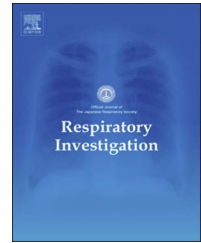




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Original article

Japanese herbal medicine-induced pneumonitis: A review of 73 patients

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ABSTRACT

Background: The number of reports concerning Japanese herbal medicine (JHM)-induced pneumonitis has increased. However, comprehensive data are lacking in this regard, and the clinical characteristics of the disease remain unclear.

Methods: A literature review was performed using PubMed and Ichushi-Web—the database of the Japan Medical Abstracts Society—to identify articles published between 1996 and 2015 describing patients with JHM-induced pneumonitis. The final cohort included 73 patients in 59 articles (7 in English; 52 in Japanese).

Results: Among the various JHMs reported, *sho-saiko-to* was the most frequently used drug (26%), followed by *sairei-to* (16%), *seishin-renshi-in* (8%), and *bofu-tsusyo-san* (8%). These drugs commonly contain *ougon* (skullcap) and *kanzo* (liquorice). The mean age at pneumonitis diagnosis was 63.2 ± 15.5 years (range: 7–89 years). The male/female ratio was 44/29. Sixty-five patients (89%) developed pneumonitis within 3 months of beginning JHM treatment. Bilateral ground-glass attenuations on chest computed tomography, as well as lymphocytosis with a low CD4/CD8 T-cell ratio in bronchoalveolar lavage fluid, were common findings. Twenty-six patients (36%) recovered from the pneumonitis after simply discontinuing the causative JHM. However, the remainder required immunosuppressive therapy, and 13 patients (18%) received mechanical ventilation. Importantly, three patients (4%) did not survive, with two showing pathological diffuse alveolar damage upon autopsy.

Conclusions: Clinicians should be cautious regarding JHM-induced pneumonitis, particularly when using drugs/ingredients known to cause this complication, and during the early treatment period. Although most events are non-severe, critical cases should be recognized.

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1. Introduction

Drug-induced pneumonitis is caused by numerous cytotoxic and non-cytotoxic drugs and can be mediated via several mechanisms: direct cell toxicity, free oxygen radical production, or immune-mediated injury [1,2]. The pathological manifestations also vary; they may include diffuse alveolar damage (DAD), fibrosing interstitial pneumonia, cellular interstitial pneumonia, organizing pneumonia, eosinophilic pneumonia, alveolar hemorrhage, and even granulomatous inflammation. In addition, these manifestations, as well as their related radiological findings, are generally non-specific in the case of any given drug [3,4]. Therefore, diagnosis of drug-induced pneumonitis is often challenging, and it is important that physicians accumulate clinical evidence in all suspected cases. In particular, a detailed medication history is essential, as are exclusion of other lung diseases and collation to previously reported literature.

Japanese herbal medicine (JHM), which makes use of various herbal ingredients, is traditionally used in Japanese clinical practice to treat a wide range of diseases or symptoms, such as allergies [5,6], infectious diseases [7,8], post-operative decreased bowel function [9], and prolonged cough [10]. Nonetheless, the pharmacological mechanisms of JHM are not fully understood.

Recently, the number of reports concerning JHM-induced pneumonitis has increased in Japan. However, most of these articles have only been published in the Japanese literature, and they are commonly limited to a single-case report. Comprehensive data regarding JHM-induced pneumonitis are lacking, particularly in the English literature. In the present study, to delineate the clinical characteristics of JHM-induced pneumonitis, we summarized all cases reported in the last 20 years.

2. Materials and methods

Using PubMed and Ichushi-Web (the database of the Japan Medical Abstracts Society), we searched the English and

Japanese literature for original articles and case reports published between January 1996 and December 2015 describing patients with JHM-induced pneumonitis (Fig. 1). We used the following keywords in English, or those with similar meanings in Japanese: (1) herbal medicine or Kampo; (2) pneumonitis or interstitial pneumonia. After reviewing all identified full-text articles and excluding irrelevant or inappropriate cases, we included 73 patients in 59 articles in the present study (Supplementary Tables 1 and 2). Seven of the articles were published in English, and 52 were published in Japanese.

We collected the following data: the causative JHM, age at pneumonitis diagnosis, gender, smoking history, body mass index, symptoms, duration of JHM treatment, laboratory data, radiological findings on chest X-ray and/or computed tomography (CT), pulmonary function test results, and bronchoalveolar lavage fluid (BALF) analyses. Furthermore, we reviewed the results of the lymphocyte stimulation test (LST) to assess lymphocytic hypersensitivity. The LST is an *in vitro* examination that uses isotope-labeled nucleotides, the patient's lymphocytes, and the suspected drug to evaluate changes in nucleic acid synthesis [11]. Finally, we recorded any pathological findings (if present), the severity of pneumonitis, treatment, and final clinical outcomes.

Data were described as either number with percentage or mean \pm standard deviation (with observed range). The Fisher's exact test or Mann-Whitney U test was used to compare groups, as appropriate. P-values of < 0.05 were considered significant. Statistical analyses were conducted using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Causative JHMs and their main ingredients

Table 1 summarizes the causative JHMs, as well as their main ingredients, in the 73 cases of JHM-induced pneumonitis. Among the various JHMs, *sho-saiko-to* (minor *bupleurum* decoction) was the most frequently used drug (19 patients; 26%); this was followed by *sairei-to* (minor *bupleurum* decoction plus *poria*

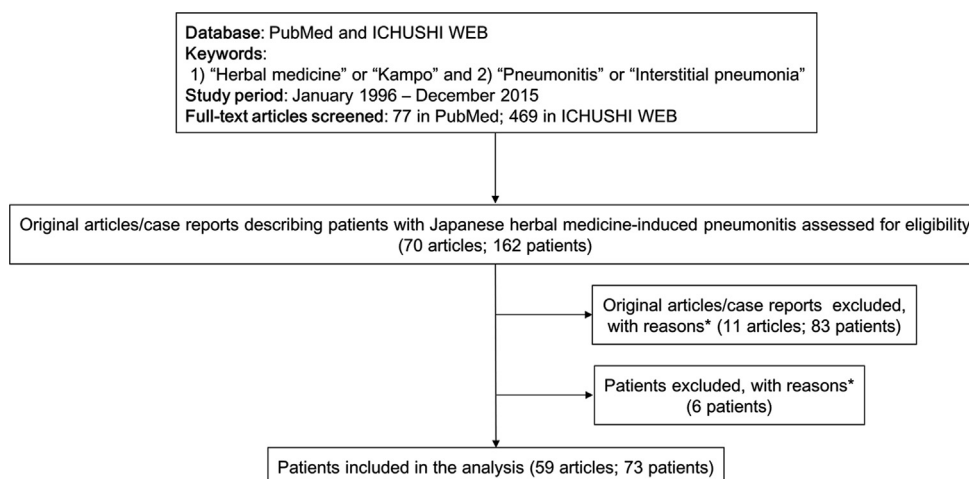


Fig. 1 – Flow diagram of the present study. *See Supplementary Table 2

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