Case Report

Pulmonary hypertension associated with veno-occlusive disease in systemic sclerosis: Insight into the mechanism of resistance to vasodilator

Hayato Tada (MD)a,⁎, Tetsuo Konno (MD, FJCC)a, Motohiko Aizu (MD)b, Junichiro Yokawa (MD)a, Toshinari Tsubokawa (MD)a, Hiroshi Fujii (MD)b, Kenshi Hayashi (MD, FJCC)a, Katsuharu Uchiyama (MD)a, Masami Matsumura (MD)b, Mitsuhiro Kawano (MD)b, Masa-aki Kawashiri (MD)a, Masakazu Yamagishi (MD, FJCC)a

a Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan
b Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Received 20 September 2011; received in revised form 1 November 2011; accepted 6 November 2011

KEYWORDS
Pulmonary veno-occlusive disease; Pulmonary hypertension; Pulmonary arterial hypertension; Epoprostenol

Summary We report a case with pulmonary veno-occlusive disease (PVOD) associated with systemic sclerosis which exhibits strong resistance to pulmonary vasodilator.

A 55-year-old female with severe pulmonary hypertension was admitted to our hospital to be introduced to epoprostenol infusion therapy. She was diagnosed as having pulmonary arterial hypertension (PAH) associated with systemic sclerosis at the age of 51. Several aggressive treatments with pulmonary vasodilators, including oral prostaglandin, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors, failed to improve her symptoms. We introduced continuous intravenous epoprostenol therapy from 2 μg/kg/min for her. However, pulmonary edema appeared and worsened in a dose-dependent manner. We made a diagnosis of PVOD clinically at that time. Thereafter, pulmonary edema gradually disappeared consistent with the reduction of the dose of epoprostenol infusion. She died of renal failure and infection 4 months after the introduction of epoprostenol infusion therapy. A histological examination revealed severe stenosis and occlusions of pulmonary veins as well as pulmonary arteries over a wide area. We suggest that prevalence of veno-occlusive type of disease could be one of the major mechanisms of less responsive or even refractory to pulmonary vasodilator therapies in patients with PAH associated with connective tissue disease.

© 2011 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

⁎ Corresponding author at: Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa 920-8641, Japan. Tel.: +81 76 265 2000/2251; fax: +81 76 234 4251.
E-mail address: ht240z@med.kanazawa-u.ac.jp (H. Tada).
Introduction

Recent advances regarding the treatment for pulmonary hypertension, especially, for pulmonary arterial hypertension (PAH) have improved the prognosis of patients with PAH \[1,2\]. Several reports have described that connective tissue diseases such as systemic sclerosis and systemic lupus erythematosus could be complicated by severe PAH which worsens their prognosis \[3,4\]. Pulmonary hypertension associated with connective tissue disease has been categorized into PAH. Pulmonary veno-occlusive disease (PVOD) has been described as a relatively rare cause of pulmonary hypertension that affects predominantly post-capillary pulmonary vessels. A major concern with PVOD is the poor responsiveness to available pulmonary vasodilators, especially, the risk of pulmonary edema with continuous intravenous epoprostenol therapy \[5,6\]. We recently experienced a case with PVOD associated with systemic sclerosis which exhibited strong resistance to pulmonary vasodilators, including continuous intravenous epoprostenol therapy.

Case report

A 55-year-old female was admitted to our hospital for the introduction of epoprostenol infusion therapy. She was diagnosed as having systemic sclerosis at the age of 39 years. The initial diagnosis of her pulmonary hypertension was made when she was 51 years old. She had been treated with beraprost since then. Thereafter, her symptoms of dyspnea gradually worsened associated with the increase of pulmonary artery pressure in spite of the introduction of sildenafil, ambrisentan, and home oxygen therapy during four years of the clinical course. Physical examination at admission revealed a heart rate of 80 bpm, a blood pressure of 90/52 mmHg, and a respiratory rate of 20 breaths/min. She had some signs of fluid overload such as jugular vein distension and lower extremity edema and

