Liver Injury Induced by the Japanese Herbal Drug Kamishoyosan

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Traditional Japanese herbal medicines (kampo medicines) are currently used for various purposes, and they have even shown effectiveness in some cases that were resistant to conventional treatments. Most general practitioners in Japan consider kampo medicine to be safe and less harmful than many conventional medications. As described in this case report, however, kamishoyosan given to a 48-year-old woman for menopausal disturbance appeared to induce liver injury.

Case Report

A 48-year-old woman was admitted to our hospital with acute liver injury. Two years earlier, she had taken the herbal medicine kamishoyosan for 1 month to treat symptoms of postmenopausal syndrome. Two months before admission, she had started taking kamishoyosan again due to a recurrence of hot flashes and night sweats. Two weeks after restarting treatment with kamishoyosan, she underwent a routine checkup that revealed abnormal liver function test results; her serum aspartate aminotransferase (AST) level was 64 IU/L, and her alanine aminotransferase (ALT) level was 102 IU/L. She was advised to go to the hospital for a detailed evaluation of her condition.

No contributory family history was identified. The patient did not drink alcohol or smoke cigarettes, and she had not used illicit drugs. She did not have any risk factors for HIV infection, had not traveled abroad, and did not have a habit of eating raw meat. She was afebrile but reported general fatigue. On physical examination, she was conscious and alert. Her conjunctivae were icteric but not anemic. Her abdomen was soft and flat with no tenderness. Her spleen and liver were not palpable, and superficial lymph nodes were not swollen. No skin rash was apparent, and neurologic examination showed no abnormalities. Her blood pressure was 106/58 mmHg, and her body temperature was 36.5° C. Laboratory tests revealed a white blood cell count of 4.7×10^3 cells/μL, hemoglobin level of 13.4 g/dL, platelet count of 29.8×10^4/μL, total protein level of 6.3 g/dL, albumin level of 3.9 g/dL, total bilirubin level of 12.8 mg/dL, direct bilirubin level of 8.9 mg/dL, AST level of 900 IU/L, ALT level of 972 IU/L, alkaline phosphatase level of 420 IU/L, and prothrombin time of 99%. Tests for markers of hepatitis A, B, and C virus infection; cytomegalovirus infection; herpes simplex virus infection; Epstein-Barr virus infection; and HIV infection yielded negative results. Test results for antinuclear antibody, anti–mitochondrial-M2 antibody, anti–smooth muscle antibody, and anti–liver/kidney/microsome-1 antibody were all negative. Levels of immunoglobulin (Ig)A, IgG, and IgM were 265 mg/dL, 969 mg/dL, and 174 mg/dL, respectively. Abdominal ultrasonography did not detect dilatation of the bile duct, swelling of the gallbladder, or abnormal liver size. Computed tomography with contrast medium showed an almost homogeneous liver. These results were compatible with acute liver injury.

Drug-induced liver injury due to kamishoyosan was suspected, and the medication was stopped. One

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week after admission, a liver biopsy was performed (Figure 1). Pathologic examination of the liver revealed necrosis and acidophilic degeneration of hepatocytes in the parenchyma. The portal tract was enlarged, with infiltration of lymphocytes and eosinophils, but few plasma cells were observed.

In addition to bed rest, treatment with intravenous glycyrrhizin (80 mL/day) was started following the liver biopsy. Aminotransferase and bilirubin levels gradually normalized. Changes in bilirubin, AST, and ALT levels are shown in Figure 2. The patient was discharged on Day 26 after admission; at this time, she was instructed to begin taking ursodeoxycholic acid (600 mg/day). Liver function test results had almost returned to normal by 42 days after discharge.

Discussion

Herbal medicines have been widely used around the world as alternative medicines. Clinicians are often confronted with situations in which conventional medicines are ineffective and patients' symptoms remain unrelieved, in which case herbal medicines may be tried. Despite a lack of evidence, kampo medicine is widely seen in Japan as offering an alternative treatment for various diseases. Kamishoyosan, which reduces levels of cytokines such as interleukin (IL)-6 and IL-8, is effective against hot flashes due to menopausal syndrome.[1] Kamishoyosan also has anxiolytic and antidepressive effects, and widespread use of kamishoyosan for psychiatric and neuropathic disorders can be expected.[2-5] Although kamishoyosan is widely used as an alternative drug, few side effects have been reported.

