Pneumonitis Induced by Ou-gon (Scullcap)

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Abstract

A 53-year-old Japanese man with recurrent interstitial pneumonia was referred to us. The patient had taken a traditional herb medicine, otsu-ji-to, before the onset of pneumonia. A provocation test for each herbal ingredient contained in otsu-ji-to revealed that the pneumonitis had been induced by ou-gon (scullcap). Lymphocytosis with the CD8+ T-cell subset predominance was found in the bronchoalveolar lavage fluid and lymphocytic alveolitis was noted in the transbronchial lung biopsy specimen after the provocation test. Ou-gon, or scullcap, should be included in the list of drugs with definite causal association with pneumonitis.

(Key words: herb medicine, drug-induced pneumonitis)

Case Report

A 53-year-old Japanese man was admitted to a local hospital with complaints of acutely developed high fever (39°C), dyspnea, and dry cough, on May 5, 1999. Chest radiography and computed tomography (CT) demonstrated ground glass-like and reticular opacities predominantly in the bilateral lower lung fields (Fig. 1). The peripheral leukocyte count was 14,200/mm³ and the serum C-reactive protein level was 19.5 mg/dl. The erythrocytes sedimentation rate was 54 mm/h. Blood biochemistry analysis revealed mild elevation of hepatic transaminase levels (AST 64 IU/l, ALT 86 IU/l). Breathing room air, arterial blood gas analyses were PaO₂ 54.2 Torr, PaCO₂ 37.6 Torr, and pH 7.42. Cefotiam was empirically administered intravenously. Fever, hypoxemia, and interstitial shadows were resolved on May 14. The patient went home on May 16, but developed fever as well as dyspnea 10 hours later. When he was readmitted to the hospital, the chest radiography and CT showed recurrence of interstitial pneumonia. Since the physicians suspected the patient had Japanese summer-type hypersensitivity pneumonitis, they referred him to us for a further evaluation on June 11. On admission to our hospital, he was afebrile and chest auscultation revealed slight fine crackles in his lower back. Pulmonary function tests showed restrictive impairment and decreased single-breath diffusing capacity of carbon monoxide. Chest CT revealed subpleural reticular shadows in the bilateral lower lung fields. On June 18, the peripheral leukocyte count and acute phase reactants were normal. The patient confessed to us that he had been taking otsu-ji-to, a kampo drug, for hemorrhoids since March 5, 1999, and had discontinued it during his stay in the hospital. He was discharged from our hospital on June 19. The patient never again took otsu-ji-to, and neither fever nor respiratory symptoms recurred. Although the lymphocyte stimulation test (LST) for otsu-ji-to
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Figure 1. Left: Chest radiograph on admission to a local hospital showing diffuse interstitial shadows predominantly in the bilateral lower lung fields. Right: Chest CT at the same time revealed extensive ground glass opacities and reticular shadows.

using lymphocytes obtained from peripheral blood was negative, we tentatively diagnosed him as having had otsu-ji-to-induced pneumonitis judging from the clinical course.

Otsu-ji-to is a herbal medicine approved by the Japanese Ministry of Health and Welfare for hemorrhoids. It is a blend of 6 kinds of plant extracts; ou-gon, sai-ko, tou-ki, kan-zou, dai-ou, and shou-ma. The patient wished to continue taking otsu-ji-to and to elucidate the cause of his bouts of pneumonia; he gave written consent to a provocation test, after being informed of the possible development of severe pneumonia. We, thus, conducted a provocation test for each herbal ingredient (Fig. 2). We used the same amount of each ingredient contained in a single dose of otsu-ji-to (1.5 g of ou-gon, 2.0 g of sai-ko, 2.0 g of tou-ki, 1.0 g of kan-zou, 0.5 g of dai-ou, and 0.8 g of shou-ma) and the patient took three doses a day for 2 days unless a positive reaction appeared. In the first place, ou-gon was administered on July 11. High fever and hypoxemia developed 7 hours later. Elevation of acute phase reactants and serum KL-6 was noticed. Chest radiography and CT demonstrated diffuse interstitial shadows predominantly in the lower lung fields (Fig. 3). Lymphocytes were markedly increased with CD8+ T-cell subset predominance in the bronchoalveolar lavage fluid (BALF) obtained on July 13 (Table 1). Lymphocytic alveolitis was seen in the transbronchial lung biopsy (TBLB) specimen taken in the left lower lung (Fig. 4). Eosinophilic infiltration was also noticed. The LST for otsu-ji-to using lymphocytes in BALF was negative. His symptoms as well as abnormal laboratory data, radiograph, and oxygenation were resolved by July 18, without using steroids or other anti-inflammatory drugs (Figs. 2, 3). Provocation tests for the other 5 plant extracts were negative. Consequently, we made a diagnosis of pneumonitis induced by ou-gon. Mild lymphocytosis of BALF was sustained until October 22, 1999 (Table 1).

Discussion

In 1989, Tsukiyama et al (7) reported, in the Japanese literature, the first case of pneumonitis induced by a kampo drug, which was sho-saiko-to, the most consumed kampo drug in Japan. This herb medicine has been approved to be effective for treating chronic active hepatitis in Japan and has recently been introduced in Western countries (8). Tsukiyama et al (7)
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Figure 2. Clinical course.

Figure 3. Serial CT scans of the chest. Left: Before the provocation tests, no abnormalities were seen. Middle: CT scan, obtained 2 days after the provocation test for ou-gon, showing ground-glass opacities and reticular shadows. Right: CT scan, obtained after the provocation tests for 5 herbs other than ou-gon, remaining normal.