Figure 1  Imaging of the case. Electrocardiogram at admission revealed right ventricular hypertrophy findings of tall R waves in right precordial leads with right ventricular strain pattern (A). Chest X-ray demonstrated bilateral hilar enlargement, a prominent medial arch and pulmonary artery trunk (B). Echocardiography revealed dilatation of right ventricle, and normal left ventricular function with flattening of ventricular septum (C). High-resolution computed tomography of her chest revealed centrilobular ground-glass opacities and septal thickness (D, arrow).
was in functional New York Heart Association class III. Arterial blood gas analysis revealed hypoxemia (pH 7.41, PaCO₂ 35 mmHg, PaO₂ 79 mmHg under O₂ 2 L/min). The electrocardiogram revealed a sinus rhythm of 80 bpm, and right ventricular hypertrophy findings of tall R waves in right precordial leads with right ventricular strain pattern (Fig. 1A). Chest X-ray (Fig. 1B) demonstrated bilateral hilar enlargement, a prominent medial arch and pulmonary artery trunk. Echocardiography confirmed dilatation of both the right atrium and right ventricle, and normal left ventricular function (left ventricular ejection fraction of 62%) with flattening of ventricular septum (Fig. 1C). Trans-mitral flow velocity pattern revealed abnormal relaxation, and the ratio of mitral inflow and mitral annular tissue Doppler imaging velocities (E'/e') was within the normal range (8.3). Right heart catheterization demonstrated severe pulmonary hypertension (pulmonary arterial systolic pressure 94 mmHg, pulmonary arterial diastolic pressure 27 mmHg, mean pulmonary arterial pressure 48 mmHg) in contrast to the normal range of pulmonary capillary wedge pressure 14 mmHg. Other important parameters were cardiac output 3.9 L/min, (thermo dilution method) and pulmonary vascular resistance 540 dynes s cm⁻⁵. After these examinations, epoprostenol infusion therapy was introduced from the dose of 2 μg/kg/min. However, pulmonary edema appeared and her oxygenation worsened in a dose-dependent manner. Based on this clinical course, we made a diagnosis of PVOD clinically and the dose of epoprostenol was 12 μg/kg/min. Thereafter, pulmonary edema gradually recovered consistent with the reduction of the dose of epoprostenol infusion. A high-resolution computed tomography (HRCT) of her chest revealed centrilobular ground-glass opacities and septal thickness (Fig. 1D). Lung transplantation was proposed as the sole treatment option to prolong her life.

Figure 2  Histopathological findings. Macroscopic finding of heart; Transverse section of the heart showing hypertrophy of both the left and right ventricles (A). Small pulmonary artery revealed pronounced intimal fibrosis, as typically seen in pulmonary arterial hypertension (B, Elastica van Gieson stain, ×200). Small pulmonary vein showed fibrotic occlusive lesions with marked intimal thickening characteristics of pulmonary veno-occlusive disease (C, Elastica van Gieson stain, ×200). The capillaries in the alveolar area showed dilatation like angioma (D, hematoxylin and eosin stain, ×200). Macroscopic findings of lung; alveolar hemorrhage was observed (E, arrow). Intra-alveolar macrophages were observed (F, arrow, hematoxylin and eosin stain, ×40). Fe-stain revealed the existence of iron in the alveoli (G, arrow, Fe-stain, ×200). LV, left ventricle; RV, right ventricle.
but she declined. The patient died of renal failure and infection 4 months after the introduction of epoprostenol infusion therapy. Histopathological examination of her heart revealed hypertrophy of both ventricles without any apparent pathological interstitial fibrotic change (Fig. 2A). In addition to the findings of small pulmonary arteries that revealed pronounced intimal fibrosis as typically seen in PAH (Fig. 2B), small pulmonary vein also showed fibrotic occlusive lesions with marked intimal thickening characteristics of PVOD (Fig. 2C). The capillaries in the alveolar area showed dilatation like angioma (Fig. 2D) as well as the findings of intra-alveolar hemorrhage (Fig. 2E–G). On the basis of these pathological findings and clinical features, the patient was diagnosed as having PVOD.

Discussion

Even though PAH and PVOD share many similarities, the clinical classification was modified to separate PVOD from other forms of PAH following the Fourth World Symposium on PAH held in 2008 at Dana Point, CA, USA [7]. It is currently well established that PAH associated with connective tissue disease such as systemic sclerosis is frequently less responsive or even refractory to pulmonary vasodilator therapies. The likely mechanism is a selective dilatation of the small pulmonary arteries without associated pulmonary venodilatation which could cause an increase in trans-capillary hydrostatic pressure. Several papers have described the usefulness of HRCT to predict the presence of PVOD [8,9]. Our case also showed centrilobular ground-glass opacities and septal thickness; however, the findings of HRCT suggesting the presence of PVOD were obtained after the introduction of epoprostenol infusion therapy. Thus, we could not suspect PVOD until then. Several studies suggested that the frequencies of veno-occlusive types of disease in the patients with PAH associated with connective tissue disease might be larger than expected, and there is some evidence from histopathological reports to support this hypothesis [5]. However, the current definite diagnosis of PVOD can be made histopathologically, thus, limiting the estimation for the accurate involvements of this type of disease.

In conclusion, we report a case with PVOD associated with systemic sclerosis which exhibits strong resistance to pulmonary vasodilator. We suggest that prevalence of veno-occlusive type of disease could be one of the major mechanisms of less responsive or even refractory to pulmonary vasodilator therapies to patients with pulmonary hypertension associated with connective tissue disease.

Acknowledgments

We express our special thanks to Kazuko Honda and Sachio Yamamoto (staff of Kanazawa University) for their assistance.

References