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Case report

Four cases with group 3 out-of-proportion pulmonary hypertension with a favorable response to vasodilators

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ABSTRACT

Some patients with group 3 pulmonary hypertension (PH) (PH due to lung disease and/or hypoxia) exhibit disproportionately advanced or "out-of-proportion" PH. In the present case series, we document four consecutive patients with progressive out-of-proportion group 3 PH. All patients exhibited progressive dyspnea or peripheral edema and were treated by pulmonary artery hypertension (PAH)-specific vasodilator(s). At the follow-up assessment 3–4 months later, symptoms/signs and pulmonary hemodynamic measurements improved in all four patients (45 ± 8% decrease in pulmonary vascular resistance). Pulmonary oxygenation deteriorated in one patient but improved or did not significantly change in the remaining three cases. Importantly, the background lung parenchymal disease (early-onset chronic obstructive pulmonary disease, rheumatoid arthritis-associated interstitial pneumonia, and combined pulmonary fibrosis and emphysema) was stable upon progression of the right heart failure symptoms/signs, and also during the 3–4-month follow-up period in all cases. We herein describe the clinical features of the four cases and discuss the potential benefits and risks of PAH-specific treatment in this emerging population.

1. Introduction

Pulmonary hypertension (PH) is defined as mean pulmonary arterial pressure (MPAP) ≥25 mmHg at rest. PH is classified as group 3 when it develops as a result of lung disease and/or hypoxia.[1] Oxygen supplementation is the treatment of choice for this population,[1] whereas the use of pulmonary arterial hypertension (PAH)-specific vasodilators is not recommended because of the lack of evidence and possible deterioration of ventilation/perfusion mismatch and hypoxia.[2,3]

The degree of PH is modest in most group 3 PH cases.[4,5] However, recent studies have highlighted a subset of patients who exhibit disproportionately advanced or "out-of-proportion" PH.[6–8] This PH is clinically characterized by dyspnea insufficiently explained by lung mechanical disturbances[1] and, more recently, a German consensus group has proposed new criteria for this population.[7] It can be assumed that patients with Group 3 out-of-proportion PH have somewhat disease-specific vasculopathy and respond differently to PAH-specific drugs as compared with typical group 3 PH patients. Indeed, a few case reports have shown amelioration of pulmonary hemodynamics by PAH-specific vasodilators,[9,10] suggesting a promising role of PAH-specific agents in this subset.

In the present case report series, we document four consecutive patients with group 3 out-of-proportion PH, who favorably responded to PAH-specific vasodilators. We describe the clinical features of the four cases, and also discuss the potential benefits and risks of PAH-specific treatment in this emerging population.

2. Case reports

2.1. Case 1

In July 2010, a 46-year-old man with early-onset chronic obstructive pulmonary disease (COPD) was referred to our hospital due to progressive peripheral edema. High resolution computed tomography (HRCT) exhibited severe emphysematous change (Fig. 1A) and pulmonary function test (PFT) showed marked decrease in vital capacity (VC), forced expiratory volume in 1 s divided by forced vital capacity (FEV_1/FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) (Table 1). Echocardiography suggested severe PH and right heart catheterization (RHC) also noted increased MPAP, reduced cardiac index (CI) and elevated pulmonary vascular resistance (PVR). Cardiac magnetic resonance (CMR)-derived right ventricular ejection fraction (RVEF) was reduced. Overall clinical assessment suggested progression of PH and right heart failure, rather than exacerbation of COPD. Sildenafil (20 mg, t.i.d.) and, a week later, beraprost (120 μg, t.i.d.)

