Survival rate of patients with SpO_2 ≤96% at baseline was significantly worse than patients with SpO_2 >96% ($P < 0.01$). (C) Parameters significant in the univariate analysis (a: mPAP, b: WHO functional class (FC), c: cardiac index (CI), d: BNP, e: 6MWD) could be used to stratify the prognosis of patients ($P < 0.01$).

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Table 1
Clinical and hemodynamic data of survivors and non-survivors at baseline.

	Survivor ($n = 49$)	Non-survivor ($n = 7$)	P
Age, years	33 ± 18	25 ± 10	0.26
Male, *n* (%)	14 (29)	1 (14)	0.43
HPAH, *n* (%)	10 (20)	0 (0)	0.41
WHO functional class (I/II/III/IV)	3 (0/2/34/13)	4 (0/0/2/5)	<0.01
6MWD (m)	257 ± 166	103 ± 179	<0.05
BNP (pg/mL)	260 ± 307	705 ± 556	<0.01
Uric acid (mg/dL)	6.3 ± 2.0	6.7 ± 1.0	0.66
mPAP (mm Hg)	61 ± 17	62 ± 14	0.95
RAP (mm Hg)	8 ± 4	13 ± 9	<0.05
PCWP (mm Hg)	9 ± 3	10 ± 5	0.82
SvO_2 (%)	66.1 ± 8.7	65.4 ± 10.1	0.86
Cardiac index (L/min/m^2)	2.4 ± 0.9	2.4 ± 0.9	0.82
PVR (dyn·s/cm^5)	1391 ± 615	1375 ± 537	0.96
Heart rate (bpm)	74 ± 16	86 ± 15	0.07
SpO_2 (%)	97 ± 3	95 ± 3	0.08
Treatment			
Oral PGI_2	9 (18)	0 (0)	0.22
IV PGI_2	37 (76)	6 (86)	0.55
Dose of epoprostenol (ng/kg/min)	79.6 ± 43.2	54.0 ± 47.8	0.19
ERA	34 (69)	4 (57)	0.52
PDE5 inhibitor	28 (57)	1 (14)	<0.05
Monotherapy	10 (20)	3 (43)	0.24
Combination therapy	38 (78)	4 (57)	0.24
Number of PAH-targeted drugs: 2	16 (33)	4 (57)	0.21
Number of PAH-targeted drugs: 3	22 (45)	0 (0)	<0.05
Warfarin	11 (22)	2 (29)	0.72
Oxygen therapy	46 (94)	7 (100)	0.50

Values other than WHO functional class are expressed as mean ± SD. WHO functional class is presented as the median and number of patients in each class. HPAH: hereditary pulmonary arterial hypertension, 6MWD: 6-miute walk distance, BNP: brain natriuretic peptide, mPAP: mean pulmonary arterial pressure, RAP: right atrial pressure, PCWP: pulmonary capillary wedge pressure; SvO_2: mixed venous oxygen saturation; PVR: pulmonary vascular resistance, SpO_2: oxygen saturation, PGI_2: prostacyclin; IV: intravenous; ERA: endothelin receptor antagonist, and PDE5: phosphodiesterase type 5.

Hemodynamic parameters (mPAP, RAP, SvO_2, cardiac index, and PVR) were also significantly improved from those at baseline ($P < 0.01$).

Prognostic factors related to survival

The Cox proportional hazard model was used to estimate the risk factors for mortality based on the baseline data of patients. Age, sex or HPAH did not correlate with survival. Whether the patient was an incident case or prevalent case or time between the diagnosis and initiation of treatment or study enrollment was not related to survival. WHO functional class at diagnosis and at referral was not correlated with survival. BNP, RAP, and SpO_2 were important for predicting the prognosis in the univariate analysis. In the multivariate analysis, none of the baseline parameters were predictors of survival. ROC curves were constructed to determine optimal threshold values for baseline BNP, RAP, and SpO_2. The cutoff value for RAP was 10 mm Hg, but this could not be used to stratify survival. Patients with a BNP level ≥350 pg/mL and SpO_2 ≤96% at baseline had a significantly worse prognosis (Fig. 1B). Patients who died during the study period did not have any pulmonary diseases. They were severely ill with overt heart failure at referral and oxygen saturation dropped because of it.

