Reactivation of Pulmonary Tuberculosis in a Patient with *Polygonum multiflorum* Thunb-Induced Hepatitis

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Several cases of *Polygonum multiflorum* Thunb-induced hepatitis have been reported worldwide. Anthraquinone is an active ingredient of *P. multiflorum* Thunb. that has been thought to play a role in its hepatotoxicity. Here we report the case of a 34-year-old Korean man who had *P. multiflorum* Thunb-induced hepatitis and reactivation of pulmonary tuberculosis caused by bone marrow suppression, which developed simultaneously. He was admitted to our hospital with recently developed fatigue and aggravated jaundice. He was a previously healthy man except for the sequelae of pulmonary tuberculosis seen on chest X-ray. He had a 30-day history of ingesting the root of *P. multiflorum* as a form of liquor and tea. The patient was diagnosed with *P. multiflorum* Thunb-induced hepatitis after excluding all other potential causes of acute hepatitis. Liver function gradually improved following the total cessation of the consumption of the material. However, he suffered from spiking fever with progressive pancytopenia during the hospital stay. A bone marrow biopsy showed markedly hypocellular marrow, suggesting transient bone marrow suppression, which was probably caused by extrinsic factors such as drugs, toxins, and viral infection. Although he began to complain of a dry cough, repeated sputum investigations revealed positive acid-fast bacillus staining. The fever subsided and pancytopenia improved after treatment for pulmonary tuberculosis. These observations suggest that *P. multiflorum* Thunb induces both bone marrow suppression and hepatotoxicity. (*Gut and Liver* 2009; 3:52-56)

Key Words: *Polygonum multiflorum* Thunb; Hepatotoxicity; Bone marrow suppression; Pulmonary tuberculosis

INTRODUCTION

Herbal or botanical use has been increasingly used for the treatment and prevention of diseases without a medical prescription on the basis of the belief that these treatments are 'natural' and 'safe'.¹⁻⁵ However, because most of herbal remedies have been used by experience, scientific bases are lacking for their effectiveness and safety in fact. Liver injuries associated with herbal or botanical use, relatively common adverse effects, were widely variable from merely abnormal liver test to hepatic failure.^{6,7} It is difficult to establish the direct causal relationship between hepatic injury and the individual herbal medicine or botanical which was a possibly suspicious cause of hepatic injury, even though we had often experienced similar clinical cases to this.

The tuberous root of *Polygonum multiflorum* has been well-known as both a tonic and an anti-aging agent in many remedies of traditional Chinese medicine.⁸ However, several cases have been reported concerning hepatotoxicity in association with *Polygonum multiflorum* Thunb worldwide.⁸⁻¹² Physicians should be also alert to notice other possible adverse effects as well as hepatotoxicity related to it.

We report a 34-year-old Korean man who had the simultaneous development of both *Polygonum multiflorum* Thunb-induced hepatitis and reactivation of pulmonary tuberculosis by bone marrow (BM) suppression.

CASE REPORT

A 34-year-old Korean man was referred to our hospital with complaints of fatigue and aggravated jaundice after a

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7-day hospital course in a private practice. He had taken *Polygonum multiflorum* Thunb. tea, boiled-down liquid form of its root, for 30 days and then drunk *Polygonum multiflorum* Thunb liquor as a tonic for 4 days recently before admission. He had been a previously healthy individual working as a heavy equipment operator in the construction site. He was a non-smoker and consumed alcohol usually once a week, approximately 70 g of alcohol each time. He denied any specific past medical history except for his chest X-ray showing sequelae of pulmonary tuberculosis, which was not related with past and recent episodes of respiratory symptoms. On physical examination, his vital signs were as follows: blood pressure 130/80 mmHg, pulse rate 70 bpm, respiration rate 20 breaths/min, body temperature 38.2°C. His weight and height were 83 kg and 178.3 cm, respectively. Jaundice was noted on whole body. But liver and spleen were not palpable. The results of initial laboratory tests conducted at our hospital

