INTERNAL MEDICINE

□ CASE REPORT □

Diffuse Alveolar Hemorrhage Associated with Makyo-kanseki-to Administration

Yuko Iida, Yuki Takano, Yusaku Ishiwatari, Akiko Yoshida, Tetsuo Shimizu, Reiko Ito, Tomohiro Hattori, Noriaki Takahashi and Shu Hashimoto

Abstract

We herein describe the first known case of diffuse alveolar hemorrhage (DAH) associated with the administration of Makyo-kanseki-to, a Chinese herbal drug. A 64-year-old man with bronchial asthma presented with persistent cough. Makyo-kanseki-to was prescribed as an adjunctive treatment for bronchial asthma. Immediately after drug ingestion, the patient expectorated bloody sputum. DAH was diagnosed based on the presence of bilateral ground-glass opacity which was identified on chest computed tomography and bloody bronchoalveolar lavage fluid. We diagnosed that the administration of Makyo-kanseki-to was the responsible medication because the hemorrhage developed immediately after drug ingestion and resolved after the cessation of such medication with no subsequent recurrence.

Key words: diffuse alveolar hemorrhage, drug-induced interstitial pneumonia, Chinese herbal drugs

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Introduction

Diffuse alveolar hemorrhage (DAH) is a recognized clinicopathological syndrome associated with hemoptysis, anemia, and respiratory failure. The pulmonary histopathology in DAH is characterized by the accumulation of alveolar red blood cells that originate from the alveolar microcirculation (1). Various diseases can cause DAH, which presents with three general characteristic patterns classified according to the nature of the underlying vascular injury as follows: (a) vasculitis or capillaritis, such as that caused by connective tissue disorders, granulomatosis with polyangiitis (Wegener granulomatosis), or antiphospholipid antibody syndrome; (b) bland pulmonary hemorrhage (without capillaritis or vasculitis) without inflammation or any destruction of vessels, caused by anticoagulants or mitral stenosis; and (c) alveolar bleeding associated with another process with capillary destruction, such as diffuse alveolar damage (2).

Further, it has been reported that many medications can cause DAH, such as propylthiouracil, chemotherapy agents, anticoagulants, and thrombolytic agents (1). However, DAH has not previously been reported to be associated with Chinese herbal drugs, which are traditional Chinese medications comprising a blended decoction of several crude herbs, though Chinese herbal drugs, including Sho-sai-ko-to and Ou-gon, have been known to cause interstitial pneumonia (3).

Case Report

A 64-year-old Japanese male presented with a mild cough which had begun two weeks prior to presentation.

He had a history of bronchial asthma, type 2 diabetes mellitus, hypertension, and hyperlipidemia. His current medications included fluticasone/salmeterol, teneligliptin, amlodipine besilate, and pitavastatin. We considered that his bronchial asthma was an atopic phenotype because he had infantile asthma and a specific IgE antibody for epidermoptidae was positive. The bronchial asthma was well-controlled with infrequent exacerbations once every few years. He had never had any food or drug allergies.

Auscultation of the lungs revealed no wheezing and oxygen saturation was 98%. Since the persistent cough seemed to be associated with the chronic symptoms of bronchial asthma, we prescribed Makyo-kanseki-to, which had not

Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine, Japan
Received for publication December 14, 2015; Accepted for publication March 1, 2016
Correspondence to Dr. Yuko Iida, meyu14010@g.nihon-u.ac.jp