With regard to follow-up data, WHO functional classes I and II (HR, 0.061; 95% CI, 0.007–0.512; $P = 0.01$), 6MWD (HR, 0.993; 95% CI, 0.989–0.998; $P < 0.01$), BNP (HR, 1.003; 95% CI, 1.001–1.005; $P < 0.01$), mPAP (HR, 1.101; 95% CI, 1.045–1.161; $P < 0.01$), RAP (HR, 1.297; 95% CI, 1.030–1.631; $P = 0.03$), and cardiac index (HR, 0.027; 95% CI, 0.001–0.650; $P = 0.03$) were important for predicting the prognosis in the univariate analysis. Neither PAH-targeted drug was associated with the prognosis. Based on the area under the curve (AUC) calculated from the ROC curves, cutoff values were calculated: mPAP (AUC, 0.956; cutoff value, 42.5 mm Hg), cardiac index (0.904; 2.5 L/min/m^2), BNP (0.885; 52 pg/mL), and 6MWD (0.883; 347 m). Cutoff values for these four parameters and WHO functional classes I and II/III and IV did stratify survival (Fig. 1C). However, none of these parameters at follow-up was a predictor of survival in the multivariate analysis.

Table 2
Clinical and hemodynamic data before and after treatment.

	Baseline	Follow-up	P
Age, years	32 ± 17		
WHO functional class (I/II/III/IV)	3 (0/1/38/17)	2 (0/38/15/3)	<0.01
6MWD (m)	234 ± 174	378 ± 114	<0.01
BNP (pg/mL)	313 ± 372	67 ± 156	<0.01
Uric acid (mg/dL)	6.4 ± 1.9	6.2 ± 1.7	0.70
mPAP (mm Hg)	63 ± 15	35 ± 10	<0.01
RAP (mm Hg)	8 ± 4	5 ± 4	<0.01
PCWP (mm Hg)	9 ± 3	8 ± 4	0.31
SvO_2 (%)	66.2 ± 8.9	77.2 ± 5.7	<0.01
Cardiac index (L/min/m^2)	2.3 ± 0.8	3.5 ± 0.9	<0.01
PVR (dyn·s/cm^5)	1473 ± 600	481 ± 421	<0.01
Heart rate (bpm)	76 ± 17	82 ± 18	0.09
SpO_2 (%)	97 ± 3	98 ± 3	0.14

Abbreviations are as stated in Table 1. Data were evaluated in 56 patients except for hemodynamic parameters, that were evaluated in 43 patients who underwent follow-up right-heart catheterization >3 months after initial catheterization at our hospital.

Discussion

The present study is the first report on the survival of Japanese patients with I/HPAH who would have benefitted from recent progress in the development of PAH-targeted drugs in the modern era. Each PAH-targeted drug has been reported to improve the prognosis or progression of PAH (Sitbon et al., 2002; McLaughlin et al., 2005; Rubin et al., 2011). There have been improvements compared with those in the National Institutes of Health (NIH) Registry (D'Alonzo et al., 1991) but overall survival has been reported to be unsatisfactory despite such improvements in treatment options (Humbert et al., 2010; Benza et al., 2012; Zhang et al., 2011).

Our data demonstrated that after treatment, hemodynamic parameters improved significantly. mPAP decreased significantly by 28 mm Hg from 63 ± 15 mm Hg with improved cardiac index. As a result, PVR was also improved significantly. These results are consistent with our reports showing that epoprostenol and bosentan can reduce mPAP (Akagi et al., 2008, 2010). The baseline hemodynamic parameters were comparable or even worse than those reported previously (Humbert et al., 2010; Lee et al., 2012; Zhang et al., 2011; Badesch et al., 2010), but the improvement was more significant. This difference could have led to a significantly better prognosis. None of the baseline hemodynamic parameters (mPAP, cardiac index, or PVR) was a prognostic factor for survival. This suggests that long-term survival can be achieved even if severe pulmonary hypertension is confirmed by hemodynamic means (high mPAP and PVR). With regard to follow-up data, WHO functional classes I and II, mPAP <42.5 mm Hg, cardiac index >2.5 L/min/m^2, BNP <52 pg/mL, and 6MWD >347 m were important for predicting the prognosis in the present study. A recent study demonstrated that changes in WHO functional class, cardiac index, SvO_2, and the level of N-terminal-pro BNP on follow-up data would be predictors of the prognosis (Nickel et al., 2012). In contrast to our study, mPAP was not included as a prognostic factor in their study, in which mPAP was unchanged despite the treatment. Considering that the initial abnormality of I/HPAH is a high mPAP, improvement of the mPAP would have led to improved survival of this cohort. In another type of pulmonary hypertension, chronic thromboembolic pulmonary hypertension, mPAP is indeed the determinant of the prognosis (Riedel et al., 1982; Lewczuk et al., 2001). In I/HPAH, reduction of mPAP might also be an important determinant for survival, as shown in Fig. 1C-a.

