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Case report

Improvement of pulmonary arterial compliance by pulmonary vasodilator in pulmonary hypertension from combined pulmonary fibrosis and emphysema

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ABSTRACT

Combined pulmonary fibrosis and emphysema (CPFE) is a common but under-recognized syndrome characterized with distinct profiles of both pulmonary fibrosis and emphysema. Pulmonary hypertension (PH) is particularly prone to develop as a common complication, leading to exercise limitation and worse prognosis of CPFE. Although the therapy of patients with PH from CPFE cannot be endorsed, an individual treatment may be considerable when accompanying severe PH. We report a case of a 71-year-old male with PH from CPFE, who improved pulmonary arterial compliance (PAC) and exercise capacity in response to pulmonary vasodilator.

1. Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is a common but under-recognized syndrome characterized with distinct profiles of clinical, functional, and radiological features from both pulmonary fibrosis and emphysema. The combination of both disorders was described over 40 years ago by Auerbach et al. who examined a pathological study of 1824 autopsy lungs [1]. Since Cottin et al. described that CPFE exhibited emphysema at upper lobes and fibrosis at lower lobes on chest high-resolution computed tomography (HRCT) in 2005 [2], CPFE has been proposed as a distinct syndrome [3–5].

Pulmonary hypertension (PH) is particularly prone to develop as a common complication, leading to exercise limitation and worse prognosis of CPFE. Cottin et al. reported 47% prevalence of PH among 61 CPFE patients [2]. In the study, 5-year survival rates were 25% and 75%, respectively, among CPFE patients with and without PH, suggesting a presence of PH in association with worse prognosis in CPFE. Mejía et al. reported more frequent and severe PH in CPFE patients than in idiopathic pulmonary fibrosis (IPF) patients [6], demonstrating a lower survival rate in CPFE patients than in IPF patients. Moreover, the worst prognosis in CPFE was demonstrated among chronic lung diseases by multi-institutional retrospective cohort study [7].

While no data currently support treatment with pulmonary vasodilators for PH from CPFE, oxygen therapy and referral for lung transplantation, if appropriate, appear to be the most reasonable option for the management [8]. Although the therapy of patients with PH from CPFE cannot be endorsed, an individual treatment may be considerable when accompanying severe PH [9]. We present a case report of a 71-year-old male with PH from CPFE, who improved pulmonary arterial compliance (PAC) and exercise capacity in response to pulmonary vasodilator.

2. Case presentation

A 71-year-old male was referred to our hospital for further examination of progressive dyspnea on exertion. He formerly smoked 20 cigarettes per day for 40 years, but had no obvious history of exposure to any dust. He was diagnosed as CPFE at another hospital 5 years ago, then

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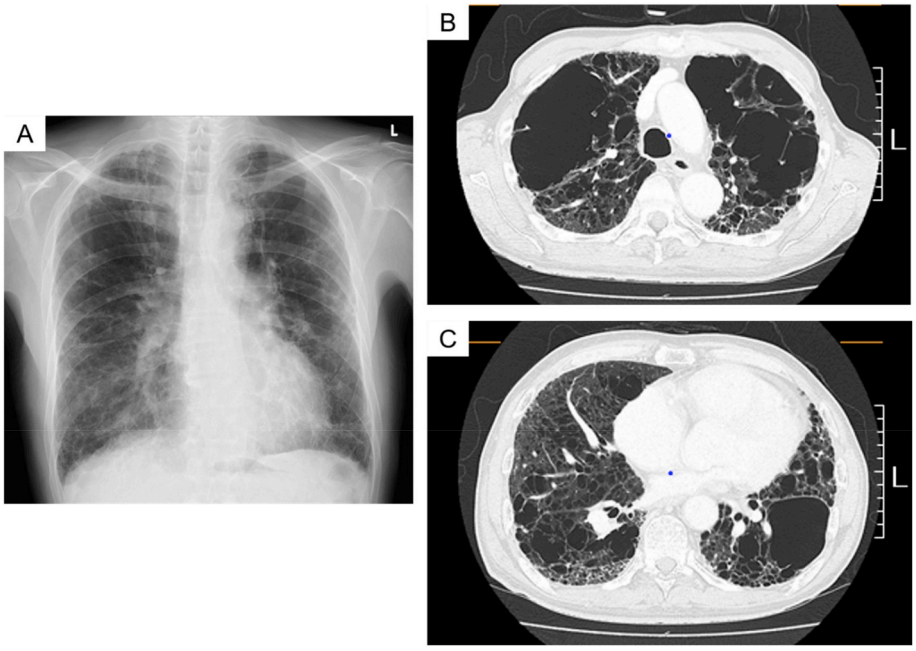

