A case study of bofutsushosan-induced pulmonary injury in a patient: Case report

KUNIHIKO MIYAZAKI[1], HIROAKI SATOH[2], HIROKO WATANABE[3], TOSHIHIRO SHIOZAWA[3], TOMOHIRO TAMURA[2], MIO KAWAGUCHI[3] and NOBUYUKI HIZAWA[3]

[1]Department of Respiratory Medicine, Ryugasaki Saiseikai General Hospital, Ryugasaki, Ibaraki 301-0854; [2]Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Mito Kyodo General Hospital, Mito, Ibaraki 310-0015; [3]Department of Respiratory Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan

Received July 1, 2016; Accepted September 22, 2016

DOI: 10.3892/br.2016.787

Abstract. Bofutsushosan, a herbal (traditional Kampo) medicine, is administered to obese patients in North-East Asia. Bofutsushosan has been reported to exert various anti-obesity effects by stimulating the adipose tissue. The present study describes the case of a patient who developed a severe pulmonary injury that was potentially associated with bofutsushosan therapy. A 52-year-old woman was admitted to Mito Medical Center, University of Tsukuba, Mito Kyodo General Hospital (Mito, Japan) due to progressive dyspnea. Two months previously, bofutsushosan had been newly prescribed for her obesity. Bilateral ground-glass opacities and progressive respiratory deterioration suggested respiratory failure due to a therapeutic agent-induced lung injury. With discontinuation of bofutsushosan and the administration of a corticosteroid, an improvement in her respiratory condition was achieved, although sequelae remained in certain areas of the lungs. Resumption of other therapeutic agents did not reinduce the lung injury. Therefore, a diagnosis of bofutsushosan-induced lung injury was made. Although bofutsushosan-induced lung injury is particularly rare, clinicians should consider it when bofutsushosan is used.

Introduction

Bofutsushosan (Tsumura Co., Tokyo, Japan), one of the traditional herbal medicines, which was developed by Liu Wansu (a well-known physician of traditional Chinese medicine in the 12th century), is known as an effective medication for obesity in North-East Asia. Many Kampo practitioners are aware of bofutsushosan and its effects on obesity, which have previously been reported in the Japanese literature (1-3). However, to the best of our knowledge, this has not been reported in the English literature. The aim of the present study is to introduce this traditional herbal medicine in areas outside of North-East Asia, for the 'non-Kampo' clinicians. Thus, the present study describes the case of a patient who was successfully treated following the development of a pulmonary injury that may have been associated with bofutsushosan therapy.

Correspondence to: Professor Hiroaki Satoh, Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Mito Kyodo General Hospital, Miya-machi 3-2-7, Mito, Ibaraki 310-0015, Japan
E-mail: hirosato@md.tsukuba.ac.jp

Key words: bofutsushosan, lung injury, herbal medicine, Japanese Kampo

Case report

A 52-year-old woman was admitted to Mito Medical Center, University of Tsukuba, Mito Kyodo General Hospital (Mito, Japan) in October, 2011 for diffuse ground-glass opacity (GGO) in each lung, which was noted on a chest X-ray. The patient was orally administered 7.5 g/day bofutsushosan to treat her obesity. Two months after initiation of bofutsushosan administration, the patient developed shortness of breath and was dyspneic at rest. On admission, the respiratory rate was 22 breaths/min and a decreased oxygen saturation of 93% was observed. A chest examination revealed inspiratory fine crackles in the base of each lung. The heart sounds were normal, the jugular vein was not dilated, and hepatomegaly and peripheral edema were absent. Upon admission, an arterial blood gas analysis on 10-liter oxygen indicated the following: pH 7.506; PO_2, 65.3 torr; PCO_2, 24.5 torr; HCO_3^-, 18.9 mEq/l; Na, 136 mEq/l; and Cl, 100 mEq/l. The blood chemistry was significant for the level of C-reactive protein (25.17 mg/dl) and KL-6 (2,370 U/ml). No elevation in antibody titers of *Mycoplasma, Legionella pneumophila*, and *Chlamydia psittaci* was observed. Antinuclear antibody testing, and serum perinuclear antinuclear cytoplasmic antibody, anti-cyclic citrullinated peptide antibody, and *Cryptococcus* and *Aspergillus* antigen testing were all negative. An electrocardiogram demonstrated a normal sinus rhythm with nonspecific ST-T changes. An echocardiographic assessment showed that the left ventricular ejection fraction and wall motion were normal. A chest radiograph taken on admission detected bilateral GGOs with consolidation (Fig. 1). Additionally, a chest computed tomography (CT) scan showed bilateral GGOs