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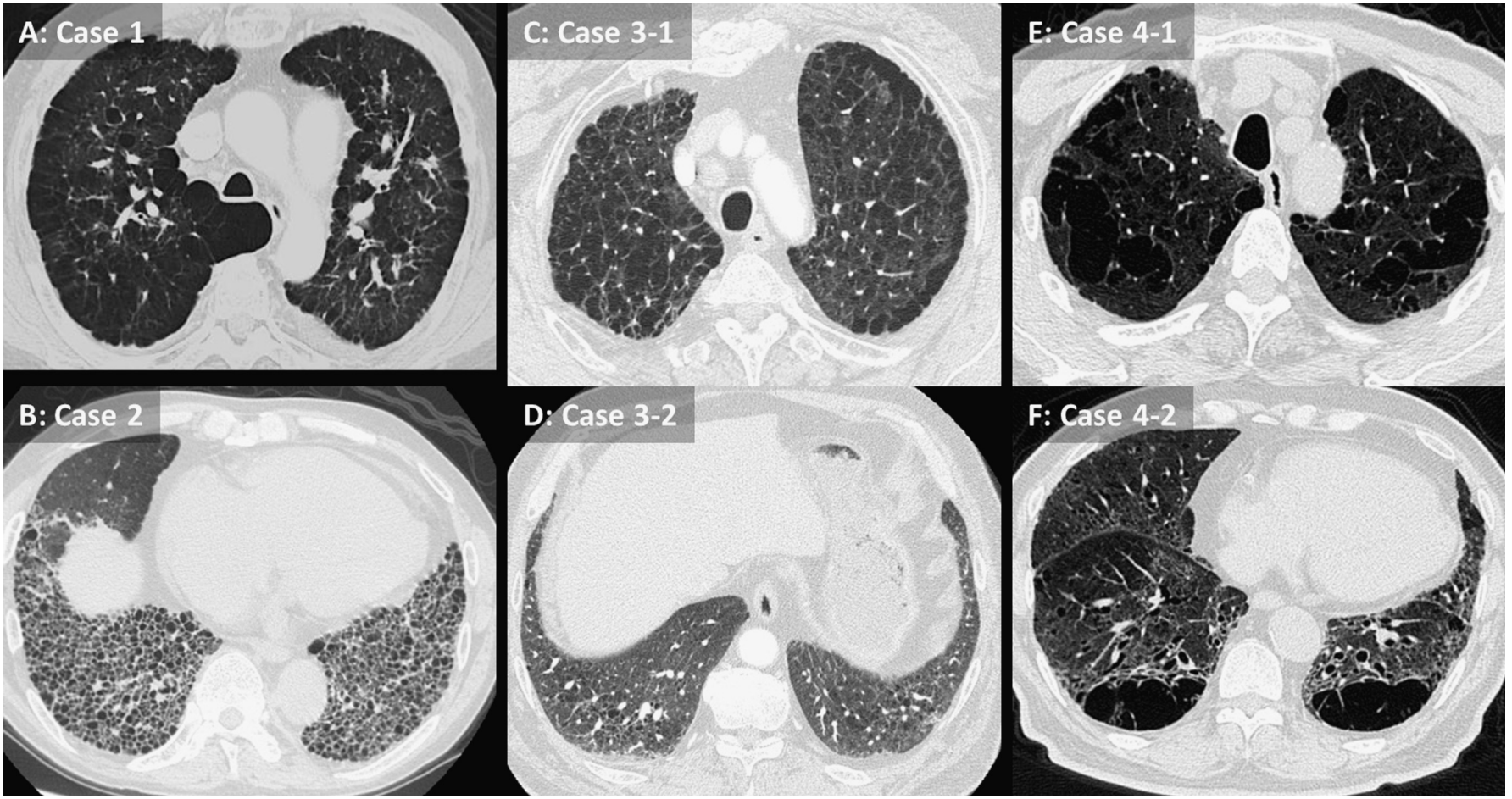

Fig. 1. High resolution chest computed tomography findings in four cases with out-of-proportion group 3 pulmonary hypertension: case 1, a 46-year-old man with early-onset chronic obstructive pulmonary disease (panel A); case 2, a 61-year-old man with rheumatoid arthritis-associated interstitial pneumonia (panel B); case 3, a 69-year-old man with combined pulmonary fibrosis and emphysema (panels C and D); case 4, an 86-year-old man with combined pulmonary fibrosis and emphysema (panels E and F).

Table 1
Demographics and responses to the vasodilating treatment of the four patients with group 3 out-of-proportion pulmonary hypertension.

	Case 1	Case 2	Case 3	Case 4
Baseline demographics				
Age (y)/gender	46/M	61/M	69/M	86/M
Background lung disease	COPD	CVD-IP	CPFE	CPFE
Pulmonary function test before vasodilator treatment				
VC (L) (%predicted)	2.31 (63.3)	1.99 (57.9)[a]	3.26 (102.8)	3.28 (108.8)
FEV_1 (L) (%predicted)	0.66 (21.5)	1.68 (63.1)[a]	1.79 (81.0)	2.26 (117.1)
FEV_1/FVC (%)	34.7	85.6[a]	55.6	71.74
%DLCO	28.4	23.2[a]	29.0	23.4
%DLCO/VA	38.9	39.3[a]	39.9	25.6
Clinical variables before and after vasodilator therapy				
PAH-specific vasodilators (dose)	Sildenafil (20 mg, t.i.d.) Beraprost (120 μg, t.i.d.)	Sildenafil (20 mg, t.i.d.)	Sildenafil (20 mg, t.i.d.) Bosentan (62.5 mg, b.i.d.)	Sildenafil (20 mg, t.i.d.)
Other treatment(s) for systemic/lung disease(s)	Tiotropium bromide (18 μg/day)	Predonisolone (5 mg/day)	Tiotropium bromide (18 μg/day)	
Duration between baseline and follow-up assessment	4 M	3 M	3 M	4 M
WHO Functional capacity	IV → III	IV → IV[a]	IV → IV[b]	III → II
PaO_2 (Torr)	61 → 45 (Room air)	62 → 115 (O_2 5 L → 5 L)	56 → 115 (O_2 9 L → 12 L)	85 → 81 (O_2 3 L → 3 L)
BNP (pg/ml)	2143 → 59.9	843 → 73	1390 → 32.8	81.3 → 27.8
Mean PAP (mmHg)	41 → 27	52 → 35	47 → 43	32 → 32
CI (L/min/m^2)	2.2 → 2.99	2.46 → 2.81	1.66 → 2.24	1.99 → 2.5
PVR (dyn s cm^{-5})	810 → 373	966 → 471	987 → 645	626 → 369
RVEF (%)	9.7 → 15.2	21.8 → 32.1	26.4 → 43.5	34.7 → 47.5