Fig. 1. A: Chest X-ray showed both reticular infiltration at basal periphery of bilateral lungs and hyperlucency with reduction in pulmonary vessels at bilateral apices. B, C: HRCT revealed both emphysematous change with bullae at upper bilateral lobes and emphysematous change with peripheral reticular opacities at lower bilateral lobes.

Table 1
Laboratory data on admission.

Pulmonary function test		Right heart catherization	
FVC (L/% predicted)	3.33/101	RAP	1 mmHg
FEV_1 (L/% predicted)	2.6/107	mean PAP	30 mmHg
6MWT		PAWP	10 mmHg
Distance	110 m	CO	2.53 L/min
Minimum SpO_2	82%	CI	1.66 L/min/m^2
BNP	71.3 pg/mL	PVR	632 dyn S cm^{-5}
Blood gas analysis (room air)			
pH	7.451		
PaO_2	54.9 mmHg		
$PaCO_2$	31.8 mmHg		
HCO_3^-	21.7 mEq/L		
BE	−1.4 mEq/L		

felt progressive dyspnea on exertion from grade 1 to 3 of modified British Medical Research Council (mMRC), equivalent to World Health Organization Functional Class (WHO-FC) III, in recent 5 years. He received long-term oxygen therapy (LTOT) with 1 L per minute at rest or 3 L per minute on exertion for 9 months. A physical examination revealed bilateral middle-to-late inspiratory fine crackles in the lower lung field. Chest X-ray showed both reticular infiltration at basal periphery of bilateral lungs and hyperlucency with reduction in pulmonary vessels at bilateral apices. High-resolution computed tomography (HRCT) revealed both emphysematous change with bullae at upper bilateral lobes and emphysematous change with peripheral reticular opacities at lower bilateral lobes (Fig. 1A–C). Partial pressure of oxygen in arterial blood (PaO_2) was less than 60 mmHg at room air, and percutaneous oxygen saturation (SpO_2) at oxygenation of 3 L per minute was 98%. Pulmonary function test results were as follows: Forced vital capacity (FVC): 3.33 L (101% predicted); forced expiratory volume in the first second (FEV_1): 2.6 L (107% predicted), showing a subnormal ventilatory findings and impaired gas exchange. Diffusing capacity of the lung for carbon monoxide (DLco) could not be evaluated because of his hypoxemia. Six min walking test (6MWT) demonstrated 110 m of distance (6MWD) and 82% of minimum SpO_2 during the test, suggesting an exercise limitation. Echocardiography estimated 78 mmHg of tricuspid regurgitation pressure gradient (TRPG), and right heart catheterization (RHC) showed pulmonary hemodynamics as follows: mean pulmonary arterial pressure (mPAP): 30 mmHg; pulmonary vascular resistance (PVR): 632 dyne.s.cm^{-5}; cardiac index (CI): 1.66 L/min/m^2), demonstrating a presence of severe PH (Table 1).