Table 1. Findings of Bronchoalveolar Lavage Fluid

<table>
<thead>
<tr>
<th></th>
<th>Jul. 13</th>
<th>Jul. 28</th>
<th>Oct. 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cell counts (×10⁵/ml)</td>
<td>26.8</td>
<td>8.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Macrophages (%)</td>
<td>18.2</td>
<td>53.5</td>
<td>77.0</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>43.6</td>
<td>43.1</td>
<td>21.5</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>30.5</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>7.7</td>
<td>3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>CD4+/CD8+ ratio</td>
<td>0.4</td>
<td>0.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

exerted a provocation test for sho-saiko-to and found that sho-saiko-to was causative of pneumonitis in their patient. Sho-saiko-to consists of 7 kinds of herbal extracts including ou-gon, but the causative agent had not been elucidated. Then, in 1999, Nishimori et al (9) reported a case of pneumonitis associated with sho-saiko-to and ouren-gedoku-to. Their patient presented a positive result in the provocation test for each drug and they speculated that ou-gon was the cause of pneumonitis in their patient since it was the only herbal ingredient common to the two drugs. Fujii et al (10) described sai-boku-to-associ-
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Figure 4. Histology of transbronchial lung biopsy specimen demonstrating mild fibrotic change in alveolar septa and lymphocytic infiltration in alveoli. Eosinophilic infiltration was also seen (HE Stain, x100).

ated pneumonitis and speculated, based on the results of LST for the ingredients, that ou-gon was the causative agent. In the English literature, Ishizaki et al (11) described 4 patients with chronic active hepatitis who developed pneumonitis while under therapy with interferon and/or sho-saiko-to. An LST using peripheral lymphocytes was positive to interferon in one and to sho-saiko-to in another of their patients, but they did not discuss about the ingredients of sho-saiko-to.

The Japanese Ministry of Health and Welfare has approved 148 types of kampo drugs up to 1999. Nakagawa et al (12) conducted a Japanese national surveillance of drug-related pneumonitis, and reported that the cases of kampo drug-related pneumonitis accounted for as much as 10% (75 cases due to 13 kinds of kampo drugs) of all the cases of drug-related pneumonitis in Japan from 1984 to 1996. Calculating from their data, 84% of the cases of kampo drug-related pneumonitis were associated with drugs containing ou-gon, i.e. sho-saiko-to, saiboku-to, sai-rei-to, sei-hai-to, dai-saiko-to, saiko-keishi-to, and saiko-keishi-kanshou-to. Including these drugs, the Japanese Ministry of Health and Welfare has approved 29 kinds of the kampo drugs which contain ou-gon.

LST is an in vitro procedure using isotope-labeled nucleotides to detect an increase in nucleic acid synthesis as an index for lymphocyte hypersensitivity (11). According to the data comparing the results of LST and those of provocation tests in patients allergic to antituberculous agents, LST showed a false negative ratio of 30% and a false positive ratio of 24%, respectively (13). Although Kawasaki et al (14) reported that LST using lymphocytes in BALF could be more sensitive than that using peripheral lymphocytes, its reliability has not been confirmed. In the present case, the results of the LST using peripheral blood and BALF were negative to otsu-ji-to. Furthermore, some kampo specialists warned that the results of LST, in case of kampo drugs, tend to be overestimated because kampo drugs are generally contaminated with non-specific mitogens from plants (15). These facts indicate that LST is not reliable for a diagnosis of pneumonitis induced by a kampo drug. Although a patient with severe pneumonitis which requires steroid or other immunosuppressive therapy for the resolution should not undergo a provocation test, it remains as the only reliable diagnostic procedure to identify the causative agent of drug-induced pneumonitis (16). Since pneumonitis in the present patient resolved immediately after discontinuing taking otsu-ji-to without using steroidal agents, we considered that a provocation test would not be so dangerous for our patient and performed it for each herbal ingredient of otsu-ji-to. Because only ou-gon and not the other herbal ingredients induced pneumonitis, we concluded decisively that the pneumonitis seen in our patient was caused by ou-gon. Although pulmonary adverse effects from some drugs may vary (6), previous reports on kampo drug-associated pneumonitis described the common clinical features: fever, dry cough, dyspnea, hypoxemia, diffuse interstitial shadows both on chest radiograph and CT, restrictive impairment on pulmonary function tests, lymphocytic alveolitis on TBLB, and lymphocytosis with predominance of the CD8+ T cell subset in BALF (7, 9–11). The findings seen after the provocation test for ou-gon in our patient were consistent with those of the previous reports.

Pneumonitis induced by a herb medicine may not only be a Japanese domestic problem. Ou-gon, an extract of Scutellaria roots, is called scullcap in the United States and Europe. Western traditional healers also utilize it as a herbal medicine because they believe that scullcap is effective for convulsions, hysteria, nervous tension, and epilepsy (17). In fact, scullcap is available in capsules, concentrated drops, liquid extract, tablets, teas, and tincture, and appears as an ingredient of numerous herbal tea blends in the United States (17). Scullcap is sold on the internet as well as in drug stores under the conviction that it is effective for insomnolence and anxiety.

Here, we clearly demonstrated that ou-gon, or scullcap, induced the pneumonitis in our patient. Based on the previous reports concerning kampo drug-related pneumonitis including the present case, the association between ou-gon and pneumonitis is definite. We emphasize that not only Japanese physicians but also those in Western countries should take much precaution against development of pneumonitis in patients taking a herb medicine that contains ou-gon or scullcap.

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References