In this case, the patient was not taking any drugs besides kamishoyosan. Nevertheless, she reported taking vitamins intermittently, so vitamins could not be absolutely excluded as possible etiologic agents. However, her use of vitamins was infrequent, so this possibility seems unlikely. Two years before admission, she had taken kamishoyosan for menopausal syndrome. After treatment for 1 month, her symptoms resolved and the medication was stopped. Several months before admission, kamishoyosan treatment was restarted because of recurrent symptoms. Liver biopsy showed invasion of eosinophils into the portal tract in the liver. The mechanism of hepatic injury was complicated, but immunoallergic mechanisms were suggested.

Melchart and colleagues investigated the frequency of liver enzyme elevations in 1,507 patients treated with traditional Chinese herbs. A greater–than–2-fold elevation in ALT values was observed in 14 patients (0.9%).[6] In another study, Nakazawa and coworkers examined 305 outpatients who were given kampo medicine and found that 15 patients showed elevated ALT levels.[7] The researchers reported that 87% of liver injury in these patients occurred more than 3 months after initiation of therapy. Liver injury was mild in almost all reported cases, but periodic evaluation of liver function is very important.

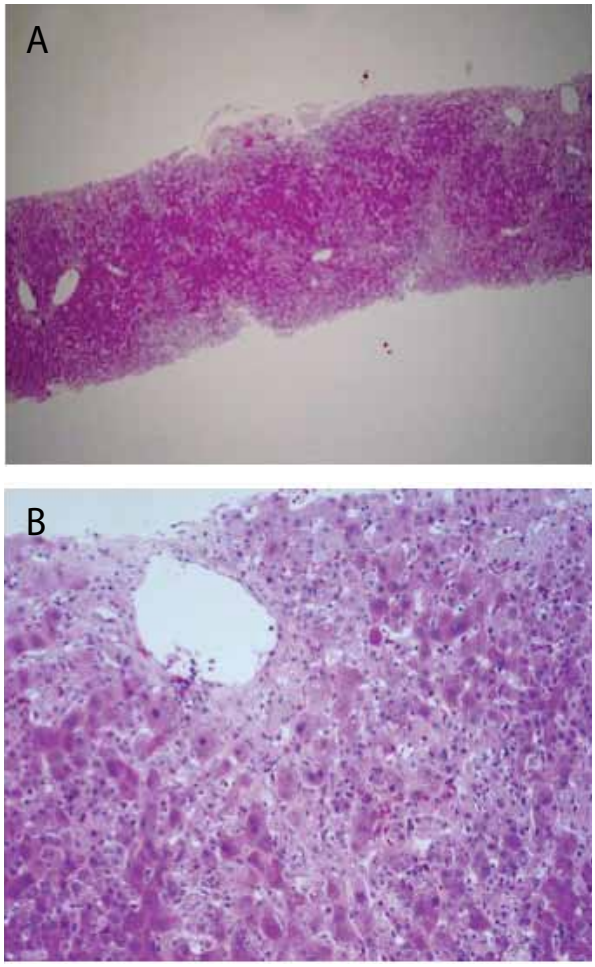

Figure 1. Histopathologic examination revealed expansion of the portal triad due to infiltration of many inflammatory cells and dropout of many hepatocytes (hematoxylin and eosin stain, 40× magnification; **A**). Acidophilic degeneration of hepatocytes and bile-stained hepatocytes are shown in the parenchyma, but no cholestasis was apparent in the small bile duct (hematoxylin and eosin stain, 200× magnification; **B**).

The same report also noted that *Scutellariae radix* was the only component common to all kampo medicines that caused liver injury.[7] Terada and colleagues studied interstitial pneumonia (IP) and liver dysfunction (LD) associated with kampo medicine and found that *Scutellariae radix* was contained in kampo medicines taken by 94% of IP patients and 89% of LD patients.[8] However, kamishoyosan is made from *Bupleurum radix*, *Peony radix*, *Atractyloidis raceae rhizome*, Japanese *Angelica radix*,