One distinct difference between our cohort and previous cohorts is the high prescription rate of PAH-targeted drugs. In Japan, there is an

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excellent national healthcare system that is supported by the government. Currently, PAH is allocated to a special program: the "Specified Disease Treatment Research Program". This program subsidizes medical care for patients with rare and intractable diseases. It also enables Japanese physicians to offer optimal treatment to patients. Epoprostenol has been reported to be the most potent vasodilator available, but it is expensive. In previous studies, the prescription rate of epoprostenol was not high; 0% in the NIH registry, 15% in a French registry, and 23% (prostanoids; not specified as epoprostenol) in a study examining the impact of follow-up data described above (Humbert et al., 2010; D'Alonzo et al., 1991; Nickel et al., 2012). In our cohort, epoprostenol was prescribed in 75% of patients. Based on a report stating a reduction of the mPAP of ≈9 mm Hg by a 1-year treatment with epoprostenol (Sitbon et al., 2002), the high prescription rate and long-term high dose of epoprostenol treatment and combination therapy including epoprostenol could have led to a large reduction in mPAP in our cohort. Combination therapy has been shown to be beneficial for patients, and upfront (rather than sequential combination) therapy is expected to be more beneficial (Vachiery & Gaine, 2012). However, upfront therapy is not always possible worldwide because of its high cost. Although a specific drug was not associated with the prognosis in the univariate Cox regression analysis in our cohort, there were significant differences in the prescription rate of PDE5 inhibitors and triple PAH-targeted therapy between survivors and non-survivors. In Japan, PDE5 inhibitors were approved relatively recently (in 2008). Non-survivors were mainly treated before that time, which could be one reason for this difference.

Another reason for the better overall survival could be a difference in ethnicity. One report from China showed better survival than that in Western countries (1- and 3-year survival estimates of 92.1% and 75.1%, respectively) (Zhang et al., 2011). This result is notable because patients often choose inexpensive medication or abandon treatment in China. Epoprostenol was not prescribed in this cohort. There might be a difference in the genetic background between Asians and Caucasians that leads to a different response to treatment.

Estimation of the risk factors for mortality using a univariate Cox proportional hazard model showed that BNP, RAP, and SpO_2 at baseline were important for the prediction of the prognosis. This result suggests that patients with I/HPAH cannot be treated successfully after establishment of severe heart failure, with BNP ≥350 pg/mL and SpO_2 ≤96% even at a referral center. This finding is consistent with reports stating that overt heart failure is a potent prognostic factor. It has also been reported that late referral to a pulmonary hypertension center is related to a delay in appropriate treatment that ultimately leads to heart failure and is a strong factor for mortality (Badagliacca et al., 2012).

The goal for treating patients with I/HPAH varies among physicians and is affected by the healthcare system of each country. Most clinical trials have set the end-point as an improvement in 6MWD. However, recently, the improvement of 6MWD has been shown not to be related to long-term survival (Savarese et al., 2012). In the present study, WHO functional class, mPAP, cardiac index, BNP, and 6MWD at follow-up were shown to be important for the prediction of the prognosis in univariate analysis. No parameters were shown to be significant in the multivariate analysis even though follow-up data (including hemodynamic parameters) were improved significantly compared with those at baseline. This finding might have been because our cohort was small and the number of events (disease-related death) was too small. Only seven (13%) subjects died out of all patients. This is a much lower number compared with those reported previously: 55% in the NIH registry, 29% in a French registry, and 49% in the study by Nickel et al. (Humbert et al., 2010; D'Alonzo et al., 1991; Nickel et al., 2012).

IPAH was originally reported to occur predominantly in younger women (D'Alonzo et al., 1991). Recently, it has been reported that in countries with aging populations, IPAH is diagnosed frequently in elderly patients (Hoeper et al., 2013). However, in the present study, patients were predominantly young women, similar to that reported in the NIH registry. Recently, it has also been reported that male patients with PAH have a worse prognosis (Humbert et al., 2010; Lee et al., 2012; Benza et al., 2012). However, our results showed that male sex was not a prognostic factor for survival.