were as follows: WBC 4,970/mm³, hemoglobin 15.6 g/dL, platelet 261,000/mm³, total bilirubin 25.3 mg/dL, direct bilirubin 16.9 mg/dL alkaline phosphatase (ALP) 111 IU/L, aspartate aminotransferase (AST) 1,335 IU/L, alanine aminotransferase (ALT) 1,452 IU/L, r-glutamyltransferase 162 IU/L, albumin 3.4 g/dL and prothrombin time 15.6 seconds. All viral markers and auto-antibodies were negative and the values of immunoglobulin G, A and M showed normal ranges. Finally, he was diagnosed with *Polygonum multiflorum* Thunb.-induced hepatitis after exclusion of all other potential causes of acute hepatitis. His liver function gradually deteriorated and neutropenia developed during the early period of the hospital stay. On the 12th hospital day, liver biopsy was performed to reveal perivenular and lobular infiltration of many inflammatory cells, patchy area of hepatocyte necrosis, some apoptosis, ballooning degenerative change, cholestasis and regenerative change of the remaining hep-

Fig. 1. Liver biopsy revealed many inflammatory cells in the perivenular and lobular area, a patchy area of hepatocytic necrosis, cholestasis, regenerative changes in the remaining hepatocytes, ballooning degenerative hepatocytes, and some apoptosis (A, H&E stain, $\times 100$; B, H&E stain, $\times 400$).

Fig. 2. Chest X-ray showing the sequelae of pulmonary tuberculosis involving the right upper lobe without interval change.

atocytes, which were compatible with drug-induced acute hepatitis (Fig. 1). Chest X-ray showed the sequelae of pulmonary tuberculosis involving right upper lobe with-

Fig. 3. Bone marrow biopsy showing markedly hypocellular marrow (H&E stain, $\times 100$).

out interval change (Fig. 2). To evaluate chest lesion, we took computed tomography (CT) scans of his chest on the 13th hospital day. As is the result of simple chest radiograph, the CT scans showed tuberculous sequelae in the right upper lobe of the lung. The patient discontinued taking the root of *Polygonum multiflorum* Thunb immediately after he had been hospitalized to begin receiving conservative treatment. He suffered from spiking nocturnal fever and progressive pancytopenia. BM biopsy was performed on the 17th day. The biopsy revealed hypocellularity and decreased trilineage hematopoiesis, suggestive of transient bone marrow suppression caused by other extrinsic factors such as drugs, toxin, and viral infection (Fig. 3). Tuberculosis polymerase chain reaction (PCR) and acid-fast bacillus (AFB) staining on the bone marrow tissue were all negative. Due to his complaints of a dry cough from the 20th hospital day, we conducted repeated sputum studies. On the 24th day, a small amount of thick sputum produced strongly positive result in the AFB stains of all specimens gained. Bronchoscopy showed no endobronchial lesion while the AFB staining of bron-

Fig. 4. Change in liver function test during the patient's hospital stay. ALT, alanine aminotransferase; TB, total bilirubin.

Fig. 5. Changes in body temperature and absolute neutrophil counts ($/\text{mm}^3$) during the patient's hospital stay. ANC, absolute neutrophil count.

chial washing fluid was positive. Therefore, we initiated the anti-tuberculous medication with 2nd-line agents in consideration of their toxicity to the liver. Clinical course including changes in liver function test, body temperature and absolute neutrophil counts ($/\text{mm}^3$) was summarized in Fig. 4 and 5 during hospital days. The fever subsided after starting the treatment for pulmonary tuberculosis. Then the pancytopenia slowly improved. He improved in his general condition a lot as well. Eventually he was transferred to a local clinic in the neighborhood of his home by his request on the 34th day. In this case, we presumed that *Polygonum multiflorum* Thunb had the potential of BM suppression as well as hepatotoxicity.

