CASE REPORT

Spontaneously Remitted Pulmonary Arterial Hypertension Associated with the Herbal Medicine “Bofutsushosan”

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Abstract

Although the link between pulmonary arterial hypertension (PAH) and exposure to certain drugs has already been identified, we herein present the first case of herbal medicine-associated PAH in which the patient demonstrated spontaneous remission. A 38-year-old woman took the herbal medicine “bofutsushosan” for two weeks then stopped taking it due to exertional dyspnea. However, her dyspnea continued, and right heart catheterization revealed a mean pulmonary arterial pressure of 41 mmHg with a normal wedge pressure. Several months after treatment with oxygen therapy, the patient’s dyspnea disappeared, and her pulmonary arterial pressure normalized. Further studies focusing on susceptibility factors to drug-induced pulmonary arterial hypertension are needed.

Key words: pulmonary arterial hypertension, herbal medicine, bofutsushosan

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Introduction

Obesity, which is characterized by an excessive accumulation of adipose tissue, is the most common risk factor for metabolic syndrome, a cluster of several abnormalities, including dyslipidemia, insulin resistance, type 2 diabetes, hypertension and atherosclerosis (1, 2). However, no drug therapies, including appetite-suppressant agents, have been established to treat or prevent obesity. The efficacy of traditional herbal medicines (Kampo formulations), such as “bofutsushosan,” in improving obesity has been examined (3-6). Although the gastrointestinal side effects of bofutsushosan, including diarrhea, are widely recognized, respiratory-associated effects, especially pulmonary vascular involvement, have not been reported (7-11). We herein report the first case of bofutsushosan-induced pulmonary arterial hypertension (PAH).

Case Report

Following the two-week administration of bofutsushosan for its anti-obesity effects, a 38-year-old woman experienced general malaise and dyspnea on exertion with liver dysfunction. After discontinuing the bofutsushosan, the patient’s liver dysfunction returned to normal; however, her dyspnea continued for three months, and echocardiography revealed a tricuspid regurgitation pressure gradient of 40 mmHg, suggesting the existence of pulmonary hypertension. The patient was admitted to our hospital for further examinations.

The patient’s height, weight and body mass index (BMI) were 153 cm, 66 kg and 28.1 kg/m², respectively. Snoring was not detected. A physical examination revealed a body temperature of 37.0°C, a blood pressure of 120/82 mmHg, a heart rate of 96 beats/min and a respiratory rate of 16 breaths/min.

The laboratory findings obtained on admission showed an
Figure 1. (A) The chest roentgenogram obtained at diagnosis showed a prominent hilar pulmonary artery. The cardiothoracic ratio was 44.2%. (B) The follow-up chest roentgenogram revealed a decrease in the cardiothoracic ratio (39.6%). (C) The contrast CT scans showed a leftward shift of the interventricular septum. (D) The follow-up contrast CT scans revealed improvement of the deviation of the interventricular septum.

elevated brain natriuretic peptide (BNP) level of 61.2 pg/mL and an endothelin-1 level of 1.98 pg/mL. The results of a blood gas analysis on room air were almost normal (PaO2 89 Torr and PaCO2 36 Torr). The patient did not have anemia. Her liver and renal functions were normal. She was negative for antinuclear antibodies, anti-ribonucleoprotein antibodies (RNP) and various auto-antibodies. She had an euthyroid function. A drug-induced lymphocyte stimulation test (DLST) for bofutsushosan was negative. No mutations of the bone morphogenetic protein receptor 2 (BMPR2) or activin-receptor-like kinase 1 (ALK-1) genes were found.

