

Development of diffuse alveolar damage after initiation of Nijutsuto

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Abstract

Chinese traditional medicine, Nijutsuto, is used to treat patients with frozen shoulder and osteoarthritis. Herbal medicine is often linked to the development of interstitial lung disease. An 83-year-old Japanese man with osteoarthritis who was on Nijutsuto was admitted to our hospital with dyspnoea and severe cough after 2 weeks from initiation of Nijutsuto. A chest computed tomography scan on admission showed diffuse ground glass opacity with traction bronchiectasis. Thus, he was diagnosed with Nijutsuto-induced interstitial lung disease, and was treated with a high dose of methylprednisolone and cyclophosphamide. However, the patient died of respiratory failure 2 weeks after admission. The patient was definitively diagnosed with diffuse alveolar damage by pathological autopsy. Nijutsuto contains *Radix Scutellariae*, which is considered to be the cause of interstitial lung disease. Chinese traditional medicine containing both *Radix Scutellariae* and *Licorice* should be carefully used because of its potential role in the development of diffuse alveolar damage.

Introduction

Herbal medicine is known to have a few side effects and is used to treat many diseases in Japan. There are several case reports about development of interstitial lung disease (ILD) induced by herbal medicine, particularly Bofutsushosan and Sho-saiko-to. Nijutsuto is used to treat joint pain, frozen shoulder, and osteoarthritis (OA). In this study, we report a rare case of development of diffuse alveolar damage (DAD) during treatment of OA with Nijutsuto.

Case Report

An 83-year-old Asian Japanese man was admitted to our hospital with dyspnoea and severe cough. Two weeks before admission, he was diagnosed with OA and was started on treatment with Nijutsuto. There were no newly administered medicines except for Nijutsuto for the last 1 year prior to admission. This patient had a past history of

hepatitis type C infection. His initial vital signs on admission were body temperature, 36.8°C; respiratory rate, 24 breaths/min; and oxygen saturation (SpO₂) on room air lying quietly, 91%. A physical examination revealed fine crackles in both lower lung fields. The laboratory test values were white blood cell counts, 10,600/μL; neutrophil counts, 8090/μL; serum lactate dehydrogenase, 444 IU/L (normal, 119–229 IU/L); serum Krebs von den Lungen-6 (KL-6), 1480 U/mL (normal, < 500 U/mL); serum pulmonary surfactant protein-D (SP-D), 962 ng/mL (normal < 110 ng/mL); serum C-reactive protein, 8.4 mg/dL (normal < 0.3 mg/dL); and plasma (1–3) beta-D-glucan < 10 pg/mL (normal < 20 pg/mL). Results for antibodies associated with collagen vascular diseases were all negative. The arterial blood gas values on room air were pH, 7.42; PaO₂, 58.2 torr; PaCO₂, 36.4 torr; and bicarbonate, 24.8 mg/dL. No organisms were isolated on culturing of the sputum, urine, and blood samples. Tests for influenza (rapid flu test), *Mycoplasma* antigen in pharynx, *Streptococcus pneumoniae*

antigen in urine, and *Legionella* antigen in urine showed negative results. A chest radiograph (Fig. 1A) showed reticular shadows in both lung fields. A chest high-resolution computed tomography (HRCT) scan showed non-segmental diffuse ground glass opacity (GGO) with traction bronchiectasis (Fig. 1B). There was no evidence of reduced heart function on echocardiography. On the third day after admission, we performed a bronchial alveolar lavage (BAL) from the left B⁵ bronchus. The total cell count and lymphocyte frequency in the BAL fluid were $2.0 \times 10^5/\text{mL}$ (normal range, $0.7\text{--}2.0 \times 10^5/\text{mL}$) and 18%, respectively. A polymerase chain reaction test for *Pneumocystis jirovecii* on BAL fluid showed negative results. Therefore, the cause of progressive respiratory failure in this patient was considered to be development of ILD. Although he was treated with methylprednisolone (1 g/day for 3 days) and cyclophosphamide (600 mg for 1 day), he died of respiratory failure 2 weeks after admission. Autopsy was performed with written informed consent from the patient's family. Macroscopically, the lungs showed increased weight (left: 620 g, right: 920 g) and consolidation (Fig. 2A). Microscopically, hyaline membranes (Fig. 2C, arrow) and interstitial/intra-alveolar oedema were observed along with organization of exudates and proliferation of fibroblasts on Elastica van Gieson staining (Fig. 2B: low-power field; Fig. 2C: high-power field). However, there were no findings of honeycombing in both macroscopic and microscopic evaluation.

