

Acute Hepatitis Induced by Chinese Hepatoprotective Herb, Xiao-Chai-Hu-Tang

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Xiao-chai-hu-tang (syo-saiko-to in Japanese) is a herbal remedy that has been widely used in China for treatment of respiratory, hepatobiliary, and gastrointestinal diseases, particularly among patients with chronic liver disease. However, its safety has recently been challenged. We, herein, report a Chinese patient with acute hepatitis induced by this herb. A 52-year-old woman presented with weakness, fatigue, and tea-colored urine after continual consumption of the decoction of xiao-chai-hu-tang for 1.5 months. Laboratory studies disclosed acute hepatitis even though all of the viral hepatitis markers were negative. Liver biopsy also revealed a picture of acute hepatocellular hepatitis. The symptoms improved after discontinuing the drug, and liver biochemical tests normalized 2 months later. The case report reminds us of the probable adverse drug reaction of herbs, even in some that are claimed to have hepatoprotective effects. [*J Chin Med Assoc* 2006;69(2):86–88]

Key Words: hepatotoxicity, herbal medicine, toxic hepatitis, xiao-chai-hu-tang

Introduction

Herbal remedies have been used worldwide for thousands of years. However, hepatotoxicities of medicinal plants have increasingly been reported recently.¹ The famous Chinese herbal medicine, xiao-chai-hu-tang (syo-saiko-to in Japanese), is a mixture of seven herbal components (bupleurum root, pinellia tuber, scutellaria root, jujube fruit, ginseng root, glycyrrhiza root, and ginger rhizome). It was first prepared in the Han dynasty (BC 206–AD 220) to treat patients with “Shaoyang syndromes” that were likely linked to respiratory, gastrointestinal, and hepatobiliary diseases. Today, it is widely used in China, Taiwan, and Japan as the most popular herbal remedy for liver disease.² Unfortunately, hepatic injury induced by this so-called hepatoprotective herb was reported among 4 Japanese women.³ We report here a Chinese woman who developed acute hepatitis from using this herbal remedy. To the best of our knowledge,

this is the first English report of hepatotoxicity induced by this herb among Chinese consumers.

Case Report

A 52-year-old Chinese woman was admitted to our hospital because of poor appetite, malaise, and fatigue for 2 weeks. She had undergone laparoscopic cholecystectomy for gall bladder stones and acute cholecystitis at another hospital 4 months earlier. Thereafter, she started a daily consumption of xiao-chai-hu-tang prescribed by a traditional Chinese medical practitioner for almost 1.5 months prior to this admission. She decocted the dried herbal mixture daily and then drank the extract twice a day. Two weeks before admission, she noted progressive development of poor appetite associated with nausea, weakness, and fatigue. She denied taking any other drug or drinking alcoholic beverages.

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On physical examination, she had no sign of chronic liver disease. Laboratory profile on admission showed elevated serum levels of aspartate aminotransferase (AST) 862 IU/L (normal, 5–45 IU/L), alanine aminotransferase (ALT) 2,028 IU/L (normal, 0–40 IU/L), γ -glutamyl transpeptidase 482 IU/L (normal, 4–51 IU/L), alkaline phosphatase 213 IU/L (normal, 10–100 IU/L), total bilirubin 1.9 mg/dL (normal, 0.6–1.6 mg/dL), and direct bilirubin 0.7 mg/dL (normal, 0–0.3 mg/dL). Other laboratory tests, including complete blood count, serum urea nitrogen, creatinine, glucose, electrolytes, total protein, albumin, and ceruloplasmin were within normal range. Coagulation studies were also unremarkable. All viral hepatitis markers, including hepatitis B surface antigen, IgM antibody to hepatitis B core antigen, IgM antibody to hepatitis A virus, antibody to hepatitis C virus, HCV-RNA, IgM antibody to cytomegalovirus, IgM antibody to herpes simplex virus, and IgM antibody to Epstein–Barr virus, were negative except for a positive serum antibody to hepatitis B surface antigen. Her serum antinuclear antibodies, antismooth muscle antibodies, and antimitochondrial antibodies were likewise negative.

A needle biopsy of the liver was performed 2 days after admission. Histologically, the liver showed acute hepatitis with many acidophilic bodies, centrilobular necrosis, spotty necrosis, and focal fatty change. Inflammatory infiltration was mainly mononuclear cells without eosinophils. There was no portal fibrosis (Figure 1). These histologic findings were compatible with the hepatocellular pattern of acute drug-induced hepatitis. After withdrawal of the herbs, her serum levels of ALT and AST fell to 425 and 112 IU/L,

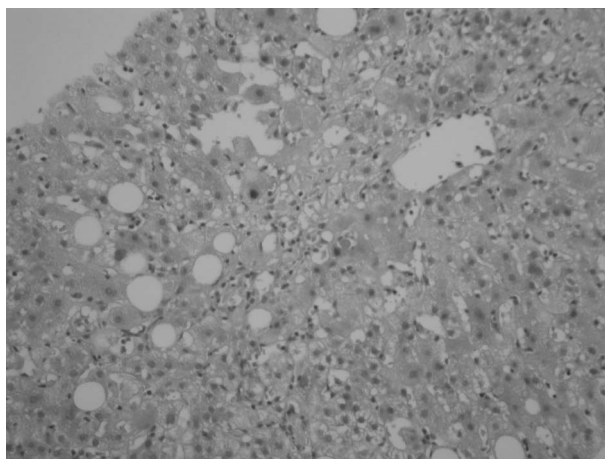


Figure 1. Needle biopsy specimen of patient's liver shows acute hepatitis with acidophilic bodies, focal necrosis, and fatty change (hematoxylin and eosin, $\times 160$).

respectively, on the 11th day after admission and normalized 2 months later (Figure 2).