No evidence of portal hypertension was detected on abdominal ultrasonography. A chest roentgenogram showed a prominent hilar pulmonary artery with a cardiothoracic ratio (CTR) of 44.2% (Fig. 1A). The patient’s lung function, including the diffusing capacity, was normal. The six-minute walk distance (6MWD) was 486 m, with a lowest oxygen saturation of 89%. An electrocardiogram did not suggest right heart overload; however, cardiac ultrasonography showed right heart overload (enlargement of the right ventricle, ventricular septal deviation to the left) and tricuspid regurgitation with a pressure gradient of 40 mmHg. The perfusion scans were normal, and contrast-enhanced CT scans showed no pulmonary embolism, although these scans indicated a leftward shift of the interventricular septum (Fig. 1C).

Right heart catheterization revealed an elevated pulmonary arterial pressure (PAP) of 64/21 mmHg with a mean pulmonary arterial pressure (mPAP) of 41 mmHg, a pulmonary capillary wedge pressure of 9 mmHg, a cardiac index (CI) of 4.67 L/min/m² and a heart rate of 93 beats/min, resulting in a calculated pulmonary vascular resistance (PVR) of 326 dynes-sec-cm⁻⁵. Following 100% oxygen inhalation for 15 minutes, mPAP decreased to 30 mmHg, CI decreased to 3.28 L/min/m² and PVR decreased to 305 dynes-sec-cm⁻⁵ (Table). Pulmonary arteriography revealed mild pruning of the pulmonary arteries, while no thrombi were detected.

Because oxygen inhalation decreased the pulmonary arterial pressure and normalized the cardiac index and heart rate, the patient was treated with oxygen and dietary therapy. Her dyspnea on exertion gradually disappeared within three months of discharge, and eight months later, she did not need oxygen. Her BNP level was normalized (6.3 pg/mL) and a chest roentgenogram revealed a decrease in the cardiothoracic ratio (39.6%) (Fig. 1B). A contrast-enhanced CT scan revealed improvement of the deviation of the interventricular septum (Fig. 1D). The patient’s 6MWD also improved to 544 m concomitant with an improved lowest oxygen saturation of 93%.

She was admitted to our hospital for a revaluation 18 months after the first catheterization. Her body weight had decreased from 66.5 to 49.2 kg. Right heart catheterization
PAH is a rare and progressive disease, often leading to right heart failure and premature death. PAH associated with drug and/or toxin exposure is a well-recognized subgroup of this disease. At the 2008 WHO meeting in Dana Point, California, updates were provided to reflect the strength of the associations as definite (aminorex, fenfluramine, dexfenfluramine and toxic rapeseed oil), possible (cocaine, phenylpropanolamine, St. John’s Wort, chemotherapeutic agents and selective serotonin receptor inhibitors), likely (amphetamine, L-tryptophan and methamphetamine) or unlikely (oral contraceptives and estrogen) (12).

The first reports of PAH associated with drug and/or toxin exposure can be traced to 1968, when the first case series of patients developing pulmonary hypertension following exposure to the anti-obesity agent aminorex was published (13). Subsequently, the use of anorectic agents was recognized to be a risk factor for pulmonary hypertension. Among aminorex users, it has been estimated that only approximately 1/1,000 persons develop PAH. Approximately 30% of patients with aminorex-related PAH exhibit significant clinical improvement after discontinuing the drug. Such spontaneous improvement is almost never observed in patients with idiopathic PAH and probably explains the trend toward better survival seen in patients with aminorex-related disease (14). Brenot et al. reported that three fenfluramine users with PAH showed spontaneous clinical and hemodynamic improvement three, six and 12 months after drug withdrawal (15). In approximately 50% of cases of acute onset pulmonary hypertension occurring within six months after starting an anorectic agent, the pulmonary artery pressure is normalized after discontinuing the drug (16).

The herbal medicine “bofutsushosan” exhibits efficacy for coexisting symptoms of obesity and hypertension. Interstitial pneumonia, myopathy, pseudohyperaldosteronism, liver dysfunction and gastrointestinal issues have been reported as adverse drug reactions associated with bofutsushosan. In fact, several case reports have shown the development of interstitial pneumonia and hepatitis in patients taking this medication (7-11).