The patient was diagnosed as severe PH from CPFE, and received diuretic agents and tadalafil. The therapeutic efficacy was satisfactory with improvement of pulmonary hemodynamics and 6MWD at 3 months after the initiation of tadalafil. PAC was also increased from 1.5 to 1.9 mL/mmHg in association with improved pulmonary hemodynamics. The satisfactory efficacy was sustained at 15 months after the initiation (Fig. 2). Pulmonary artery wedge pressure (PAWP) were 2 mmHg and 1 mmHg, respectively, 3 months, and 15 months after the initiation. Stroke volume (SV) were 55.5 mL/beat, 63.6 mL/beat, and 66.6 mL/beat, respectively, on admission, 3 months, and 15 months after the initiation. SV index (SVI) were 36.3 mL/beat/m^2, 39.2 mL/beat/m^2, and 39.4 mL/beat/m^2, respectively, on admission, 3 months, and 15 months after the initiation. No systemic hypotension was observed throughout the whole course. Rating of Perceived Exertion Scale (Borg) was improved from 8 to 2 during 6MWT, and WHO-FC was also improved from III to II, while no deleterious effect of tadalafil on ventilatory function and gas exchange was observed at rest. However, although elongation of 6MWD was sustained, minimum SpO_2 during 6MWT was slightly worsened at 15 months after the initiation (Table 2). No bronchodilators were used because of his subnormal ventilatory findings.

3. Discussion

Limited literatures demonstrated dismal prognosis and no beneficial therapeutic management in PH from CPFE. Cottin et al. reported 1-year survival rate of 60% among 40 patients with CPFE and PH, mPAP of 40 ± 9 mmHg by examination of RHC, indicating that both reduced CI (<2.4 L/min/m^2) and elevated PVR (>485 dyne.s.cm^{-5}) are considered as predictors of poor prognosis. The authors also demonstrated no significant benefit of therapeutic management, including pulmonary vasodilators, corticosteroids, immunomodulators, and bronchodilators, for the treatment [10].