This was a single-center retrospective study, so the possibility of selection bias and survivor bias could not be avoided. Our cohort involved 57% of prevalent cases, and this might be one reason why the survival seems better than that reported previously. The number of patients and events was small and there was variation in the follow-up period. These features could have affected the results of our study. A multicenter prospective study with scheduled repetitive catheterization is needed to confirm the importance of the improvement of hemodynamic data.

Conclusion

The present study revealed long-term survival of Japanese patients with I/HPAH treated at a single referral center. Patients with right-heart failure at referral had a poor prognosis. Hemodynamic parameters were improved significantly with treatment despite severe hemodynamic parameters at baseline. This observation could be related to the high prescription rates of PAH-targeted drugs in the present study. Further investigation with a multicenter registry is needed to reveal the prognostic factors in Japanese patients with I/HPAH.

Conflict of interest statement

H.M. received lecturer fees from GlaxoSmithKline, Actelion Pharmaceuticals Japan, and Nippon Shinyaku.

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INTERNAL MEDICINE

□ CASE REPORT □

Imatinib is Partially Effective for the Treatment of Pulmonary Capillary Hemangiomatosis

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Abstract

A 43-year-old man presented with dyspnea on exertion. Right heart catheterization demonstrated pulmonary arterial hypertension (PAH). He was treated with bosentan, sildenafil and intravenous epoprostenol. Despite the administration of such intensive therapy, the patient's condition deteriorated to a World Health Organization functional class (WHO-FC) of IV. He participated in a clinical trial of imatinib for PAH. After three months of treatment with imatinib, the chest X-ray and echocardiography findings improved, and the WHO-FC class was III. One year after, however, the PAH worsened again, and the patient died 2.6 years after the first diagnosis. At autopsy, patchy capillary proliferation was observed in the lungs. The definitive diagnosis was pulmonary capillary hemangiomatosis.

Key words: pulmonary hypertension, pulmonary capillary hemangiomatosis, imatinib, tyrosine kinase inhibitor

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Introduction

Pulmonary capillary hemangiomatosis (PCH) is an extraordinarily rare cause of pulmonary arterial hypertension (PAH). In the Dana Point classification, both PCH and pulmonary veno-occlusive disease (PVOD) are classified as Group 1' PAH (1). Patients with PCH typically survive for only two to three years unless they undergo lung transplantation (2). The definitive diagnosis depends solely on pathological findings. We herein present a case of PCH that was resistant to conventional PAH therapy, including bosentan, sildenafil and intravenous epoprostenol, but responsive to imatinib, which enabled the patient to return home for one year until his final admission.

Case Report

A 43-year-old man presented with progressive dyspnea on exertion. He had worked as a carpenter two years earlier. His past medical and familial history were unremarkable. He had never smoked and denied any illicit drug use. On a physical examination, his blood pressure was 95/65 mmHg, his heart rate was 105 bpm and his respiratory rate was 22 breaths/min. An electrocardiogram showed right ventricular hypertrophy with ST changes. The level of plasma brain natriuretic peptide (BNP) was 202 pg/mL. A Doppler echocardiogram demonstrated a peak tricuspid regurgitation pressure gradient of 70 mmHg. Pulmonary function tests showed a normal forced vital capacity (FVC) (3.10 L, 83.6% of the predicted value), normal forced expiratory volume 1.0% (FEV 1) (2.76 L, 86.8% of the predicted value) and normal FEV1/FVC ratio (86%); however, the diffusing capacity for carbon monoxide (DL_{CO}) was severely decreased (6.19, 22.5% of the predicted value). High-resolution computed tomography (HRCT) of the chest revealed centrilobular ground glass opacity, septal thickening and mediastinal lymph node enlargement. Medical examinations indicated no

