Adult Respiratory Distress Syndrome Induced by a Chinese Medicine, Kamisoyoyo-San

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We report the first case of Kamisoyoyo-san-induced adult respiratory distress syndrome (ARDS). A 59-year-old female was given Kamisoyoyo-san for treatment of seborrheic dermatitis. She then presented with a respiratory illness having clinical, radiologic and functional characteristics of ARDS. Bronchoalveolar lavage fluid showed an increased number of lymphocytes, neutrophils and eosinophils. The lymphocyte stimulation test with Kamisoyoyo-san was positive. (Internal Medicine 35: 494–496, 1996)

Key words: lymphocyte stimulation test, bronchoalveolar lavage

Introduction

In Japan, Chinese medicines have been used in various diseases for centuries. More recently, the number of reports of Chinese medicine-induced pneumonitis has gradually increased. We report here a case of adult respiratory distress syndrome (ARDS), which was induced by the Chinese medicine, Kamisoyoyo-san. The patient required mechanical ventilation because of severe hypoxemia. To our knowledge, this is the first report of Chinese medicine-induced ARDS.

Case Report

A 59-year-old female had been well until 6 days before admission, when she started to take hydroxyzine pamoate, minocyclin and a Chinese medicine, Kamisoyoyo-san, for treatment of seborrheic dermatitis. One day before admission, she developed high fever, dry cough and dyspnea. Physical examination at the time of hospital admission revealed no abnormalities except fine crackles at the left lung base. Her body temperature was 39.5°C. Laboratory data revealed a white blood cell count of 5,470 with 73.5% neutrophils and 10.3% eosinophils, an erythrocyte sedimentation rate of 55 mm/h, C-reactive protein (CRP) of 16.3 mg/dl, fibrinogen degradation product (FDP) of 12 µg/dl, and hypoxemia (PaO₂: 68.1 mmHg; and PaCO₂: 32.0 mmHg).

Tests of anti-*Legionella*, anti-*Mycoplasma* and anti-*Chlamydia psittaci* antibodies were all negative. Sputum culture yielded normal respiratory flora. The findings from routine blood chemistries and urinalysis were normal. Chest X-ray film on admission revealed bilateral diffuse reticular infiltrates. A computed tomographic (CT) scan of the thorax showed bilateral patchy air-space consolidation (Fig. 1). Bilateral small pleural effusions were visible. Cefazolin and rifampicin were administered. On the second hospital day an X-ray film of the chest showed marked progression of the air-space disease (Fig. 2). PaO₂ was 48.4 mmHg and PaCO₂ was 34.9 mmHg on room air. The patient was admitted to an intensive care unit. An endotracheal tube was inserted and ventilatory assistance was begun. While the patient was ventilated with 80% oxygen, with intermittent mandatory ventilation (IMV) of 20 and with positive end-expiratory pressure (PEEP) of 3 cm, PaO₂ was 85.5 mmHg and PaCO₂ was 53.1 mmHg. On the third hospital day methylprednisolone, 500 mg daily, was started. After 5 days of administration, methylprednisolone was discontinued and prednisolone (60 mg) was begun. On the sixth hospital day a chest X-ray film showed moderate resolution of infiltrates. Bronchoalveolar lavage (BAL) was performed and the recovery of BAL was 53%; differential count of the white blood cells showed that 18.4% were macrophages, 35.8% lymphocytes, 8.6% eosinophils, and 37.0% neutrophils. The analysis of surface markers of lymphocytes in the BAL fluid showed that 68.5% were CD4 positive cells and 6.7% were CD8 positive cells. The concentration of carcinoembryonic antigen of BAL fluid was markedly elevated (21.7 ng/ml). Clearing of the pulmonary

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Figure 1. Computed tomography of the chest shows multiple patchy air-space consolidation with a small amount of pleural effusion.

Figure 2. Chest X-ray film on the second hospital day shows marked bilateral air-space consolidation.

Figure 3. Chest X-ray film at discharge shows complete clearing of alveolar opacities.

infiltrates occurred by the 8th hospital day, and bilateral small infiltrates remained peripherally. The ventilator was discontinued on the 9th hospital day. Lymphocyte stimulation tests with Kamisoyoyo-san and other drugs were performed just before the start of methylprednisolone. Only Kamisoyoyo-san significantly induced lymphocyte blastogenesis with a stimulation index of 5.2. The diagnosis of Kamisoyoyo-san-induced ARDS was then considered to be likely. Prednisolone was tapered and finally discontinued. All of the levels of ESR, CRP, PaO₂ and PaCO₂ became normal and X-ray film and CT of the thorax showed complete clearing of alveolar opacities at the time of discharge from hospital (Fig. 3).