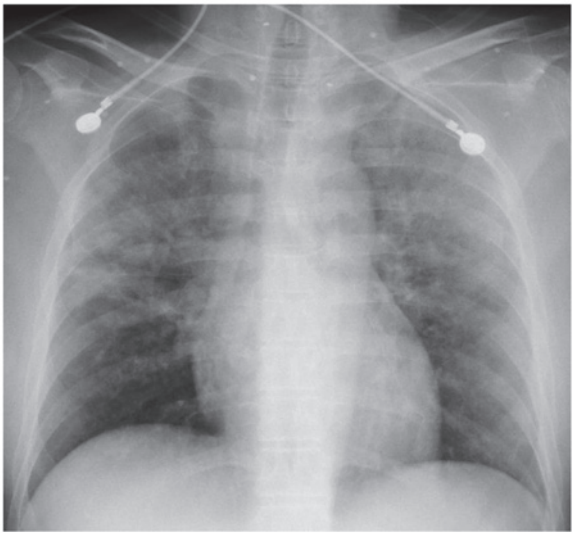

Figure 1. Chest radiograph performed on admission detected bilateral ground-glass opacities in each lung.

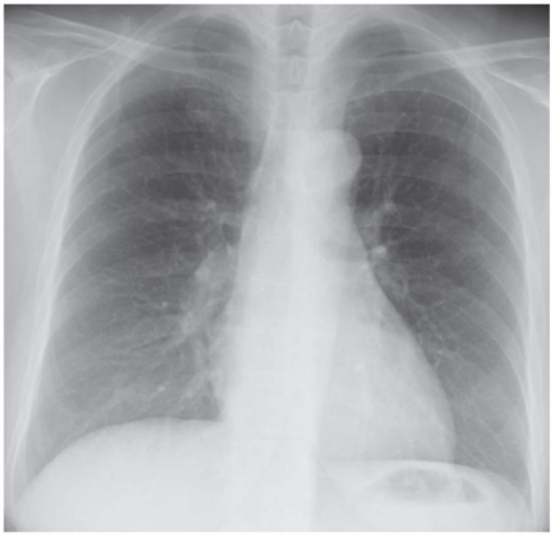

Figure 3. Chest radiograph 2 weeks after the initiation of steroid therapy demonstrated the absence of the ground-glass opacities in each lung.

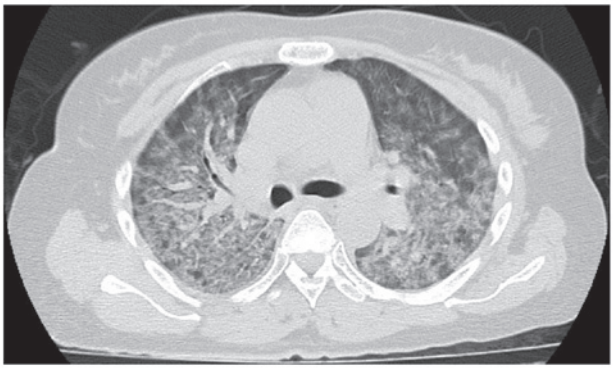

Figure 2. Chest computed tomography scan at the time of admission exhibited bilateral ground-glass opacities.