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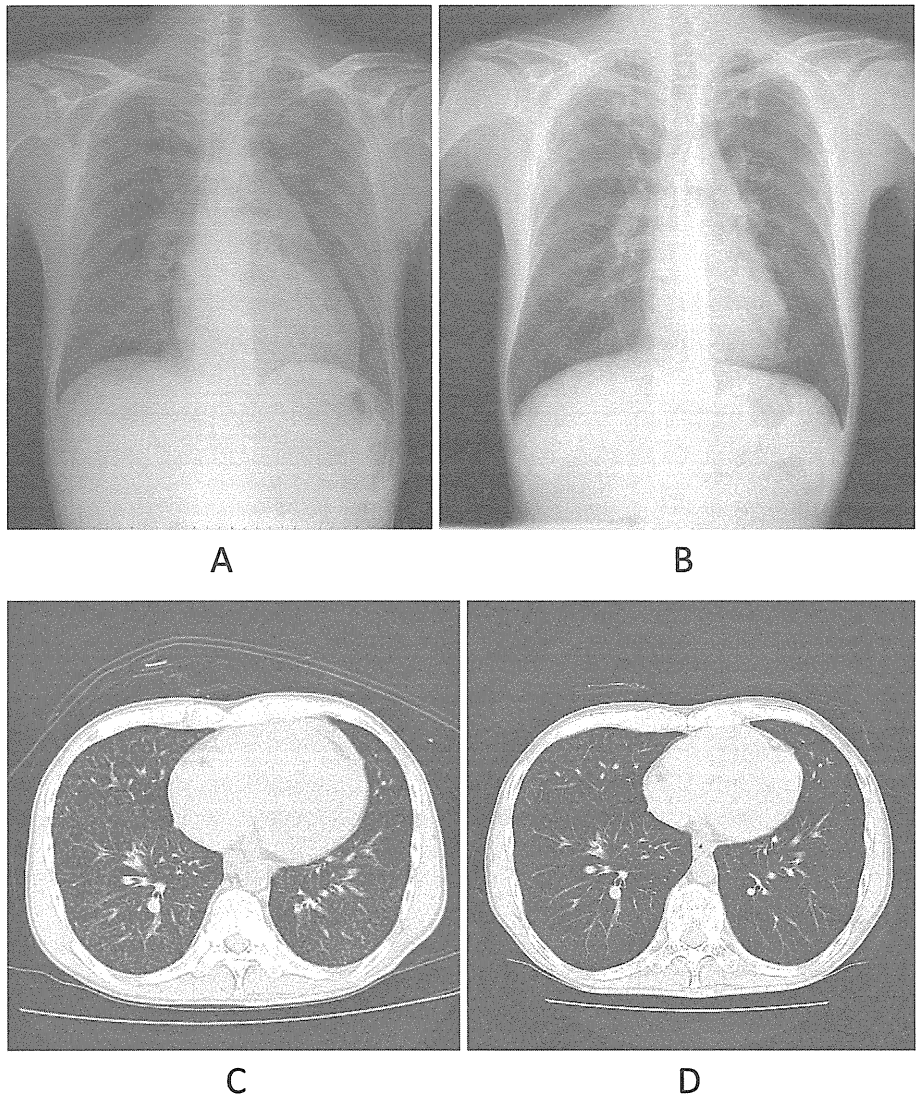

Figure 1. Chest X-ray and high-resolution computed tomography (HRCT) before and after imatinib treatment. A: A chest X-ray obtained before imatinib treatment showed dilation of the pulmonary artery trunk and cardiomegaly. B: A chest X-ray obtained after imatinib treatment showed improvements in the dilation of the pulmonary artery trunk and cardiomegaly. C: HRCT performed before imatinib treatment showed diffuse bilateral centrilobular ground glass opacity and septal thickening. D: HRCT performed after three months of imatinib treatment. The ground glass opacity and septal thickening had improved, and the pericardial effusion had decreased.

specific cause leading to pulmonary hypertension. Right heart catheterization demonstrated a pulmonary arterial pressure (PAP) of 64/22/35 mmHg (systolic/diastolic/mean) and a pulmonary capillary wedge pressure of 2 mmHg. The pulmonary vascular resistance (PVR) was 1,310 dynesec/cm^5. Perfusion lung scintigraphy did not show any abnormal perfusion defects. Therefore, we diagnosed the patient with idiopathic PAH or Group 1' PAH.