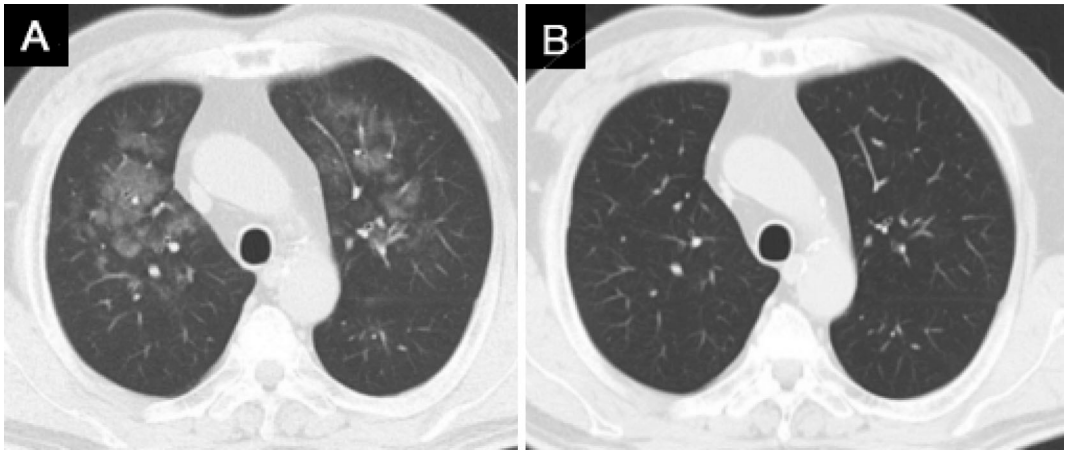

Figure 1. **Chest computed tomography on admission (A) showed the presence of bilateral ground-glass opacity in the upper lung, which disappeared by day 12 (B).**

Table. **Findings of Bronchoalveolar Lavage Fluid.**

Total cell counts (/μL)	270
Erythrocytes (%)	many
Macrophages (%)	79.5%
Hemosiderin-laden macrophages (%)	38.5%
Lymphocytes (%)	10.5%
Neutrophils (%)	6.0%
Eosinophils (%)	3.0%
CD4/CD8	3.20

been administered before, as an adjunctive treatment for bronchial asthma.

Makyo-kanseki-to is a major Chinese herbal drug, comprising Chinese herbs, including Mao, Sekko, Kanzo, and Kyonin. These agents have bronchodilatory and anti-inflammatory effects (4).

A few hours after taking Makyo-kanseki-to, the patient expectorated bloody sputum, which continued for 9 days. Subsequently, he returned to our hospital and was hospitalized. Upon examination, the body temperature was 36.0°C, respiratory rate was 16 breaths/min, and oxygen saturation was 98%. He had bloody sputum but had no skin lesions or hematuria. Chest auscultation revealed slight wheezes which meant that we could not rule out a mild bronchial asthma attack.

Laboratory examinations showed a leukocyte count of 8,000/μL, an eosinophil count of 360/μL (4.5%), a hemoglobin level of 13.6 g/dL, and a platelet count of 215,000/μL. The hemoglobin level had not decreased. The KL-6 level was negative (455 U/mL). Coagulation studies, biochemical results, and urine tests revealed no abnormalities. Myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) and proteinase-3 anti-neutrophil cytoplasmic antibody (PR-3 ANCA) tests were negative.

CT scans on admission showed the presence of bilateral ground-glass opacity (Fig. 1A). Bronchoalveolar lavage (BAL) was performed since the CT scan findings and persistent bloody sputum suggested an alveolar hemorrhage (Table). The bronchoalveolar lavage fluid (BALF) was red in color (Fig. 2A) and a microscopic examination revealed 38.5% of hemosiderin-laden macrophages (Fig. 2B).

Makyo-kanseki-to medication was suspected to be responsible for causing DAH, since it had never been administered previously and the drug lymphocyte stimulation test (DLST) showed strongly positive results. The stimulation index (SI) was 450%.

The Chinese herbal drug was discontinued; subsequently, hemosputum decreased on day 4 after discontinuation and disappeared completely by day 8. At 12 days after discontinuation, the bilateral ground-glass opacity on CT disappeared (Fig. 1B). The patient did not ingest Makyo-kanseki-to again, and no recurrence of DAH occurred after the patient's discharge from hospital.

Discussion

We herein described a case of DAH associated with the administration of Makyo-kanseki-to, a traditional Chinese herbal drug.

DAH is a clinicopathological syndrome characterized by bleeding from the alveolar capillaries, leading to symptoms of hemoptysis, anemia, dyspnea, and respiratory failure (1). In DAH, chest radiography and CT show variations of diffuse and sometimes patchy, ground-glass infiltration and consolidation. The diagnosis of DAH can be confirmed by progressively hemorrhagic BALF containing over 20% of hemosiderin-laden macrophages (5). In our case, DAH was diagnosed based on bilateral ground-glass opacity identified on the CT findings and the presence of 38.5% of hemosiderin-laden macrophages in BALF.