A possibility of using pulmonary vasodilators (e.g. endothelin-1

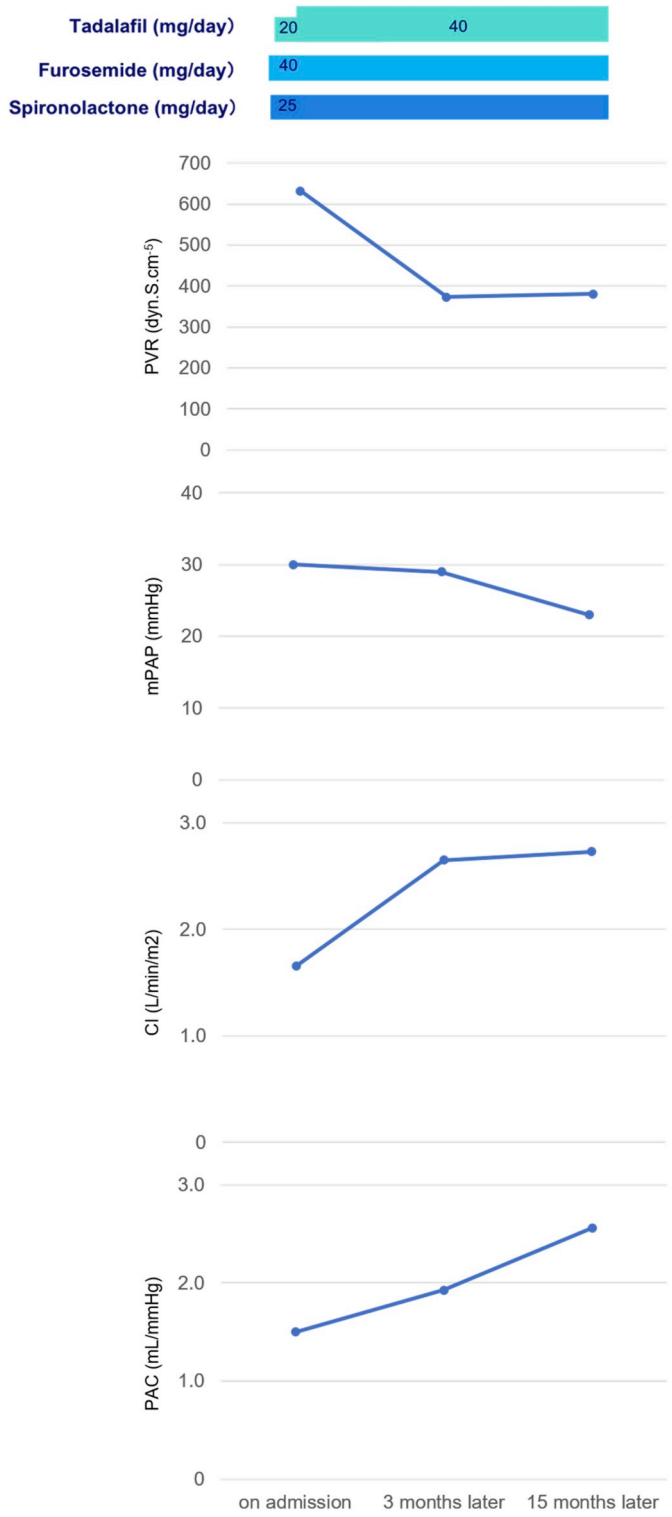

Fig. 2. Clinical treatment course. The serial changes of mPAP, PVR, CI, and PAC are shown.

receptor antagonist, prostanoids, or phosphodiesterase type 5 inhibitors (PDE5Is)) has been raised for therapeutic strategy of PH in CPFE, but no studies have been published to date on the issue. While no randomized controlled trials (RCTs) demonstrated [9], a couple of retrospective cohort studies demonstrated benefit of pulmonary vasodilators on survival in PH among chronic lung diseases [7,11]. On the other hand, several clinical benefits (e.g. improvement of exercise capacity, pulmonary hemodynamics, or quality of life) were demonstrated in RCTs, but with a paucity of the evidence [9].

Table 2
Changes of parameters during clinical treatment course.

	on admission	3 months later	15 months later
FVC (L/% predicted)	3.33/101		3.29/100
FEV_1 (L/% predicted)	2.6/107		2.16/90
6MWT (O_2 5L/min)			
Distance (m)	110	140	207
Minimum SpO_2 (%)	82	87	79
Borg score	8	2	2
BNP (pg/mL)	71.3	43.5	44.8
Blood gas analysis (O_2 3L/min)			
pH	7.431	7.465	7.446
PaO_2 (mmHg)	75.8	69.0	99.7
$PaCO_2$ (mmHg)	40.6	34.3	38.2
HCO_3^- (mEq/L)	26.4	24.1	25.7
BE (mEq/L)	2.0	0.9	1.8

In the present case, the patient had severe PH from CPFE, and was expected his poor prognosis with both reduced CI and elevated PVR. After initiation of tadalafil, improvements of both pulmonary hemodynamics and 6MWD were seen, and PAC was also increased more than 1.4 mL/mmHg in accordance with improved pulmonary hemodynamics. The increase in PAC was sustained at least for 15 months. PAC is calculated as stroke volume/pulse pressure, and considered as a strong hemodynamics predictor of prognosis in patients with pulmonary arterial hypertension (PAH). Ghio S et al. estimated survival rate between more than or equal to 1.4 mL/mmHg and less than 1.4 mL/mmHg of PAC among PAH patients who were re-evaluated RHC after initiation of PAH-targeted therapy. The authors reported that PAH patients whose PAC was less than 1.4 mL/mmHg worsened survival rate, suggesting that failure to improved PAC after the therapy is a strong hemodynamics predictor of poor prognosis [12]. In addition, the patient sustained improvement of WHO-FC and 6MWD at least for 15 months in the present case. Favorable survival was demonstrated among patients with idiopathic interstitial pneumonias and severe PH, who improved WHO-FC and 6MWD in response to pulmonary vasodilators [13]. As mentioned above, the patient may be in good course for long-term in the present case.

The mechanism of improvement of PAC is uncertain. Cardiopulmonary protection against PH of PDE5Is has been demonstrated in animal models and human. As PDE5I prevented and reversed cardiac hypertrophy and function in experimental models [14], PDE5I also preserved exercise capacity in patients with IPF and right-sided ventricular dysfunction [15]. In the present case, during improvement of pulmonary hemodynamics and exercise capacity after initiation of tadalafil, both SV and SVI were also increased, suggesting a restoration of cardiac function. Alternatively, there may raise a possibility that pulmonary vasodilators and LTOT attenuated pulmonary vascular remodeling [16]. As mentioned above, tadalafil may play a role for amelioration of both cardiac function and pulmonary vasculature, resulting in the improvement of PAC for long-term in the present case.