Treatment was initiated with bosentan, and both sildenafil and intravenous epoprostenol (maximum dose: 26 ng/kg/min) were carefully added. However, the patient's respiratory condition deteriorated with the development of pulmonary edema, and his arterial oxygen saturation on pulse oximetry (SpO_2) was 90.0% with inhalation of 10 L/min 100% oxygen using a face mask. He remained in World Health Organization functional class (WHO-FC) IV. Although lung transplantation was considered, the patient refused the procedure. Instead, we decided to administer imatinib after obtaining approval from the domestic ethics committee of the National Hospital Organization Okayama Medical Center. Soon after imatinib was started with an initial dose of 100 mg once per day, the patient's respiratory condition rapidly improved. The dose of imatinib was increased to 150 mg once per day, and the intravenous epoprostenol was tapered off. The patient's condition improved to WHO-FC III, with an SpO_2 of 98% with inhalation of 5 L of nasal oxygen. The cardiomegaly on chest X-rays and ground glass opacity and septal thickening on HRCT improved (Fig. 1). The degree of left ventricle compression was also reduced on an echocardiogram (Fig. 2). After three months of imatinib treat-

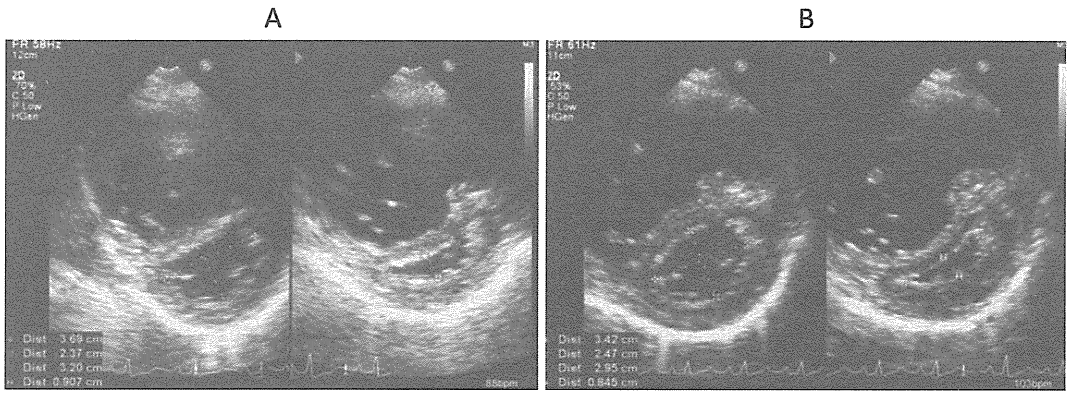

Figure 2. Parasternal short-axis view of an echocardiograms obtained before and after imatinib treatment. A: Before imatinib treatment. A flat septum and D-shaped left ventricle were observed. B: After three months of imatinib treatment. The flat septum and D-shaped left ventricle had improved.