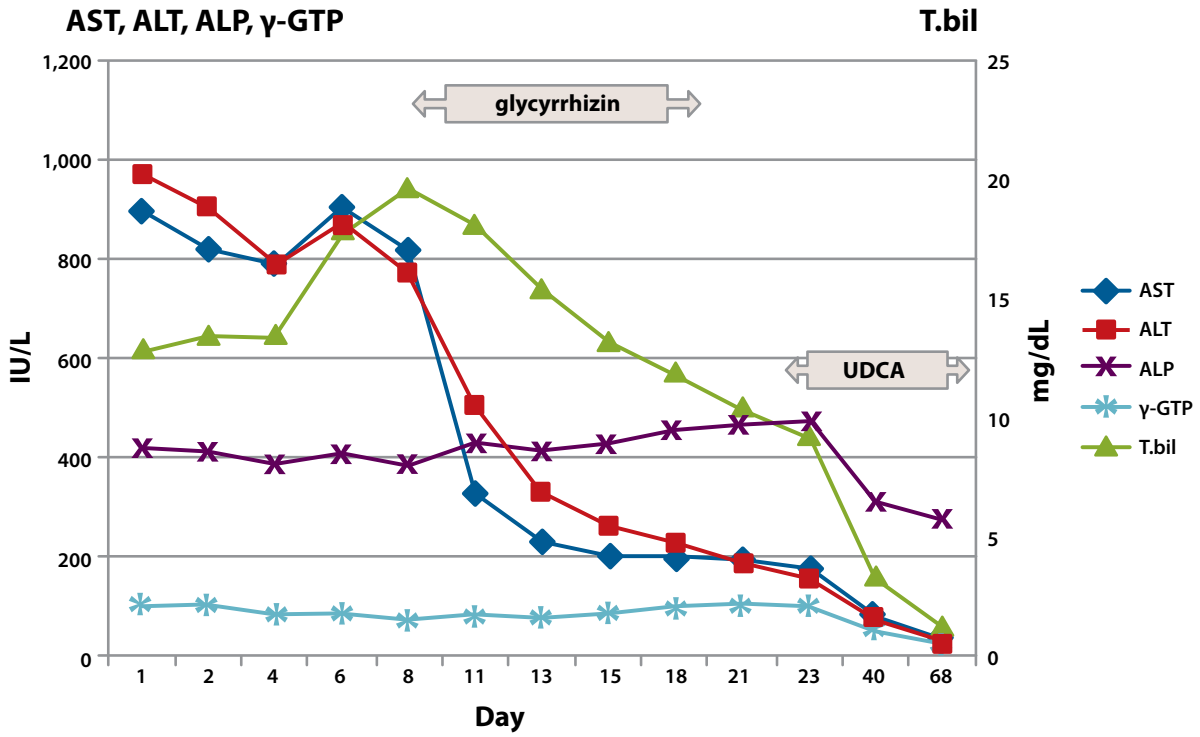

Figure 2. After infusion of glycyrrhizin, levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (T.bil) improved, but levels of alkaline phosphatase (ALP) and gamma-glutamyltransferase (γ-GTP) were unchanged. Ursodeoxycholic acid (UDCA) was started after discharge, and values of ALP and γ-GTP returned to normal ranges. Prothrombin time was maintained above 95% during admission (data not shown).

Hoelen, *Gardenia fructus*, *Moutan cortex*, *Ginger rhizome*, *Glycyrrhiza root*, and *Mentha herb*; it does not contain *Scutellariae radix*. Thus, care must be taken regarding kampo medicine–induced liver injury even if the formulation does not contain *Scutellariae radix*. Kampo medicine contains several components (and each component contains multiple ingredients), which makes detecting causative ingredients difficult. However, mechanisms of liver damage caused by several herbal medicine ingredients have recently been elucidated.[9,10] Further investigation is necessary.

In this case, the patient was middle-aged, so it was important to differentiate kampo medicine–induced liver injury from autoimmune hepatitis. In the acute phase of autoimmune hepatitis, test results might be negative for antinuclear antibody, and hypergammaglobulinemia may not be detected.[11] The possibility of autoimmune hepatitis must, therefore, be taken into account. However, liver biopsy in this case showed scarce infiltration of plasma cells despite the presence of many eosinophils in the portal tract. The results of liver biopsy were thus compatible with drug-induced liver damage. Histologic evaluation, as in this case, is important.[12]

As mentioned above, use of kampo medicine has been increasing. Therefore, further clarification of the mechanisms underlying kampo medicine activity is warranted; as a first step, clinicians need to accumulate case reports such as this one.

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Review

Herbal and Dietary Supplement–Induced Liver Injury

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Herbal and dietary supplements (HDS) are used by nearly 1 in 5 Americans, but their use is not commonly reported to, or detected by, healthcare providers.[1,2] HDS use is even more common outside the United States.[3,4] Patterns of liver injury are highly variable, even among cases where injury is purported to result from the same product. The liver is often the target of HDS toxicity, given its integral role in metabolism, and HDS-induced liver injury is a common cause of acute liver failure in the United States.[5,6]

Determining causality in HDS-induced liver injury is often difficult, as patients frequently take supplements along with many prescribed and nonprescribed medications. As such, the interaction between HDS and other medications often cannot be gauged. Further confounding the attribution of causality in cases of hepatotoxicity among patients consuming HDS are the potential multiplicity of ingredients within any given product (some of which may not be identified on the label) and seasonal variations in the harvesting of natural products, which could affect their strength and composition.