Discussion

Chinese medicines generally consist of several different ingredients; some ingredients are commonly shared by different Chinese medicines. Kamisoyoyo-san contains 10 ingredients. Because of their mild and gradual therapeutic effects, little

attention has been paid to their side effects. Chinese medicine-induced interstitial pneumonitis was reported for the first time in 1989 by Tsukiyama et al (1). To our knowledge, 17 cases of Chinese medicine-induced pneumonitis have been reported up to 1995 (Table 1) (1–7). Provocation tests with the Chinese medicines have been performed in 9 of these cases. Eleven of the cases were induced by Sho-saiko-to and two cases by Saiboku-to. Pneumonia-inducing ingredients of Chinese medicines have been identified in only three cases. Those ingredients include scutellaria root (case 1), scutellaria root, pinellia tuber and bupleum root (case 12) and pinellia tuber (case 16). Kamisoyoyo-san consists of Tang-Kuei, peony, gardenia, atracylodes lancea rhizome, hoelen, mentha, bupleurum root, moutan, ginger rhizome and perilla herb and does not contain either scutellaria root or pinellia tuber. In these 17 cases the length of treatment with Chinese medicines prior to the development of symptoms varied from 2 hours to 1 year, with a mean duration 4.6 months. Signs and symptoms developing in these patients included fever, cough and dyspnea on exercise. BAL lymphocytosis was found in all 8 cases studied. In 7 of the 8 cases, the ratio of CD4 to CD8 lymphocytes of BAL fluid was less than 1.0. The present report, however, indicates that lung injury in this case was associated with a significant increase in the percentage of CD4-positive rather than CD8-positive lymphocytes. The reasons that the CD4/CD8 ratios of lymphocytes in BAL fluid are increased in some cases and not in others are unknown. In this case the corticosteroid therapy might have increased the CD4/CD8 ratio of lymphocytes in the BAL fluid.

In the context of marked respiratory distress, diffuse pulmonary infiltration on chest roentgenogram and impairment of

Table 1. Age, Sex, Chief Complaints, BAL Findings, Diagnostic Procedures and Treatment of Chinese Medicine-Induced Lung Injury

No.	Author	Year	Age	Sex	Medicine	Chief complaint	Duration of medicine intake	Cells in BAL		LST	Challenge test
								Lymphocyte (%)	CD4/CD8		
1	Tsukiyama	1989	71	F	Sho-saiko-to	Fever	6 months	N.D.	N.D.	+	+
2	Sujiura	1990	61	M	Sho-saiko-to	Dyspnea on exercise	1 year	71	0.11	—	+
3	Iinuma	1990	46	M	Sho-saiko-to	Fever	5 weeks	66	0.04	—	+
4	Koyanagi	1991	50	M	Sho-saiko-to	Dyspnea	2 weeks	N.D.	N.D.	—	+
5	Koyanagi	1991	63	M	Sho-saiko-to	Fever	3 months	N.D.	N.D.	—	+
6	Miyazawa	1991	66	F	Sho-saiko-to	Fever	3 weeks	41	1.8	+	N.D.
7	Miyazawa	1991	65	M	Sho-saiko-to	Fever	3 weeks	48	0.25	+	N.D.
8	Kubota	1991	58	M	Sho-saiko-to	Dyspnea on exercise	3 months	N.D.	N.D.	+	N.D.
9	Kubota	1991	50	F	Juzentaiho-to	Fever, Cough	6 months	N.D.	N.D.	+	N.D.
10	Kubota	1991	48	M	Keishibukuryou-gan	Dyspnea on exercise	4 weeks	N.D.	N.D.	+	N.D.
11	Souda	1991	56	F	Saiboku-to	Fever, Cough	5 months	N.D.	N.D.	+	N.D.
12	Imokawa	1992	49	F	Sho-saiko-to	Fever	2 months	37.5	0.3	+	+
13	Watanabe	1992	56	F	Sho-saiko-to	Dyspnea	6 weeks	90	0.1	±	+
14	Tomioka	1992	66	M	Sho-saiko-to	Dyspnea on exercise	3 months	25	0.57	+	N.D.
15	Daibo	1992	56	M	Sho-saiko-to	Fever	2 months	N.D.	N.D.	+	+
16	Maruyama	1994	79	F	Rikkunshi-to	Dyspnea on exercise	6 months	45.9	0.18	+	N.D.
17	Temaru	1994	60	F	Saiboku-to	Dyspnea	2 hours	N.D.	N.D.	+	+
18	present case		59	F	Kamisyo-yo-san	Dyspnea, Fever	4 days	35.8	10.2	+	N.D.

LST: lymphocyte stimulation test, N.D.: not determined, D.M.: discontinuation of medicine.

oxygen transport, this patient's disorder is in accordance with the adult respiratory distress syndrome (8). The increased number of eosinophils in the peripheral blood and bronchoalveolar lavage fluid suggests that eosinophilic pneumonia might have been induced by Kamisyo-yo-san initially, followed by the development of ARDS. Due to the lack of histological documentation of the lesion at early stages of the disease, we can not confirm this.

There are several previous reports of drug-induced ARDS (9, 10). This is the first report of ARDS induced by Chinese medicines. Hereafter appropriate consideration must be given to the possible occurrence of medication-induced lung injury in patients being treated with Chinese medicines.

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