Bofutsushosan is made from 18 kinds of herbal medicines and contains ephedra. Ephedra includes ephedrine and similar substances and has a chemical structure similar to amphetamine and methamphetamine, both of which cause pulmonary hypertension.

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Table. The Findings of Right Heart Catheterization

<table>
<thead>
<tr>
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<th>At diagnosis</th>
<th>On 100% oxygen inhalation</th>
<th>At follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate / min</td>
<td>93</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>Systemic artery pressure</td>
<td>mmHg</td>
<td>110 / 77</td>
<td>109 / 76</td>
</tr>
<tr>
<td>systole/diastole (mean)</td>
<td>(85)</td>
<td>(85)</td>
<td>(81)</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>mmHg</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary arterial pressure</td>
<td>mmHg</td>
<td>64 / 21</td>
<td>46 / 18</td>
</tr>
<tr>
<td>systole/diastole (mean)</td>
<td>(41)</td>
<td>(30)</td>
<td>(15)</td>
</tr>
<tr>
<td>Pulmonary capillary wedge</td>
<td>mmHg</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index L / min / m²</td>
<td>4.67</td>
<td>3.28</td>
<td>3.70</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>dyne · sec · cm⁻³</td>
<td>326.4</td>
<td>304.8</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Torr</td>
<td>89.1</td>
<td>516.0</td>
</tr>
<tr>
<td>Body weight</td>
<td>kg</td>
<td>66.5</td>
<td>49.2</td>
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vasoconstriction and obstruction of the pulmonary vascular resistance. The patient's exertional dyspnea was principally caused by the association of obstructive sleep apnea and obesity-induced hyperventilation (19). We did not perform polysomnography in the present case. However, the patient did not have any symptoms suggesting sleep apnea syndrome, such as excessive daytime sleepiness, morning headaches or snoring. Therefore, it is unlikely that the sleep apnea caused the pulmonary hypertension. We did not use vasodilators in the present case due to the patient’s slightly elevated cardiac output with increased heart rate partly caused by her obesity and the normalization of the cardiac function during oxygen inhalation.

The pathogenesis of pulmonary hypertension consists of vasoconstriction and obstruction of the pulmonary vascular beds (20). Very few spontaneously remitted cases have been reported. The contribution of vasoconstriction and fixed obstruction to pulmonary hypertension may vary within and between patients. Although we were unable to conduct an acute vasoreactivity test using nitric oxide in the present patient, the administration of oxygen markedly decreased the pulmonary arterial pressure with a slight decrease in the pulmonary vascular resistance. The patient’s exertional dyspnea appeared after two weeks of taking the herbal medicine and continued and progressed for three months. After confirming the presence of PAH and initiating oxygen therapy, the patient’s dyspnea gradually improved over the course of three months. Therefore, the mechanisms responsible for the pulmonary hypertension observed in our patient were primarily due to vasoconstrictive components possibly associated with elevated endothelin levels (endothelial injury) and medial hypertrophy. In addition, these mechanisms were reversible.

Finally, only a minority of individuals exposed to certain drugs develop pulmonary arterial hypertension. Humbert et al. reported that BMPR2 mutations appear to be rare in the general population but may combine with exposure to fenfluramine derivatives to greatly increase the risk of PAH. Moreover, in that study, the mutation-positive patients had a somewhat shorter duration of fenfluramine exposure before the onset of illness than the other patients (21). The present patient did not have BMPR2 or ALK1 mutations, and most of the previous patients who suffered from drug-induced PAH had no known mutations. Therefore, other genetic and/or environmental factors may be involved.

In conclusion, to our knowledge, this is the first report of spontaneously remitted PAH induced by an herbal medicine. This report may provide clinicians important information to help them develop early suspicion in order to recognize pulmonary hypertension in patients with exertional dyspnea who have taken herbal medicines. This may help to avoid further deterioration of the patient’s condition. Further research should focus on identifying susceptibility factors for drug-induced pulmonary arterial hypertension.

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

References