Herb-induced autoimmune-like hepatitis associated with Xiang-tian-guo (Swietenia macrophylla seeds)

A case report and literature review

Yue-Ming Shao, MDa, Yu Zhang, MDa, Xin Yin, MDB, Ting-Ting Qin, MDa, Qing-Long Jin, MD, PhDa, Xiao-Yu Wen, MD, PhDa,*

Abstract

Rationale: Drug-induced liver injury (DILI) has a relatively low incidence, whereas the incidence of herb-induced liver injury (HILI) is still under investigation. As a special type of DILI, the diagnosis of drug-induced autoimmune-like hepatitis presents a persistent challenge, because this condition has partial characteristics of both DILI and autoimmune hepatitis (AIH), such as a certain history of medication use and histology that similar is to AIH. Thus, the differential diagnosis between DILI and AIH can be confusing.

Patient concerns: A 67-year-old woman taking xiang-tian-guo for 6 months was admitted to our hospital with a complaint of experiencing jaundice for 2 weeks.

Diagnosis: A liver biopsy exhibited interface inflammation, foam cells, and “rosette”-like hepatocytes. She was diagnosed with herb-induced liver injury (hepatocellular and acute), a RUCAM score of 7 (probable), a severity for grade 4 liver injury, and accompanied autoimmune-like changes.

Interventions: The patient was instructed to cease the administration of suspicious drugs. The patient also received liver protection and albumin transfusion.

Outcomes: After 25 days of hospitalization, the patients aminotransferase levels returned to normal. No recurrence was observed after the administration of the treatments and a close follow-up.

Lessons: We must to be vigilant about the safety of xiang-tian-guo as a herbal medicine. When faced with the difficulty of distinguishing between AIH and DILI, long-term follow-up observations for recurrence can aid clinicians in making a judgment.

Abbreviations: AIH = autoimmune hepatitis, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANA = antinuclear antibodies, AST = aspartate aminotransferase, DILI = drug-induced liver injury, HILI = herb-induced liver injury, SMS = Swietenia macrophylla seeds, TBL = total bilirubin, ULN = upper limit of normal.

Keywords: case report, chemical and drug induced liver injury, literature review, xiang-tian-guo

1. Introduction

The incidence of DILI is relatively low, and the clinical phenotype is diverse. Additionally, there is a lack of specific biomarkers for DILI, which results in the diagnosis of this disorder to be one of the most challenging diseases that is faced by hepatologists.1 There are few reports of drug-induced liver injury caused by xiang-tian-guo (Swietenia macrophylla seeds [SMS]). The challenge we faced in our patient was in the identification of AIH. To a certain extent, serology and histology can aid us in diagnosis; however, but when the evidence is insufficient, a long-term follow-up observation can indicate the correct direction of treatment. Therefore, in this report, we reviewed the clinical reports of liver injury caused by xiang-tian-guo in recent years, and we explained the method of how to distinguish between AIH and DILI. Additionally, we suggest that more experiments are needed to verify the human safety of the use of xiang-tian-guo.

2. Case presentation

A 67-year-old female was admitted to our department due to the presence of dark urine for 2 weeks and yellow sclera for 5 days. Accompanying symptoms included fatigue and abdominal distension. She had a history of hypertension and had not regularly taken any antihypertensive medication. To control her blood pressure, she reported that she had been taking xiang-tian-guo (Swietenia macrophylla seeds [SMS]) for the past 6 months. She denied having histories of diabetes, blood transfusions, viral hepatitis, or a consumption of alcohol.
A physical examination demonstrated no signs of chronic liver disease except for jaundice. Liver function tests revealed severe changes in the following variables: aspartate aminotransferase (AST) level was 672.4U/L (normal range: 13–35 U/L), alanine aminotransferase (ALT) level was 681.7U/L (normal range: 7–40 U/L), glutamyl transpeptidase (γ – GT) level was 161.2U/L (normal range: 7–43 U/L), alkaline phosphatase (ALP) level was 140.4U/L (normal range: 50–135 U/L), and total bilirubin (TBL) level was 332.3 µmol/L (normal range: 6.8–30.0 µmol/L). Additionally, her prothrombin time was 18.8 second (normal range: 9.0–13.0 second). The etiologies of hepatitis A, B, C and E were negative. Autoimmune tests revealed only positive indication of the granule type of antinuclear antibodies (ANA). The anti-mitochondrial M2 antibody test was negative. The immunoglobulin tests reported the following results: IgG level at 15.00 g/L (normal range: 7.0–16.0 g/L), IgA level at 4.57 g/L (normal range: 0.7–4.0 g/L), and IgM level at 1.33 g/L (normal range: 0.4–2.3 g/L). Abdominal CT scans indicated liver damage. An ultrasound-guided liver biopsy was also performed. The liver biopsy revealed that the focal liver acinar structure was abnormal. Specifically, the hepatocytes were diffuse with hydropic degeneration and ballooning degeneration, with a “rosette”-like hyperplasia of the hepatocytes (Fig. 1), which had progressed to a severe focal necrosis and multiple bridging necrosis (Fig. 2). A partial liver plate surrounding the central vein was collapsed, with infiltrations of foam cells, some little lymphocytes, and plasma cells. Kupffer cells had proliferated, and several lymphocytes had infiltrated into the hepatic sinuses.