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The diagnosis of hepatotoxicity associated with HDS is typically made after excluding viral, autoimmune, metabolic, and anatomic causes of liver test abnormalities. Several models to assess causality exist in the literature, including the Roussel Uclaf Causality Assessment Model (RUCAM) and the Maria & Victorino (M&V) scale.[7,8] Still, expert opinion remains the gold standard for diagnosis.[9] RUCAM is the most frequently referenced scoring system, but it is not commonly used in clinical practice. The M&V scale is more specific but less sensitive, and it gives weight to prior reports in the literature for medications that have been in existence for less than 5 years. The M&V scale tends to underattribute causality compared to RUCAM, while RUCAM tends to underattribute causality compared to expert opinion.[9,10] Expert opinion can also vary significantly between evaluators. To help minimize this variation, consensus expert opinion can be sought, although interobserver variability can still exist, even at this level of adjudication.[10]

Since the holy grail of causality continues to be elusive, many efforts are underway worldwide to better understand the mechanisms behind drug-induced liver injury (DILI). These efforts include investigation of host factors using pharmacogenetic and proteomic testing, as well as other diagnostic tools.[11] In the United States, the Drug-Induced Liver Injury Network (DILIN) was created to identify a large number of patients with bona fide DILI and to collect epidemiologic and biologic data for future studies.[12] Additionally, the DILIN focuses on developing and testing causality assessment measures for drug, herbal, and over-the-counter medication–induced liver injury.[12]

While the case reported by Inoue and colleagues lacks a formal causality assessment, causality is more straightforward in this case than in most cases of HDS-induced liver injury, as this patient was taking no other supplements or medications preceding the acute liver injury.[13] However, like many HDS implicated in hepatotoxicity, kamishoyosan is not just one ingredient. Rather, it is comprised of 10 different extracts, including glycyrrhizin—the same supplement that the authors used to treat the liver injury they surmised was related to this supplement. Thus, attribution of the liver injury to one ingredient is quite problematic. Among the noted ingredients of kamishoyosan, glycyrrhizin and mentha (pennyroyal) are the 2 ingredients that are most often associated with liver test abnormalities.[14,15] In a large study conducted in Germany that

examined the incidence of liver test abnormalities among recipients of traditional Chinese medicines, glycyrrhizin and *Atractylodis* were the ingredients most commonly associated with liver test abnormalities, occurring with a frequency approaching 1%.[16] Additionally, the patient described by Inoue and coauthors was taking kamishoyosan for the second time.[13] Liver test results during her first exposure were not reported; had they been elevated, however, a rechallenge may not have been recommended. To conclude that the second exposure may have led to injury due to a rechallenge, despite a lack of knowledge about the first exposure, is a tenable but risky assumption.

Two problems that complicate assessment of HDS-induced liver injury related to traditional Chinese and Japanese medicines are contamination and adulteration. In the United States, governmental oversight of HDS is less stringent than for prescription pharmaceuticals, so contamination and/or adulteration of HDS is not uncommon. In one study, heavy metals or pharmaceuticals not listed on the package label were detected in 32% of traditional Chinese medicines collected in California.[17] Among the most frequently measured adulterants and contaminants were methyltestosterone, ephedrine, phenacetin, arsenic, and mercury. For these reasons, monitoring of liver tests should be strongly considered in patients who are taking HDS, especially traditional Chinese and Japanese medicines.

Inoue and colleagues are likely accurate in concluding that hepatotoxicity was due to kamishoyosan in this case, given the exclusion of other causes of acute liver injury, timing, biopsy findings, and improvement with dechallenge, but confidence in the diagnosis could have been increased by using a formal causality assessment and providing baseline liver test information.[13] The assignment of attribution to suspected DILI in case reports can be more confidently endorsed by incorporating all of the essential elements for diagnosis.[18]

In summary, HDS-induced liver injury is not common, but it remains a real concern worldwide. With increasing prevalence of HDS use, the incidence of acute liver failure and liver test abnormalities attributable to HDS should be expected to continue to rise. Clinicians should have a heightened suspicion for HDS-induced liver injury, especially when common causes of liver disease have been excluded.

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