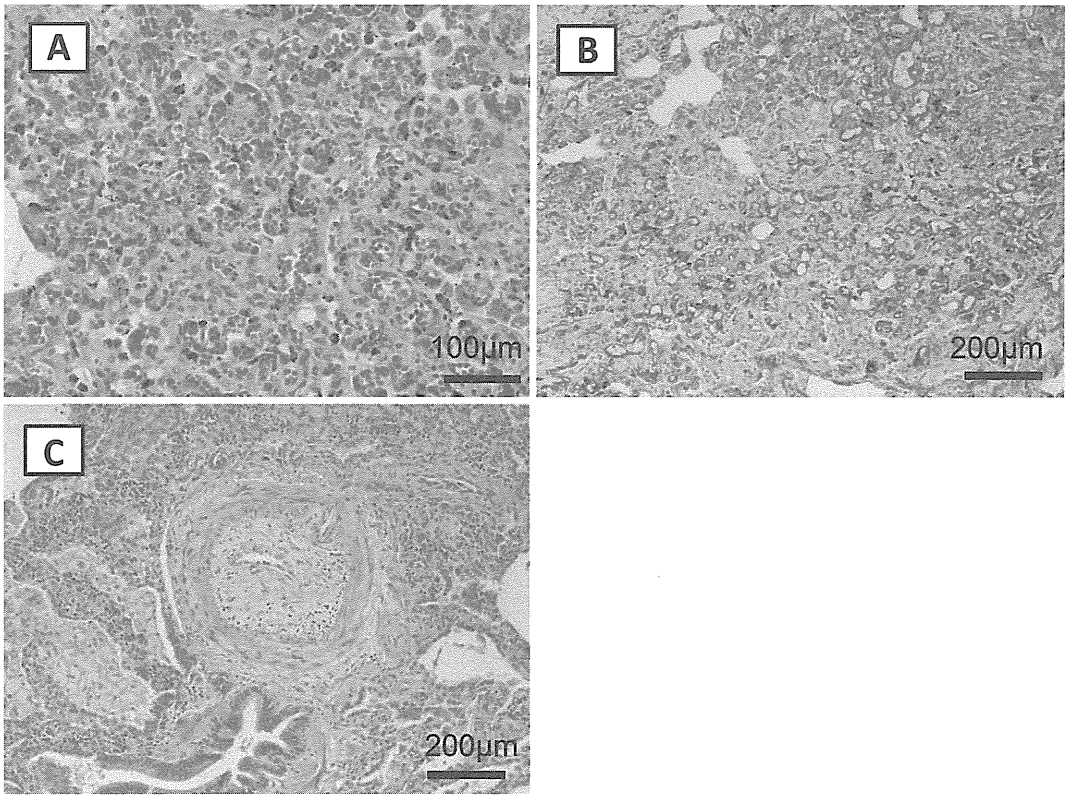

Figure 3. Histological findings of the pulmonary lesion. A: Nodular and hemangioma-like proliferation of capillaries in the alveolar walls. The capillaries are dilated and filled with red blood cells (Hematoxylin and Eosin staining; original magnification ×200). B: Immunostaining of CD34 highlighting proliferating capillaries (original magnification ×100). C: Some muscular arteries exhibited marked intimal fibrosis and occlusion of the lumen (Hematoxylin and Eosin staining; original magnification ×100).

ment, the patient was discharged home. He remained in WHO-FC class III, with a plasma BNP level of 71 pg/mL. One year after discharge, however, the dyspnea reappeared, and he again required hospitalization. The plasma BNP level increased to 1,037 pg/mL and the systolic PAP estimated on an echocardiogram increased to 135 mmHg. Right-sided heart failure rapidly progressed despite the initiation of catecholamine treatment for nine days after hospitalization, and the patient died 2.6 years after the first diagnosis. At autopsy, the pathological findings revealed dominant nodular and hemangioma-like proliferation of capillaries in the alveolar walls, and PCH was diagnosed (Fig. 3).

Discussion

Imatinib, a tyrosine kinase inhibitor, has been reported to

be effective in some cases of PAH (3-5); however, there are no precise case reports of PCH. In the present case, a diagnosis of PCH/PVOD was suspected based on the clinical, laboratory and HRCT findings (6, 7). The pathological findings revealed dominant patchy hemangioma-like capillary proliferation, although no venous fibrosis or occlusion were observed in any lobes of the lungs. The muscular arteries showed only mild intimal and medial thickening. Therefore, PCH was the definitive etiologic diagnosis in this patient.

In this case, the administration of imatinib rapidly improved the patient's symptoms, laboratory test results and echocardiography and HRCT findings. Among the medications prescribed for this patient, only imatinib proved effective enough to allow him to be discharged home and improved his quality of life. In a previous report of a case of PVOD, imatinib was added to diuretics, anticoagulants and epoprostenol, and neither bosentan nor sildenafil were used (3). However, in the present case, all PAH-targeted therapies were used. Therefore, it is clear that only imatinib was effective for this patient.

Imatinib may be specifically effective for PCH due to the inhibitory effects of several tyrosine kinase activities (3-5). Moreover, imatinib exhibits antiproliferative and pro-apoptotic effects on smooth muscle cells stimulated with platelet-derived growth factor (PDGF) in subjects with idiopathic PAH (8). There are several possible mechanisms by which imatinib may elicit pulmonary vasodilation. These include: (1) inhibition of PDGF receptor-mediated elevation of the intracellular Ca^{2+} levels (9); (2) inhibition of other off-target protein kinases, such as epidermal growth factor receptor, Src and protein kinase C (10-12); and (3) inhibition of c-Abl-mediated actin polymerization (13).

Imatinib may work in PAH patients with higher PVR values. In the International Multicentre PREvalence Study on Sepsis (IMPRESS) study, treatment with imatinib improved exercise capacity and hemodynamics in patients with advanced PAH already treated with two or more pulmonary vasodilators; however, serious adverse events and imatinib discontinuation were common (14). In particular, subdural hematomas developed in 4.2% of the patients treated with imatinib, all of which occurred in patients receiving concomitant anticoagulation. In the present case, the patient was not treated with oral anticoagulants, but rather with bosentan and sildenafil, and no obvious side effects caused by imatinib were observed.