COPD, chronic obstructive pulmonary disease; CVD-IP, collagen vascular disease-interstitial pneumonia; CPFE, combined pulmonary fibrosis and emphysema; PAP, pulmonary artery pressure; CI, cardiac index; PVR, pulmonary vascular resistance; VC, vital capacity, FEV_1, forced expiratory volume in 1 s; RVEF, right ventricular ejection fraction.
[a] Pulmonary function test was conducted in Feb 2011.
[b] Resting short breath disappeared at follow-up.

were started in August 2010. He tolerated treatment well without acute side effects. At follow-up admission 3 months later, his exertional dyspnea and peripheral edema had improved. RHC showed significant improvement in MPAP, CI and PVR. CMR-derived RVEF had also improved, whereas arterial blood gas analysis (AGA) indicated deterioration of pulmonary oxygenation as compared with that before the vasodilator treatment (Table 1). PFT results did not change remarkably although tiotropium bromide inhalation (18 μg/day) was started with PAH-specific agents 3 months before.

2.2. Case 2

A 61-year-old man diagnosed with rheumatoid arthritis-associated interstitial pneumonia in 2009 noted progressive dyspnea, peripheral edema and hypoxemia in Dec 2011. HRCT revealed ground glass opacity and honeycomb lung in lower lobes (Fig. 1B). PFT was not performed due to advanced dyspnea. Echocardiography suggested PH and RHC showed marked increases in MPAP and PVR, and CMR-derived RVEF was reduced. These clinical evaluations suggested right heart failure caused by advanced PH, and sildenafil (20 mg, t.i.d.) was started in Jan 2012. At the follow-up 4 months later, he had no resting dyspnea and less peripheral edema, and RHC showed significant reductions in MPAP and PVR. Pulmonary oxygenation and CMR-derived RVEF had also improved (Table 1).

2.3. Case 3

A 69-year-old man, diagnosed with combined pulmonary fibrosis and emphysema (CPFE) 2 years previously, was referred to our hospital due to progressive exertional dyspnea and hypoxia in October 2010. HRCT revealed emphysematous changes in both upper lungs (Fig. 1C) and subpleural ground glass opacity in lower lobes (Fig. 1D). PFT showed preserved VC and mildly reduced FEV_1/FEV whereas DLCO was markedly decreased (Table 1). RHC showed elevation of MPAP and PVR, and CMR-derived RVEF was reduced. Sildenafil (20 mg, t.i.d.) and, a week later, bosentan (62.5 mg, b.i.d.) were started. He noted no acute adverse events and exertional short breath improved slightly. At follow-up assessment 3 months later, he noted further improvement in his short breath. RHC showed significant reductions in MPAP and PVR, and CMR-derived RVEF also improved (Table 1).

2.4. Case 4

An 86-year-old man with CPFE (Fig. 1E and F) was admitted due to progressive exertional dyspnea and hypoxia in Dec 2011. HRCT and PFT results were consistent with the clinical features of CPFE (Table 1). RHC showed elevation in MPAP and PVR, whereas tiotropium bromide inhalation (18 μg/day) and oxygen treatment for about a month slightly ameliorated his dyspnea and he was followed conservatively. Three months later, however, his exertional dyspnea remained and RHC showed further elevation in PVR. Sildenafil of 20 mg, t.i.d. was started in May 2012. At follow-up assessment 4 months later, his exertional dyspnea had improved. RHC showed significant reduction in PVR and CMR-derived RVEF was also improved, but pulmonary oxygenation evaluated did not show remarkable change (Table 1). In this case, tiotropium bromide was stopped in July 2012 because of difficulty in urination.