Interfacial inflammation was also observed (Fig. 3). There was no evidence of destruction, degeneration, or disappearance in the bile duct, whereas the small bile duct exhibited obvious proliferation (Fig. 4). Mixed inflammatory cells had also infiltrated into the stroma. The degree of pathological change was equivalent to G4S1 changes. Our pathologist considered that the liver injury may have been caused by drugs or environmental toxoids. The patients were given liver protection and albumin transfusions for 25 days. The liver function gradually recovered, after which the patient was discharged.

The patient was followed up regularly after the discharge. Thus far, her liver function has been normal, and no signs of recurrence were evident. Based on the symptoms, signs, and examination, the clinicians considered that the diagnosis was herb-induced liver injury (hepatocellular and acute), a RUCAM score of 7 (probable), a severity for grade 4 liver injury, and accompanied autoimmune-like changes.

This case report was approved by the ethics committee of the First Hospital of Jilin University, Changchun, China, and the informed consent form was signed by patient.

3. Literature review and discussion

Herbal medicines are extensively used for treating various diseases and are universally perceived as being safe, on account of their wide use in traditional Chinese medicine for thousands of years. Currently, with the increasing popularity of herbs, the...
We observed that interfacial inflammation, lymphocytic/plasmocytic infiltration in the portal area, and the “rosette”-like structures in the hepatocytes are the histological features for AIH. However, a retrospective study in recent years demonstrated that the “rosette”-like structures in the patients with drug-induced, autoimmune-like hepatitis are more common than those in patients with drug-induced liver injury without evidence of autoimmune hepatitis, but the difference was not statistically significant. A recent study also demonstrated that “rosette”-like changes are difficult to define and are difficult to diagnose based on the simplified criteria DILI with autoimmune characteristics cannot be reliably distinguished from AIH from the sole perspective of histology. Another recently published retrospective study also demonstrated that 243 liver biopsy-proven HILI cases were immune-mediated, which accounted for 53.9% of the total cases. Manuel reported a case of hyperammonemia that was caused by Olmesartan. The patients pathological characteristics were similar to AIH, but no immunosuppressants were used. Only the discontinuation of the suspected drug, hypertransaminasemia was recovered. The researchers considered that the drug-induced liver injury may be mediated by an immune mechanism. According to the EASL guidelines, for the patients with initial onsets, a clear medication history, and obvious autoimmune characteristics that cannot be diagnosed, even after the discontinuation of the suspected drugs, immunosuppressive therapy can be considered, and this therapy can be gradually reduced the amount until the drug is stopped. If there is no sign of recurrence during the follow-up process, then the DILI diagnosis can be established. If there is no indication of remedication and the disease recurs, then it can be diagnosed as AIH. Our patients serum IgG level was normal. Additionally, only granule types of cells were positive in the ANA series. A widely accepted study demonstrated that, although nonspecific, ANA results are positive in 50% to 83% patients with autoimmune-like, drug-induced liver injury.

Another case report published in Hepatology also demonstrated that the ANA series can be positive for immune-mediated, drug-induced liver injury. No immunosuppressive therapy was used. The liver function was normal within 6 months after discharge; therefore, the evidence of the diagnosis of AIH was insufficient. At the same time, the guidelines indicates that individuals carrying the HLA allele DRB1*03:01/04:01 can be more easily diagnosed with idiopathic AIH, and the presence of the DILI risk allele DRB1*15:01 supports the diagnosis of AIH.