DISCUSSION

The use of herbals and botanicals, the most common form of complementary and alternative medications used in Asia as well as the US, has been gradually increased.^{3,5,13-15} What was worse, some surveys conducted in several clinics of hepatology in the USA and Europe revealed that 30-65% in distinct cohorts of the patients with liver diseases spent botanical drugs.^{5,14,16} Although there are substantial potential toxicities in relation to Chinese herbal remedies, it is difficult to identify which specific ingredient is toxic because the remedies usually consist of botanical components.^{17,18}

The root tuber of *Polygonum multiflorum* was recorded in herbal “Kaibao Bencao” issued by the imperial court of the Song Dynasty (973-974 AD).⁸ The review of references told us that Shou-Wu-Zhi is a manufactured product from *Polygonum multiflorum* Thunb as a tonic in China. Shou-Wu-Pian, translated as “Mr. Black Hair”, is sold for various symptoms in association with aging, including baldness, graying of hair and so on. Shou-Wu-Pian is also sold under the name “He-Shou-Wu”. Shen-Min is another Chinese herbal product with a mixture of some plants and vitamins including *Polygonum multiflorum*.^{8,11,12} Some clinical studies indicated that *Polygonum multiflorum* Thunb could also ameliorate hypercholesterolemia, coronary heart disease, neurosis and other diseases commonly associated with aging.¹⁹⁻²¹ On the other hand, several cases have been reported regarding hepatotoxic reaction associated with the Chinese herbal products from *Polygonum multiflorum* Thunb.⁸⁻¹² Although the mechanism of how *Polygonum multiflorum* Thunb injures the liver has not been elucidated yet, it is thought that anthraquinone, an active ingredient of *Polygonum multiflorum* Thunb, might play a role in the process of its hepatotoxicity.¹⁹

Before admission, our patient had been a healthy operator of heavy equipment in construction industry and in-

gested the root of *Polygonum multiflorum* Thunb blended with soju, a distilled beverage native to Korea and traditionally made from rice, and boiled water of the root as a tonic by a neighbor's recommendation. Laboratory tests showed hepatocellular type of toxic liver injury and liver biopsy findings were consistent with acute hepatitis. According to the above described clinical and lab findings, the modified CIOMS/RUCAM score was 10.²² Therefore, it could be interpreted that this case was definitely diagnosed as having *Polygonum multiflorum* Thunb-induced hepatitis. After admission, he complained of intermittent and progressive fever. To investigate the cause of fever, we performed repeated sputum studies, chest CT scans, abdominal CT scans, liver biopsy, BM biopsy and bronchoscopy. Finally, he was diagnosed with reactivation of pulmonary tuberculosis, which was the cause of fever of unknown origin.

Unlike previously reported cases, our case can be said to be so interesting in point of the hematotoxicity as well as hepatotoxicity. The serious problem of our case was not so much liver injury itself as neutropenic fever during hospital course. Albeit searching in Medline as to its adverse effects, we were not able to find out any report depicting the bone marrow suppression associated with the ingestion of *Polygonum multiflorum* Thunb. We had no idea whether *Polygonum multiflorum* Thunb actually induced BM suppression or not. Nevertheless, we finally diagnosed this case as the simultaneous development of both *Polygonum multiflorum* Thunb-induced hepatitis and BM suppression, based on the fact that we were unable to point out any other definite causes of BM suppression despite the intensive workup to establish a diagnosis. Like this case, it is frequent that many Korean people take the material in a variety of forms such as a tea or liquor made from herbals and botanicals in their usual life.

According to previous reports, we also presume *Polygonum multiflorum* Thunb to have many possible beneficial effects in clinical medicine. Although a lot of investigators have attempted to assess the proposed benefits of herbal and botanical products by conducting scientifically valid studies, there was just no more than accumulation of personal experiences until now. Nevertheless, those products are routinely utilized without a scientific basis supporting their use, their adverse effects of toxicity or drug interactions involved with prescribed medications are overlooked as well.

Therefore physicians should also be alert in noticing potential adverse reactions as well as beneficial effects of them. Furthermore evidence-based information with respect to their usage rather than conventional advice to avoid them should be urgently needed.

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