Discussion

To our knowledge, this is the first case report of autopsy findings describing development of DAD during treatment with Nijutsuto. The first report of the development of ILD induced by Sho-saiko-to, another form of herbal medicine, was published in 1989 [1]. Although there are many case reports on herbal medicine-induced ILD, the total incidence of ILD during treatment with herbal medicine, including Nijutsuto, remains unknown because many herbal medicines are sold commercially in Japan. Additionally, it is difficult to calculate and evaluate the incidence of the development of ILD induced by Nijutsuto because the number of patients treated with Nijutsuto are few compared with those treated with any other herbal medicine [1]. Nijutsuto has several ingredients, such as *Atractylodes Lancea*, *Atractylodes Rhizome*, *Pinellia Tuber*, *Licorice*, and *Radix Scutellariae*, which has been implicated in the development of ILD. With regard to other herbal medicines, various cases have reported development of ILD during treatment with Sho-saiko-to or Sai-rei-to, which has resulted in mortality. Among these two herbal medicines and Nijutsuto, the common ingredients are *Radix Scutellariae* and

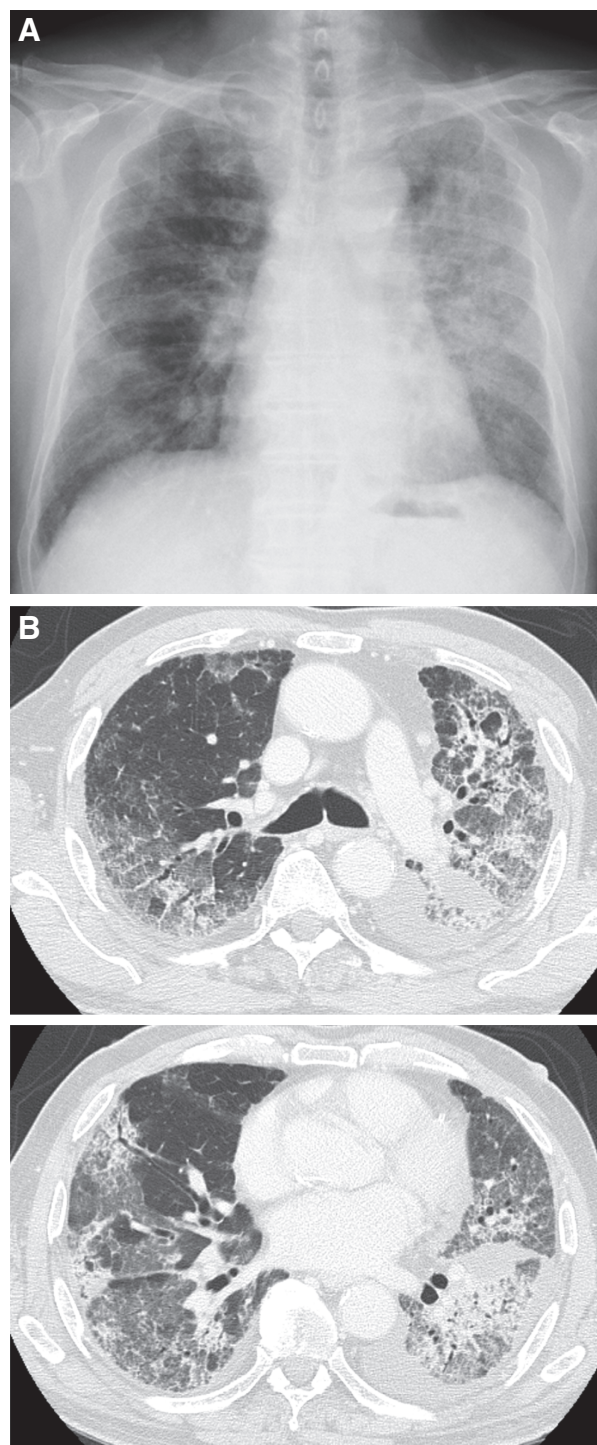


Figure 1. Chest radiological findings. (A) Chest radiographic findings on admission show diffuse ground glass opacity (GGO). (B) Chest high-resolution computed tomography findings on admission demonstrate diffuse subpleural GGO with traction bronchiectasis and slight pleural effusion.