### Table 1: Characteristics of xiang-tian-guo-induced hepatotoxicity cases.

| Cases | Sex/Age | Previous illness | AST (U/L) | ALT (U/L) | ALP (U/L) | TBL (umol/L) | RUCAM score | Type of DILI | Liver biopsy | Treatment Period (days) | References |
|-------|---------|------------------|-----------|-----------|-----------|-------------|-------------|--------------|-------------|------------------------|-------------|
| Patient 1 | F/45 | Depression | 1255 | 1267 | 124 | 258 | 7 | Hepatocellular | Y | 10 | Valerie Yap, 2018 |
| Patient 2 | M/72 | N/A | 789 | 678 | 254 | 212.4 | 7 | Hepatocellular | Y | 28 | Tan Youwen, 2019 |
| Patient 3 | M/75 | Diabetes | N/A | 363 | 122 | N/A | 7 | Hepatocellular | N | 28 | Tan Youwen, 2019 |
| Patient 4 | M/80 | Hypertension | N/A | 224 | 108 | N/A | 7 | Hepatocellular | N | 14 | Tan Youwen, 2019 |
| Patient 5 | F/66 | Diabetes | 664 | 528 | 168 | 67.9 | 9 | Hepatocellular | N | 27 | Qi Chuan Wang, 2019 |
| Patient 6 | M/62 | Diabetes | 561.2 | 765.9 | 190.7 | 710.7 | 8 | Hepatocellular | N | 33 | Zhao Xi, 2019 |
| Patient 7 | F/81 | Diabetes | 398 | 276 | 138 | 312.3 | 8 | Hepatocellular | N | 15 | DING Nan, 2019 |
| Patient 8 | M/52 | Diabetes, hypertension | 187 | 521 | N/A | N/A | N/A | 7 | Hepatocellular | Y | 25 | Our case |
| Patient 9 | F/67 | Hypertension | 672.4 | 681.7 | 140.4 | 332.3 | 7 | Hepatocellular | Y | 25 | Shao et al. Medicine (2021) 100:2 |

1 The laboratory test results in the table are at the time of admission.

AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phosphatase, DILI = drug-induced liver injury, F = Female, M = Male, N = No, N/A = not applicable, TBL = total bilirubin, Y = Yes.
drug-induced AIH. The limitation of this case was that we did not assess for the presence of this gene, which may be related to the identification of the AIH and DILI, as these tests were not available in our hospital. Therefore, our patient was diagnosed with herb-induced liver injury and accompanied autoimmune-like changes. This is the first case of herb-induced, autoimmune-like hepatitis caused by xiang-tian-guo that was reported in China.

Xiang-tian-guo belongs to the mahogany genus Meliaceae. It is known as the Swietenia macrophylla seeds and is also called the Tunjuk Langit in Malaysia and skyfruit in the English language. The seeds are used to treat diabetes and hypertension. In 2015, Balijepalli et al. evaluated the safety of SMS in Sprague-Dawley (SD) rats. Their conclusion was that the rat dose of 2 g/kg bw, which is equivalent to the human dose of 32.5 mg/kg bw and well below the common amount that is consumed by people, did not exhibit any signs of toxicity in rats. Chng YS demonstrated that SM50 has the potential to be used as an herbal medication to treat hypertension. However, there have been no further clinical trials of this herb to confirm its safety. We collected clinically relevant case reports, and all of these cases exhibited good prognoses after treatment. We envision further research on this phenomenon, and we hope to alert clinicians of this drug’s potential liver toxicity.

Acknowledgment

We appreciate the histological images provided by Jin Meishan from the Department of Pathology, the first hospital of Jilin university.

Author contributions

Conceptualization: Yue-ming Shao, Yu Zhang, Xin Yin, Xiao-yu Wen.
Data curation: Yue-ming Shao.
Funding acquisition: Xiao-yu Wen.
Investigation: Yue-ming Shao, Yu Zhang.
Resources: Yu Zhang, Xin Yin, Ting-ting Qin.
Supervision: Qing-long Jin.
Writing – original draft: Yue-ming Shao.
Writing – review & editing: Xiao-yu Wen.