Both hypoxic pulmonary vasoconstriction (HPV), a phenomenon to avoid worsening arterial oxygenation, and imbalance in ventilation/perfusion ratio (V_A/Q) due to abnormal changes in pulmonary vascular bed and airway in CPFE may predispose PH. Pulmonary vasodilators have a possibility to worsen arterial oxygenation due to inhibition of HPV and potentiation of V_A/Q mismatch by nonselective vasodilation of pulmonary vessels [4]. In the present case, although neither ventilatory function nor gas exchange was worsened at rest, minimum SpO_2 during 6MWT was slightly worsened at 15 months after initiation of tadalafil, probably due to its potentiation of V_A/Q mismatch.

4. Conclusion

We present here a case report of a 71-year-old male with PH from CPFE, who improved PAC and exercise capacity in response to

pulmonary vasodilator. While no data currently support treatment with pulmonary vasodilators for PH from CPFE, an individual treatment may be considerable when accompanying severe PH. Since such therapy cannot be currently endorsed, registries and future studies in this area are strongly encouraged.

Declaration of competing interest

The authors have no conflict of interest to declare. Morio Y. is an equally contributed author in the present case report.

References

[1] O. Auerbach, L. Garfinkel, E.C. Hammond, Relation of smoking and age to findings in lung parenchyma: a microscopic study, Chest 65 (1974) 29–35.

[2] V. Cottin, H. Nunes, P.Y. Brillet, et al., Combined pulmonary fibrosis and emphysema: a distinct under recognised entity, Eur. Respir. J. 26 (2005) 586–593.

[3] K. Portillo, J. Morera, Combined pulmonary fibrosis and emphysema syndrome: a new phenotype within the spectrum of smoking-related interstitial lung disease, Pulm Med 2012 (2012), 867870.

[4] M.D. Jankowich, S.I. Rounds, Combined pulmonary fibrosis and emphysema syndrome: a review, Chest 141 (2012) 222–231.

[5] V. Cottin, The impact of emphysema in pulmonary fibrosis, Eur. Respir. Rev. 22 (2013) 153–157.

[6] M. Mejía, G. Carrillo, J. Rojas-Serrano, et al., Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension, Chest 136 (2009) 10–15.

[7] N. Tanabe, H. Taniguchi, I. Tsujino, et al., Multi-institutional retrospective cohort study of patients with severe pulmonary hypertension associated with respiratory diseases, Respirology 20 (2015) 805–812.

[8] W. Seeger, Y. Adir, J.A. Barberà, et al., Pulmonary hypertension in chronic lung diseases, J. Am. Coll. Cardiol. 62 (2013) D109–D116.

[9] D.S. Nathan, J.A. Barbera, S.P. Gaine, et al., Pulmonary hypertension in chronic lung disease and hypoxia, Eur. Respir. J. 53 (1) (2019), https://doi.org/10.1183/13993003.01914-2018 pii: 1801914.

[10] V. Cottin, J. Le Pavec, G. Prévot, et al., Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome, Eur. Respir. J. 35 (2010) 105–111.

[11] T.J. Lange, M. Baron, I. Seiler, et al., Outcome of patients with severe PH due to lung disease with and without targeted therapy, Cardiovasc Ther 32 (2014) 202–208.

[12] S. Ghio, M. D'Alto, R. Badagliacca, et al., Prognostic relevance of pulmonary arterial compliance after therapy initiation or escalation in patients with pulmonary arterial hypertension, Int. J. Cardiol. 230 (2017) 53–58.

[13] M.M. Hoeper, J. Behr, M. Held, et al., Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias, PLoS One 10 (2015), e0141911.

[14] E. Takimoto, H.C. Champion, M. Li, et al., Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy, Nat. Med. 11 (2005) 214–222.

[15] M.K. Han, D.S. Bach, P.G. Hagan, et al., Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction, Chest 143 (2013) 1699–1708.

[16] L.A. Shimoda, S.S. Laurie, Vascular remodeling in pulmonary hypertension, J. Mol. Med. (Berl.) 91 (2013) 297–309.