RUCAM-based assessment of liver injury by xiang-tian-guo (Swietenia macrophylla) seeds, a plant used for treatment of hypertension and diabetes

Dear Editor,

Xiang-tian-guo (Swietenia macrophylla seeds [SMS]) belongs to the family Polygonaceae. Traditionally, Malaysian natives chew and swallow SMS as a cure for hypertension and diabetes [1]. However, there are no reports on the hepatotoxicity of SMS in the literature. We recently encountered a case of liver injury caused by SMS and retrospectively found two other cases highly suggestive of SMS-induced liver injury.

1. Case 1

A 72-year-old man was admitted with a 2-week history of fatigue, nausea, dark urine, and jaundice. He had a >20-year history of diabetes and had discontinued metformin and insulin treatment 5 years before admission. However, he had a 2-month history of SMS use, during which he would eat only one raw seed at a time three times a day (usually no more than 5 mg/kg). He reported no history of hepatitis A–E, autoimmune hepatitis, or metabolic diseases or exposure to other drugs or alcohol. His liver test results were abnormal (Table 1), but the findings of an upper abdominal ultrasound were normal. SMS treatment was ceased after admission.

The findings from a liver biopsy corresponded with drug-induced liver injury (DILI), including hemorrhage around the terminal hepatic venule; prominent intra-acinar lymphocytes; and occasional neutrophils, canicular and hepatocellular cholestasis, and hepatocyte necrosis (Fig. 1). The patient’s symptoms and liver tests improved rapidly. Methylprednisolone 40 mg/day was administered for 1 week, decreased to 20 mg/day, and stopped after 4 weeks. The patient was then discharged.

2. Cases 2 and 3

The two other patients (a 75-year-old man with a 20-year history of diabetes and insulin therapy and an 80-year-old man with a 20-year history of hypertension and long-term valsartan use) were seen at the outpatient clinic in March and May 2017, respectively. Both had a 1.5-month history of SMS use and complained of fatigue 2 weeks after the start of SMS use at the recommended dosages. The liver enzyme levels of the first patient were alanine aminotransferase (ALT), 363 U/L; and alkaline phosphatase (ALP), 122 U/L. The patient’s clinical symptoms and liver tests recovered rapidly (ALT, 115 U/L; ALP, 86 U/L) 1 week after ceasing SMS and returned to normal after 4 weeks. The third patient’s ALT level changed from 224 U/L to 113 U/L and his ALP level changed from 108 U/L to 98 U/L only 3 days after ceasing the SMS and returned to normal after 2 weeks.

Three patients tested negative for anti-hepatitis E immunoglobulin M.

3. Discussion

Suspected cases of herb-induced liver injury (HILI) have been reported in many publications [2–5]. SMS is increasingly used in China. On evaluating SMS safety, Balijepalli et al. [6] reported that oral administration of SMS to rats caused no hepatotoxicity.

The clinical and histopathologic features of DILI may mimic any liver injury histopathologic model. Ayako Suzuki et al. [7] stated that these pathological features are more inclined to be caused by

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**Table 1**

Changes in liver tests of the first patient.

<table>
<thead>
<tr>
<th>Time</th>
<th>TBIL (1.71–21 mol/L)</th>
<th>DBIL (0–7.32 mol/L)</th>
<th>ALT (40–400 U/L)</th>
<th>AST (40–400 U/L)</th>
<th>ALP (40–120 U/L)</th>
<th>GGT (1–42 U/L)</th>
<th>INR (0.7–1.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>212.4↑</td>
<td>136.4↑</td>
<td>678↑</td>
<td>789↑</td>
<td>254↑</td>
<td>154↑</td>
<td>1.43</td>
</tr>
<tr>
<td>1st week</td>
<td>136.3↑</td>
<td>84.6↑</td>
<td>312↑</td>
<td>362↑</td>
<td>212↑</td>
<td>118↑</td>
<td>1.32</td>
</tr>
<tr>
<td>2nd week</td>
<td>114.2↑</td>
<td>53.7↑</td>
<td>182↑</td>
<td>189↑</td>
<td>166↑</td>
<td>85↑</td>
<td>1.11</td>
</tr>
<tr>
<td>3rd week</td>
<td>47.2↑</td>
<td>25.8↑</td>
<td>103↑</td>
<td>64↑</td>
<td>143↑</td>
<td>93↑</td>
<td>1.21</td>
</tr>
<tr>
<td>4th week</td>
<td>22.1↑</td>
<td>13.2↑</td>
<td>53↑</td>
<td>44↑</td>
<td>86↑</td>
<td>74↑</td>
<td>1.04</td>
</tr>
<tr>
<td>6th week</td>
<td>14.3</td>
<td>6.3</td>
<td>32</td>
<td>34</td>
<td>76</td>
<td>46↑</td>
<td>1.02</td>
</tr>
<tr>
<td>8th week</td>
<td>11.3</td>
<td>5.5</td>
<td>36</td>
<td>26</td>
<td>80</td>
<td>35</td>
<td>1.11</td>
</tr>
</tbody>
</table>


**Table 2**

Details scores of RUCAM for three patients.

<table>
<thead>
<tr>
<th>Contents</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = [ALT/ULN]/[ALP/ULN]</td>
<td>8.001</td>
<td>8.89</td>
<td>6.72</td>
</tr>
<tr>
<td>Time to onset</td>
<td>+2</td>
<td>+2</td>
<td>+2</td>
</tr>
<tr>
<td>Course</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
</tr>
<tr>
<td>Risk factors</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Concomitant drug</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Search for non drug cases</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Previous information on hepatotoxicity of the drug</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Response to readministration</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total score</td>
<td>7</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

Judgment: >8: highly; 6–8: probable; 3–5: possible; 1–2: unlikely; ≤0: excluded; ULN: upper limit normal.

Fig. 1. Microscopic features of the liver biopsy specimens (hematoxylin and eosin stain, ×100). Hemorrhaging around the terminal hepatic venule (white arrow), prominent intra-acinar lymphocytes and occasional neutrophils (black arrow), and canicular and hepatocellular cholestasis (arrowhead) are visible.
the pathological manifestations of DILI, such as hemorrhage around
the terminal hepatic venule, prominent intra-acinar lymphocytes,
hepatocellular and canalicular cholestasis, and prominent portal
neutrophils. The first patient had these histological findings.

DILI and HILI currently have no specific diagnostic criteria. Thus,
we must first exclude other causes of liver diseases and then deter-
mine the correlation between liver damage and suspicious drugs
through a standardized causality assessment. The updated RUCAM
is a specific causality assessment of liver injury [8]. The RUCAM
score of 7 in each case (Table 2) indicated that the liver injuries
were probably induced by SMS. Thus, clinicians should be aware
of the toxic potential of *Swietenia macrophylla* upon encountering
cases of unexplained liver injury.

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