This study was conducted in accordance with the amended Declaration of Helsinki. Independent ethics committees of Hokkaido University Graduate School of Medicine approved the protocol, and written informed consent was obtained from all patients.

3. Discussion

The clinical benefit of PAH-specific vasodilators in group 3 PH is controversial.[2,11] However, we used vasodilator(s) in the present four patients for the following reasons. First, all four patients noted progressive symptoms/signs of PH and right heart failure, with RHC measurements fulfilling the recent criteria of severe group 3 PH.[7] Further deterioration of the pulmonary hemodynamics was likely to critically impair functional capacity of the patients and might be

lethal if untreated. Second, background lung parenchymal disease was relatively stable in all cases. Indeed, there was no marked exacerbation of cough or sputum in all four cases. In addition, sequential PFT (available in cases 1 and 4), and HRCT (available in cases 1, 3 and 4), and chest X-ray of the four cases did not show any marked worsening, thus suggesting that parenchymal lung disease was not the primary cause of the advancing symptoms/signs. Third, respiratory infection was not indicated by symptoms/signs, blood tests or imaging studies in the four cases. We thus used PAH-specific vasodilators and had favorable outcomes in patient symptoms/signs and pulmonary hemodynamics.

The degree of hemodynamic improvement was marked in the four cases. Indeed, MPAP and PVR reduced by 19 ± 15% and 45 ± 8%, respectively. In addition, CI and CMR-derived RVEF improved by 28 ± 9% and 51 ± 10%, respectively. These clinical courses suggested that PAH-specific vasodilators improved pulmonary hemodynamics along with right heart function, which subsequently appeared to improve patient symptoms such as exertional dyspnea and peripheral edema.

The underlying pathophysiology of the vascular response to PAH-specific treatment was not elucidated in this observational study. However, it is of clinical interest how the vasodilators could have improved pulmonary hemodynamics. First, it can be speculated that vascular lesions appeared to have more or less reversible components. Indeed, PAH-specific vasodilators would have been less efficacious if vessel loss or ablation in the damaged lung parenchyma was the primary mechanism of increased PVR. Second, it can also be assumed that PAH-specific treatment was efficacious because the vasculopathy was in its early phase. In fact, pulmonary vasculopathy would respond poorly to any vasodilator if the vascular lesion is progressed to heavily fibrotic or hyalinized phase.[12] Finally, the target proteins of vasodilators, particularly of sildenafil, might have been expressed in the diseased vessels.[13]

Deterioration of hypoxia is the major concern when using vasodilators in hypoxic PH patients with lung disease. Theoretically, vasodilators can dilate vessels in the poorly ventilated lung fields, leading to further deterioration of ventilation/perfusion mismatch and hypoxia.[3] In this regard, PDE-5 inhibitors enhance the nitric oxide pathway in the well-ventilated lung areas,[14] minimizing the worsening of perfusion/ventilation mismatch when compared with other PAH-specific agents. In addition, sildenafil is reported to better improve arterial oxygenation as compared with other PDE-5 inhibitors.[15] We therefore used sildenafil as the first line agent in all four cases, whereas beraprost (case 1) and bosentan (case 3) were added for the purpose of further decreases in MPAP. Importantly, the change in pulmonary oxygenation varied among the cases. In fact, pulmonary oxygenation improved in case 2, deteriorated in case 1, and did not change markedly in cases 3 and 4. Further studies are warranted to better predict both favorable and unfavorable response(s) to PAH-specific agents in group 3 PH patients.

Limitations of the present report include a small number of the subjects and possible selection bias. Regarding the selection bias, however, we treated four consecutive patients with group 3 out-of-proportion PH since 2010, in whom suitable interventions to the progressive vasculopathy were clinically necessary. Another limitation is that medical treatments other than vasodilating therapy may have affected clinical outcomes. In fact, long-term oxygen therapy, bronchodilators and/or steroids were used in all four cases, although these treatments were not modified during the 3–4 month follow-up period. In case 1, however, tiotropium bromide was stared simultaneously with vasodilators and might have affected the changes in dyspnea and PFT results. Furthermore, the follow-up period was 3–4 months and the long-term impact of PAH-specific vasodilators remains to be elucidated.

The present report suggests a potential role for PAH-specific vasodilators in the treatment of out-of-proportion group 3 PH patients, particularly when the vasodilators are started in the early phase of the disease progression. It should be considered, however, that any vasodilator therapy potentially worsens hypoxia in such patients. In addition, a recent phase III trial of ambrisentan, a selective endothelin receptor-A antagonist, showed higher rates of disease progression or death in idiopathic pulmonary fibrosis.[16] Further studies are necessary with regard to the safety and efficacy of PAH-specific vasodilators in patients with lung disease and “out-of-proportion” PH.

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Conflict of interest

None declared.

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