References

[1] European Association for the Study of the Liver. EASL clinical practice guidelines: drug-induced liver injury. J Hepatol 2019;70:1222–61.
[2] Hong M, Li S, Tan HY, et al. A network-based pharmacology study of the herb-induced liver injury potential of traditional hepatoprotective Chinese herbal medicines. Molecules 2017;22:632.
[3] Wang R, Qi X, Yoshida EM, et al. Clinical characteristics and outcomes of traditional Chinese medicine-induced liver injury: a systematic review. Expert Rev Gastroenterol Hepatol 2018;12:425–34.
[4] Ma X, Peng JH, Hu YY. Chinese herbal medicine-induced liver injury. J Clin Transl Hepatol 2014;2:170–5.
[5] Zhang P, Ye YG, Yang XZ, et al. Systematic review on Chinese herbal medicine induced liver injury. Evid Based Complement Alternat Med 2016;2016:3560812.
[6] Yeap V, Tan TJY, Loh T, et al. Liver failure associated with mahogany seed extract consumption. BMJ Case Rep 2018. doi:10.1136/bcr-2018-223382.
[7] Tan YW, Chen HB, Zhou XB, et al. RUCAM-based assessment of liver injury by xiang-tian-guo (Swietenia macrophylla) seeds, a plant used for treatment of hypertension and diabetes. Ann Hepatol 2019;18:406–7.
[8] Qi CW, Xian JC. Liver injury induced by Dioscorea bulbifera, Swietenia macrophylla seeds, and Periplaneta forresti: a report of 3 cases. J Clin Hepatol 2019;35:2780–2. (in Chinese).
[9] Zhao X, Qi Y, Cai YJ. Fructus Swietenia Macrophylla-induced liver injury: a report of 2 cases. J Clin Hepatol 2019;35:1086–8. (in Chinese).
[10] Ding N. A suspected liver damage caused by xiang-tian-guo: a case report. Central South Pharmacy 2019;17:2013–4. (in Chinese).
[11] Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci 2015;17:14.
[12] Jing J, Teschke R. Traditional Chinese medicine and herb-induced liver injury: comparison with drug-induced liver injury. J Clin Transl Hepatol 2018;6:57–68.
[13] Balitzer D, Shafizadeh N, Peters MG, et al. Autoimmune hepatitis: review of histologic features included in the simplified criteria proposed by the international autoimmune hepatitis group and proposal for new histologic criteria. Mod Pathol 2017;30:773–83.
[14] deLemos AS, Fourreau DM, Jacobs Carli, et al. Drug-induced liver injury with autoimmune features. Semin Liver Dis 2014;34:194–204.
[15] Liu FF, Duan XZ, Zang H, et al. Analysis of clinical and pathologic features of drug-induced autoimmune-like hepatitis. Chin Hepatol 2013;18:444–7. (in Chinese).
[16] Manuel TA, Mercedes I. Drug liver injury induced by Olmesartan mediated by autoimmune-like mechanism: a case report. Eur J Case Rep Intern Med 2020;7:001407.
[17] Lucena MI, Kaplowitz N, Hallal H, et al. Recurrent drug-induced liver injury (DILI) with different drugs in the Spanish Registry: the dilemma of the relationship to autoimmune hepatitis. J Hepatol 2011;53:820–7.
[18] Stone JG, Northup PG. Autoimmune-like drug-induced liver injury: a review and update for the clinician. Expert Opin Drug Metabs Toxicol 2016;12:1291–301.
[19] Bjorhnsson E, Talwalkar J, Treeprasertsuk S, et al. Drug-induced liver injury (DILI): a review and update for the clinician. Expert Opin Drug Metab Toxicol 2015;10:2040–8.
[20] Hsiaomochi A, Kage M, Ide Tatsuya, et al. An analysis of drug-induced liver injury, which showed histological findings similar to autoimmune hepatitis. J Gastroenterol 2016;51:597–607.
[21] Bange S, Ziel M, Nault C. Autoimmune-like chronic hepatitis induced by olmesartan. Hepatology 2017;66:2086–8.
[22] Balijepalli MK, Suppaiah V, Chin AM, et al. Acute oral toxicity studies of Swietenia macrophylla seeds in Sprague Dawley rats. Pharmcognosy Res 2015;7:38–44.