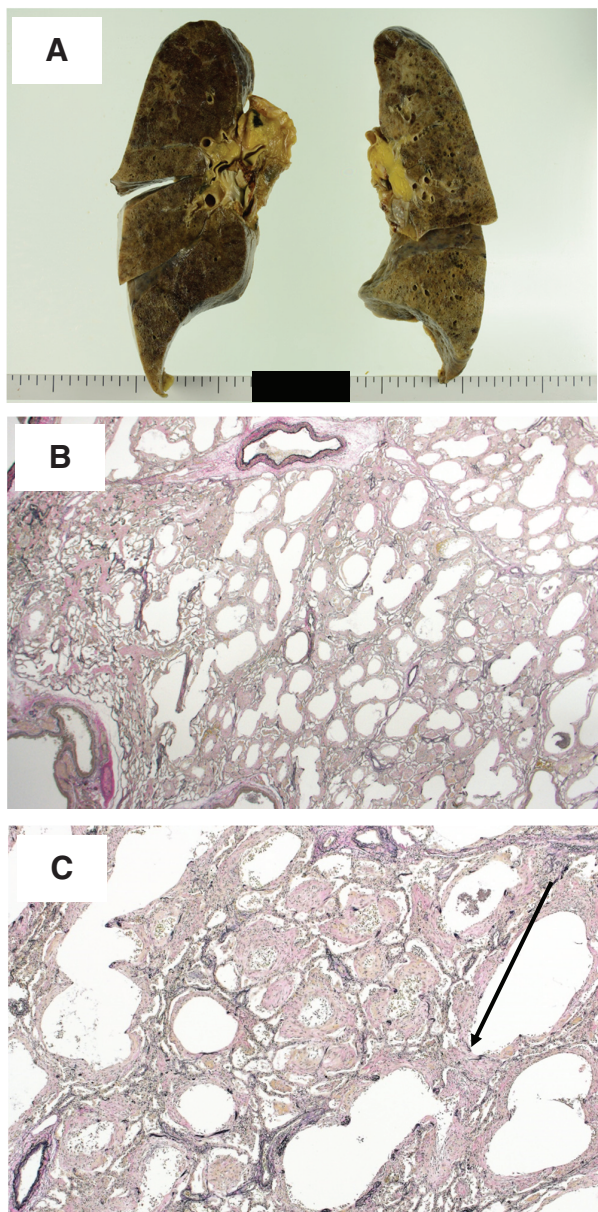


Figure 2. Pathological findings from autopsy. (A) Macroscopic findings demonstrating lungs with increased weight and appearance of consolidation; microscopic findings from the right lower lobe show hyaline membrane and fibroblast growth on Elastica van Gieson stain. Arrow: hyaline membrane. (B) Low-power field. (C) High-power field.

Licorice. However, there have been few reports of mortality due to development of ILD induced by herbal medicines that contained only one of the two ingredients, *Scutellariae radix* or *Licorice*. It has been reported that *Licorice* has various immunomodulatory activities that can interfere with immune responses [2]. Furthermore, many cases have been reported regarding

development of ILD during treatment with herbal medicine containing *Radix Scutellariae*. Therefore, a combination of these two ingredients, *Licorice* and *Radix Scutellariae*, may cause severe ILD.

On the other hand, no mortality has ever been reported related to herbal medicine-induced ILD associated with hepatitis type C viral infection and treatment with interferon for chronic hepatitis [3]. Although our patient was diagnosed with chronic hepatitis C and had received interferon for 10 years until 2005, he was considered to be in complete remission; furthermore, the hepatitis C virus had not been detected until this admission. Therefore, there was no association between development of ILD induced by Nijutsuto and hepatitis C in our patient.

In our case, KL-6 and SP-D levels were strongly elevated above the normal range. These markers are often used for distinguishing different types of drug-induced ILD. Thus, it has been reported that KL-6 levels are significantly higher in patients diagnosed with DAD or chronic interstitial pneumonia (IP) than in patients with other types of drug-induced ILD [4].

Pathological findings distinguish five types of drug-induced ILD, such as DAD, chronic IP, eosinophilic pneumonia, hypersensitivity pneumonia, and organizing pneumonia. However, it is unknown which types of ILD are specifically associated with the use of herbal medicine. Pathological findings in our patient demonstrated the presence of hyaline membranes, interstitial/intra-alveolar oedema, and organization of exudates with proliferation of fibroblasts. Based on these findings, our case may be considered to have had an organized phase of DAD [5,6].

The result of serum drug lymphocyte stimulation test (DLST) for Nijutsuto was negative in this case. However, there are many cases of false-negative results in serum DLST for herbal medicine. Therefore, we diagnosed this case as DAD induced by Nijutsuto based on chest HRCT findings [7], serum markers, exclusion of other causes of ILD, exclusion of any infections, heart, and renal failure, and the fact that there were no newly administered drugs besides Nijutsuto.

In conclusion, this is the first pathological finding of a case of DAD development associated with Nijutsuto. Herbal medicine containing both *Radix Scutellariae* and *Licorice* should be carefully used because of its potential ability to induce development of DAD.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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