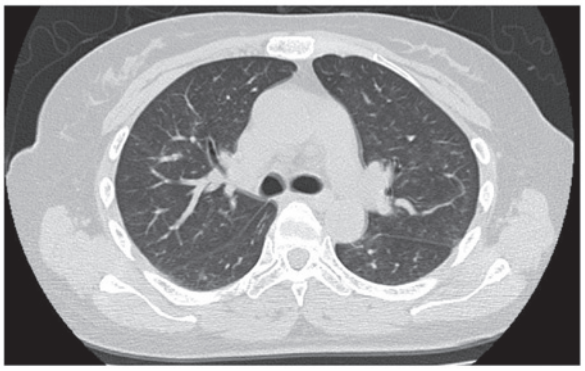

Figure 4. Chest computed tomography scan 2 weeks after the initiation of steroid therapy demonstrated the absence of the ground-glass opacities in each lung.

with consolidation (Fig. 2). Blood, sputum and urine cultures did not indicate any bacterial infections. A bronchoalveolar lavage obtained from the left upper lobe demonstrated a total cell count of $6.4x10^5$/ml with 53.0% lymphocytes. Despite the administration of oxygen therapy and a broad-spectrum intravenous antibiotic, levofloxacin, the patient's respiratory condition progressively deteriorated within a few hours of admission. Considering the possibility of medication-induced lung injury, all medications were withdrawn, including bofutsushosan. Due to the rapid deterioration of the patient, methylprednisolone pulse therapy (1,000 mg/day for 3 days) was initiated. The respiratory condition of the patient improved in response to the pulse therapy and the chest CT scan, which was performed 2 weeks after initiation of steroid therapy, showed that the GGOs in each lung had disappeared, although dense consolidations remained in certain areas of the lungs (Figs. 3 and 4). The patient was discharged without oxygen inhalation. Maintenance steroid therapy using prednisolone was tapered off within 3 weeks, and a relapse requiring oxygen therapy did not occur. The patient's respiratory condition remained stable 1 year after this occurrence of acute respiratory failure.

Discussion

Bofutsushosan, a herbal (traditional Kampo) medicine, is administered to treat obese patients in North-East Asia. Bofutsushosan was reported to exert various anti-obesity effects by stimulating the adipose tissue in rodents (4,5). Azushima *et al* recently reported that bofutsushosan exerted a favorable effect on metabolism, including an antihypertensive effect, via its beneficial effect on adipose tissue function, as well as its appetite inhibitory effect in a mouse model of human metabolic disorders with obesity (6). The present study describes the case of a patient who was successfully treated for a pulmonary injury that was potentially associated with bofutsushosan therapy.

Numerous types of therapeutic agent cause lung injury (7,8); however, the incidence varies for each individual therapeutic agent. Typically, therapeutic agent-induced lung injury occurs with acute (day to weeks) or subacute (months) presentation. Symptoms, such as dyspnea on exertion and a non-productive cough, as well as specific markers, such as KL-6, are generally unremarkable. Although the most common abnormality observed by chest CT is GGOs with or without consolidation,

although chest radiography and chest CT findings are unremarkable. There are no universal diagnostic criteria for therapeutic agent-induced lung injury. Therefore, the diagnosis of therapeutic agent-induced lung injury generally depends on a definite temporal association between an exposure to the causative agent and the development of respiratory symptoms. The most important factor for an accurate diagnosis is the exclusion of all other possible explanations for the cause of the lung injury (8).

In the present study, heart failure and pulmonary infection were ruled out to establish a final diagnosis of bofutsushosan-induced lung injury. As mentioned above, no signs of suspected congestive heart failure, such as jugular venous distention, edema, and extra heart sounds were identified. The echocardiographic assessment showed that the left ventricular ejection fraction and wall motion were normal. Diuretics, a β-blocker, an angiotensin-converting enzyme inhibitor and *Digitalis* were not required for the treatment of this patient. Therefore, this episode was determined to be unrelated to heart failure. Additionally, respiratory infection was excluded from the differential diagnosis, as the broad-spectrum antibiotics were invalid. The patient in the present study had been taking bofutsushosan for 2 months prior to the development of her symptoms. The dyspnea had rapidly worsened since that time, but improved following the discontinuation of bofutsushosan and the initiation of steroid therapy. Certain cases of therapeutic agent-induced interstitial lung injury demonstrated sequelae of fibrosis, consolidation and organization (9,10). However, with considerable resolution of the GGOs, an improvement of the respiratory condition of the current patient was achieved.