With respect to the cause of DAH, a diagnosis of drug-induced DAH is mainly made after excluding all other possible causes, an improvement in symptoms after discontinuation of the suspected medication, and/or a recognized exacerbation with drug rechallenge (6). In the present case, we diagnosed that Makyo-kanseki-to to have caused DAH because there were no other symptoms of connective disorder

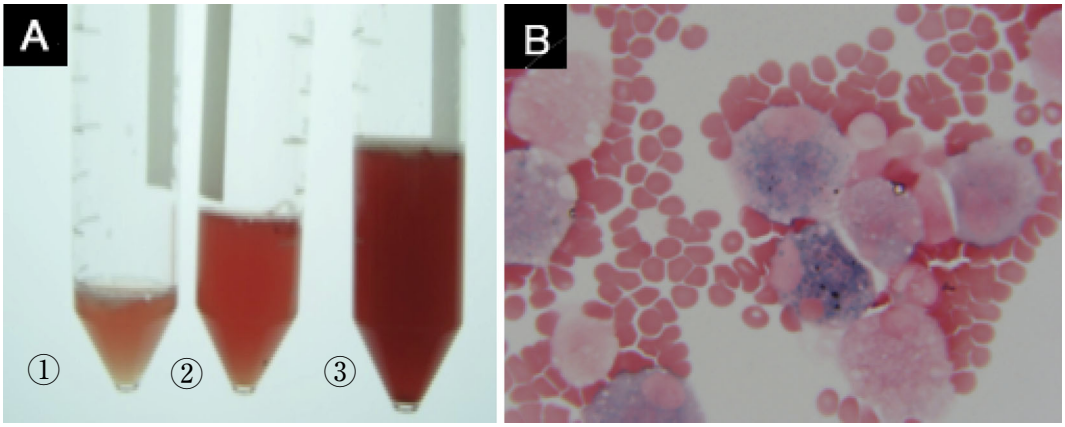

Figure 2. **The direct appearance of bronchoalveolar lavage fluid (A). Hematoid color increased on every lavage (total of 3). Bronchoalveolar lavage fluid (B) showed 38.5% of hemosiderin-laden macrophages for iron staining.**

or vasculitis. In addition, DAH resolved quickly with the discontinuation of Makyo-kanseki-to.

The etiological classification of drug-induced DAH includes three types: hypersensitivity, direct toxicity, and coagulation defects (2). In our patient, the expectoration of bloody sputum started within a few hours after taking the medication. In addition, DLST for the candidate medication was strongly positive. These factors suggested hypersensitivity to be the possible mechanism of DAH in our patient.

The mechanism of DLST involves active DNA synthesis by blastogenesis of lymphocytes, which react with the drug as an antigen. However, some reports have described that Chinese herbal drugs may sometimes have immunomodulatory activities, which could be associated with contaminant non-specific mitogens from plants, resulting in false-positive results for the test (7). Thus, positive DLST results could not be regarded as definitive evidence in our case; however, we considered it to be supportive evidence and diagnosed drug-induced DAH based on the other clinical evidence.

Chinese herbal drugs have been reported to cause interstitial pneumonia via hypersensitivity mechanisms, with positive DLST results (7). It is unclear why similar Chinese herbal drugs could cause different patterns of lung injury, i.e., interstitial pneumonia and hemorrhage, although hypersensitivity was a possible mechanism responsible for both injury patterns.

In conclusion, we herein reported the first known case in which a Chinese herbal drug can cause DAH, although the precise underlying mechanism remains to be elucidated.

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

References

1. Schwarz MI, Fontenot AP. Drug-induced diffuse alveolar hemorrhage syndromes and vasculitis. Clin Chest Med **25**: 133-140, 2004.
2. Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest **137**: 1164-1171, 2010.
3. Kubo K, Azuma A, Kanazawa M, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. Respir Investig **51**: 260-277, 2013.
4. Kao ST, Yeh TJ, Hsieh CC, Shiau HB, Yeh FT, Lin JG. The effects of Ma-Xing-Gan-Shi-Tang on respiratory resistance and airway leukocyte infiltration in asthmatic guinea pigs. Immunopharmacol Immunotoxicol **23**: 445-458, 2001.
5. De Lassence A, Fleury-Feith J, Escudier E, Beaune J, Bernaudin JF, Cordonnier C. Alveolar hemorrhage. Diagnostic criteria and results in 194 immunocompromised hosts. Am J Respir Crit Care Med **151**: 157-163, 1995.
6. Camus P, Fanton A, Bonniaud P, Camus C, Foucher P. Interstitial lung disease induced by drugs and radiation. Respiration **71**: 301-326, 2004.
7. Takeshita K, Saisho Y, Kitamura K, et al. Pneumonitis induced by ou-gon (scullcap). Intern Med **40**: 764-768, 2001.