Discussion

Xiao-chai-hu-tang is the most common traditional drug in Asian countries for patients with chronic hepatitis and liver cirrhosis.² However, there has never been concern for its safety until Itoh et al³ presented 4 women who suffered from xiao-chai-hu-tang-induced acute liver injury. The latent period was 1.5–3 months, with a mean of 2 months. Two of them were icteric and the ALT levels ranged from 246 to 1,335 IU/L at the initial presentation. All of the patients recovered without complication and liver enzyme tests normalized within 3 months. Pathologic examination revealed acidophilic degeneration, central lobular necrosis, spotty necrosis, and microvesicular necrosis in addition to eosinophilic infiltration in all specimens. Positive re-challenge with xiao-chai-hu-tang confirmed the causality.

Our diagnosis of acute hepatitis associated with xiao-chai-hu-tang was based on the exclusion of other causes of hepatitis, the temporal relation of the drug consumption, and the onset of acute hepatitis. Liver biopsy in our patient revealed acute hepatitis without eosinophilic infiltration. Therefore, hypersensitivity reaction was not the possible mechanism of toxicity because of the long latent period and the absence of eosinophilic infiltration on liver biopsy. A direct hepatotoxic effect or an idiosyncratic reaction to xiao-chai-hu-tang may be the cause. However, re-challenge with xiao-chai-hu-tang was not performed on our patient because of ethical considerations.

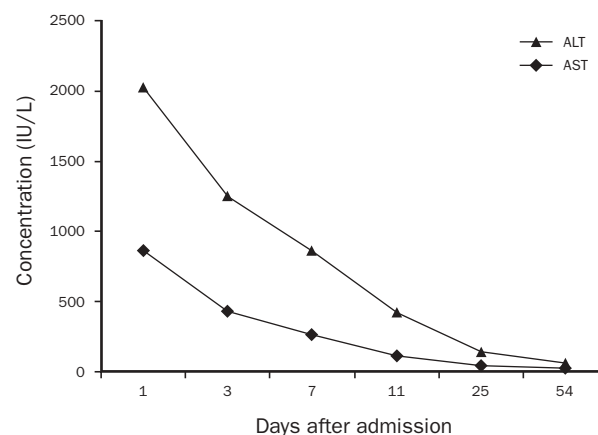


Figure 2. Sequential change of serum aminotransferase levels in the patient with xiao-chai-hu-tang-induced acute hepatitis. AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Xiao-chai-hu-tang is easily available in Taiwan as a traditional decoction or a concentrated powder. In general, the risk of herbal toxicity is higher in a traditional decoction because of misidentification of the correct plant materials, selection of a wrong part of the prescriptive plant materials, inadequate storage, contamination of the plant materials by various chemicals, heavy metals, microorganisms, adulteration during conditioning, and mislabeling of the final products.⁴ Our patient decocted the herb by herself, which obviously increased the risk of hepatotoxicity.

The main component of xiao-chai-hu-tang that causes liver injury has been attributed to scutellaria.³ Scutellaria, commonly called skullcap, is a member of the mint family. The root of *Scutellaria baicalensis* (Chinese skullcap) is commonly used in traditional Chinese herbal medicine.⁵ On the other hand, the aerial part of *Scutellaria lateriflora* (American skullcap) is used to treat anxiety disorder in Western countries.⁶ These are quite different and not interchangeable.⁷ The American skullcap used for relieving stress has been implicated in the reported hepatotoxicity of 4 women.⁸ The skullcap diterpenoids derived from the aerial part of *Scutellaria lateriflora* were shown to be toxic to rat hepatocytes.⁹

In addition to hepatic injury, xiao-chai-hu-tang also leads to acute lung injury, probably due to allergic-immunologic mechanisms that increase the incidence of lung injury when used together with interferon- α .¹⁰⁻¹³ Skullcap was reported in a drug-related pneumonitis in a Japanese man.¹⁴ Kiguchi et al¹⁵ also reported a patient who developed severe thrombocytopenia after taking xiao-chai-hu-tang for treatment of chronic hepatitis. The jujube fruit of the compound was suggested to have induced the thrombocytopenia in this case.

Herbal medicine was long believed to be safe without significant side effects. In Taiwan, about 40% of patients with chronic liver or gastrointestinal diseases use herbal preparations, but only 36% of them inform their doctors.¹⁶ Therefore, a drug history in patients with acute and chronic liver disease should include the use of herbal medicine. Physicians should be aware of the potential side effects of any herbal preparations. This case report reminds us that even the most well-known so-called hepatoprotective herb may have the potential for hepatic injury.

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