

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, canalicular 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

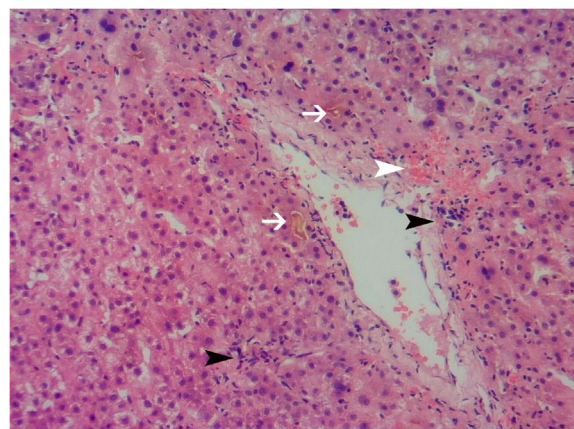


Fig. 1. Microscopic features of the liver biopsy specimens (hematoxylin and eosin stain, ×100). Hemorrhaging around the terminal hepatic venule (white arrow), prominent intra-acinar lymphocytes and occasional neutrophils (black arrow), and canalicular and hepatocellular cholestasis (arrowhead) are visible.

Table 2

Details scores of RUCAM for three patients.

Contents	Case 1	Case 2	Case 3
Drug	SMS	SMS valsartan	SMS
R = [ALT/ULN]/[ALP/ULN]	8.001	8.89	6.72
Time to onset	+2	+2	+2
Course	+3	+3	+3
Risk factors	+1	+1	+1
Concomitant drug	0	0	0
Search for non drug cases	+1	+1	+1
Previous information on hepatotoxicity of the drug	0	0	0
Response to readministration	0	0	0
Total score	7	7	7

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

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

Table 1

Changes in liver tests of the first patient.

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

TBIL: total bilirubin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: glutamyl transpeptidase, INR: international normalized ratio.

the pathological manifestations of DILI, such as hemorrhage around the terminal hepatic venule, prominent intra-acinar lymphocytes, hepatocellular and canalicular cholestasis, and prominent port neophils. 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 determine 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.

References

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