Thus, the present study describes a case of lung injury associated with bofutsushosan in a patient. To the best of our knowledge, this is the first case report showing bofutsushosan-induced lung injury in English literature. Diffuse GGOs were present throughout each of the lungs, which is a common finding in therapeutic agent-induced lung injury (11). Bofutsushosan is becoming an increasingly prescribed medication for obesity control. Although the underlying mechanism by which bofutsushosan induces lung injury remains unclear, clinicians must be aware of the possibility of this condition to prevent further morbidity and mortality in obese patients.

References

1. Matsushima H, Takayanagi N, Ubukata M, Tokunaga D, Mori S, Sato N, Kurashima K, Yanagisawa T, Sugita Y, Kawabata Y, *et al*: A case of pneumonitis induced by Bofu-tsusho-san. Nihon Kokyuki Gakkai Zasshi 40: 955-959, 2002 (In Japanese).
2. Suzuki S, Tanaka A, Arai T and Adachi M: Case of interstitial pneumonitis induced by a Chinese herbal medicine, bofu-tsusho-san. Nihon Kokyuki Gakkai Zasshi 42: 777-781, 2004 (In Japanese).
3. Hatanaka N, Yamagishi T, Kamemura H, Nakazawa I, Hirano Y, Hosaka K, Sanno K and Takahashi K: A case of hepatitis and pneumonitis caused by Bofutsusyo-san herbal medicine. Nihon Kokyuki Gakkai Zasshi 44: 335-339, 2006 (In Japanese).
4. Yoshida T, Sakane N, Wakabayashi Y, Umekawa T and Kondo M: Thermogenic, anti-obesity effects of bofu-tsusho-san in MSG-obese mice. Int J Obes Relat Metab Disord 19: 717-722, 1995.
5. Ono M, Ogasawara M, Hirose A, Mogami S, Ootake N, Aritake K, Higuchi T, Okamoto N, Sakamoto S, Yamamoto M, *et al*: Bofutsushosan, a Japanese herbal (Kampo) medicine, attenuates progression of nonalcoholic steatohepatitis in mice. J Gastroenterol 49: 1065-1073, 2014.
6. Azushima K, Tamura K, Wakui H, Maeda A, Ohsawa M, Uneda K, Kobayashi R, Kanaoka T, Dejima T, Fujikawa T, *et al*: Bofu-tsu-shosan, an oriental herbal medicine, exerts a combinatorial favorable metabolic modulation including antihypertensive effect on a mouse model of human metabolic disorders with visceral obesity. PLoS One 8: e75560, 2013.
7. Copper JA Jr: Drug-induced lung disease. Adv Intern Med 42: 231-268, 1997.
8. Camus P, Fanton A, Bonniaud P, Camus C and Foucher P: Interstitial lung disease induced by drugs and radiation. Respiration 71: 301-326, 2004.
9. Nakajima R, Sakai F, Mimura T, Tokuda H, Takahashi M and Kimura F: Acute- or subacute-onset lung complications in treating patients with rheumatoid arthritis. Can Assoc Radiol J 64: 200-207, 2013.
10. Papiris SA, Triantafillidou C, Kolilekas L, Markoulaki D and Manali ED: Amiodarone: Review of pulmonary effects and toxicity. Drug Saf 33: 539-558, 2010.
11. Kuhlman JE: The role of chest computed tomography in the diagnosis of drug-related reactions. J Thorac Imaging 6: 52-61, 1991.