Abe et al. reported that the administration of imatinib reduces a high right ventricular systolic pressure in pulmonary hypertensive rats (15). Imatinib therapy has also been reported to improve the arterial oxygen saturation (SaO_2), PVR and cardiac output, although the 6-minute walk distance as the primary end point did not change significantly (5). Meanwhile, a subanalysis showed that, among the patients with a PVR of ≥1,000 dynesec/cm^5 only, the pulmonary artery pressure, cardiac output and 6-minute walk distance significantly improved (6). These results suggest that the administration of imatinib in addition to other therapies, such as endothelin receptor blockers and phosphodiesterase-5 inhibitors, has the potential to be effective for severe pulmonary artery hypertension. In the present case, the PVR before treatment with imatinib was 1,310 dynesec/cm^5. Therefore, imatinib appeared to be effective for this patient.

Hatano M. et al. reported that treatment with imatinib improves the DL_{CO} because the medication decreases the serum PDGF concentration (16). However, it should be noted that the effects of imatinib were reduced after 1.5 years of treatment. Namely, the effects of imatinib may decrease with long-term treatment. Further studies are needed to investigate the long-term safety and efficacy of imatinib in patients with PCH.

In summary, imatinib was partially effective in a PCH patient who exhibited an inadequate response to bosentan, sildenafil and intravenous epoprostenol.

The authors state that they have no Conflict of Interest (COI).

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INTERNAL MEDICINE

□ CASE REPORT □

Pulmonary Tumor Thrombotic Microangiopathy with Circulatory Failure Treated with Imatinib

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Abstract

Pulmonary tumor thrombotic microangiopathy is a lethal, yet difficult to diagnose, complication of gastrointestinal carcinoma. Even if properly diagnosed, there is no treatment, especially after a circulatory collapse. We herein report a case of pulmonary tumor thrombotic microangiopathy with circulatory failure due to pulmonary hypertension. The patient was temporarily successfully treated with imatinib, an inhibitor of the platelet-derived growth factor receptor. Pulmonary hypertension was dramatically ameliorated and the patient was able to be weaned from percutaneous cardiopulmonary support within 20 days of treatment. Imatinib may be effective for ameliorating pulmonary hypertension that is caused by pulmonary tumor thrombotic microangiopathy.

Key words: pulmonary tumor thrombotic microangiopathy, circulatory failure, treatment, imatinib

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Introduction

Pulmonary tumor thrombotic microangiopathy (PTTM) presents with rapidly progressive pulmonary hypertension related to carcinoma (1). The condition was originally reported in 1990, and since then, more than 50 cases have been pathologically diagnosed at autopsy. However, a clinical diagnosis of PTTM is difficult. In addition, there have not yet been any reported cases of patients who survived after the development of severe pulmonary hypertension with circulatory failure due to PTTM.

Case Report

A 47-year-old woman with no previous medical history was referred to our hospital for further treatment of pulmonary hypertension in August 2007. She had a three month history of dry cough, general fatigue and dyspnea upon effort. She visited a nearby hospital, was diagnosed with pulmonary hypertension and admitted to the hospital. Two days later, she presented with syncope and was transferred to our hospital. At the time of admission, a continuous infusion of dopamine (3 μg/kg/min) and dobutamine (3 μg/kg/min) was required. Her oxygen saturation was 99% with oxygen supplementation at 5 L/min. Electrocardiography showed sinus tachycardia with an SIQIIITIII pattern and negative T wave in V2 and V3, thus suggesting acute right ventricular overload (Fig. 1A). A chest radiography showed dilated pulmonary arteries, cardiomegaly and congestion (Fig. 1B). A high-resolution computed tomography (CT) scan demonstrated a nodular shadow and septal thickening with a slight amount of pleural effusion in the lung (Fig. 1C). A contrast-enhanced CT scan showed no tumor emboli to be present in the pulmonary arteries (Fig. 1D). Due to impaired hemodynamics, we could not perform either lung perfusion scintigraphy or pulmonary angiography at the time of admission. Echocardiography showed a dilated right atrium and ventricle. A right heart catheterization revealed an elevated pulmonary arterial pressure and a reduced cardiac output (Fig. 2). We immediately started bosentan and epoprostenol therapy in order to treat pulmonary hypertension. On Day 9, despite treatment with a continuous infusion of epoprostenol (3.8 ng/kg/min) with catecholamines, the hemodynamic data deteriorated. She manifested circulatory collapse and needed percutaneous cardiopulmonary support. Imatinib, an inhibi-

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