Hepatic veno-occlusive disease related to Gynura segetum
A case report
Ziyi Sun, MS,a,b Jianmei Kang, MS,c Yongchang Zhang, MD,a,*

Abstract
Introduction: Hepatic veno-occlusive disease (HVOD), as known as hepatic sinusoidal obstruction syndrome (HSOS), is an obliterative venulitis of the terminal hepatic venules, which is responsible for considerable mortality. The potential mechanism is destruction of hepatic sinusoidal endothelial cells (SEC), with sloughing and downstream occlusion of terminal hepatic venules. Here, we report a case of HVOD who have a history of ingestion of Gynura segetum for 1 month. The patient presents for abdominal pain and distension. He was diagnosed for HVOD using computerized tomography (CT) and ultrasonography of liver. And then best supportive care was added. However, without liver transplantation for financial reason, he died in 1 month after discharged from hospital.

Conclusions: We think portal flow reversal was a characteristic imaging findings of HVOD, which can be listed as a specific diagnostic criterion of HVOD. Once the condition was worsening, liver transplantation should be considered as the first choice of treatment planning.

Abbreviations: ALB = albumin, ALT = alanine aminotransferase, AST = aspartate transaminase, DBILI = direct bilirubin, HVOD = hepatic veno-occlusive disease of liver, SEC = sinusoidal endothelial cells, SOS = sinusoidal obstruction syndrome; TBILI = total bilirubin, TIPS = transjugular intrahepatic portosystemic shunt, VOD = veno-occlusive disease of liver.

Keywords: Gynura segetum, hepatic veno-occlusive disease, ultrasonography of liver

1. Introduction
Veno-occlusive disease of liver (VOD), as known as hepatic sinusoidal obstruction syndrome (SOS), is an obliterative venulitis of the terminal hepatic venules, which serves as a high risk of mortality. This kind of disease is often related with some kind of toxic and other pyrrolizidine alkaloid-containing herbal. The potential mechanism is destruction of hepatic sinusoidal endothelial cells (SEC), with sloughing and downstream occlusion of terminal hepatic venules. Contributing factors are SEC glutathione depletion, nitric oxide depletion, increased intrahepatic expression of matrix metalloprotei-nases. Here, we report a case of HVOD that has a history of ingestion of Gynura segetum for 1 month.

2. Case description
A 46-year-old male was enrolled in the Second Xiangya Hospital of Central South University on Mar 3, 2015, due to abdominal pain, abdominal distension, and loss of appetite for 1 week. He had drunk 200 mL of spirit on a daily for 10 years. To treat his traumatic injuries, the patient had taken large doses of Gynura segetum before he developed symptoms. Physical examination revealed development of right upper-quadrant pain, ascites with shifting dullness, and unexplained weight gain. Laboratory tests showed that total albumin 50.5 g/L (60-85 g/L), albumin: 35.1 g/L (35-51 g/L), total bilirubin 17.8 μmol/L (5.13-22.24 μmol/L), direct bilirubin 9.2 μmol/L (1.70-8.55 μmol/L), alanine aminotransferase (ALT) 460 U/L (9-50 U/L), aspartate aminotransferase (AST) 469 U/L (0-40 U/L), total bile acid 68.4 μmol/L (0.1-10.0 μmol/L), and prothrombin time was 18.3 s (INR 1.52). The results of laboratory tests indicated liver injury. CT showed that uniform distribution of parenchymal spot, less clear border, unclear intrahepatic vessels, abnormal liver blood flow distribution at the rate of 9.5 cm/s and characteristic portal flow reversal (Fig. 2A–E). Based on the history of Gynura segetum taking, typical clinical presentation, laboratory tests, the results of CT, and ultrasonography of liver, the patient was diagnosed with VOD.

For the treatment, glutathione (1800 mg, ivgtt, Qd) and magnesium isoglycyrrhizinate (100 mg, ivgtt, Qd) was added to protect the liver and ceftazidime (2 g, ivgtt, Q8hours) was
aimed to control the infection; spironolactone tablets (20 mg, po, Q8h) as diuretics to dehydrate, pantoprazole (40 mg, ivgtt, Qd) to protect the stomach; human serum albumin (5 g, ivgtt, Qd) to maintain oncotic pressure and several times abdominal paracentesis to control the symptoms of abdominal oppression. For 9 days, the AST level and the ALT level were decreased to 355 U/L (9-50 U/L) and 308 U/L (0-40 U/L), respectively. However, the total bilirubin level, the direct bilirubin level and the total bile acid level were elevated to 35.5 μmol/L (5.13-22.24 μmol/L), 19.7 μmol/L (1.70-8.55 μmol/L), and 82.5 μmol/L (0.1-10.0 μmol/L), respectively. For 18 days, the AST level and the ALT level were decreased to 224.1 U/L (9-50 U/L) and 265.1 U/L (0-40 U/L), respectively. However, the total bilirubin level, the direct bilirubin level and the total bile acid level were significantly elevated to 43.3 μmol/L (5.13-22.24 μmol/L), 22.8 μmol/L (1.70-8.55 μmol/L), and 139.9 μmol/L (0.1-10.0 μmol/L), respectively. Due to the worsening condition, we suggested the patient to receive liver transplantation. However, for the financial reasons, he failed to receive liver transplantation. The follow-up data showed that he died in 1 month after discharged from hospital.

3. Discussion

VOD of liver was first reported by Dr. Stillman and Lawrence.[5,6] The main characters of VOD were hepatalgia, hepatomegaly, and ascites. It is often caused by high-dose chemotherapy before bone marrow transplantations and ingestion of pyrrolizidine alkaloids contained in herbal. In China, *Gynura segetum* is regarded as a good herbal medicine, which has the main function of invigorating the circulation of blood to treat trauma. However, several articles reported that *Gynura segetum* has the hepatotoxicity component, namely pyrrolizidine alkaloids which could cause some special disease.[3,7]
HVOD described by Dr. Dai was associated with the ingestion of Gynura root containing pyrrolizidine alkaloids.\textsuperscript{3,4} In 2011, Dr. Lin provided strong evidence for the correlation between HVOD and exposure to the Gynura segetum.\textsuperscript{7} In 2 literatures, Dai and Lin both provided precise confirmation of HVOD, which was based on the histology examination of liver tissue. Meanwhile, they also offered other common clinical examination methods to diagnose, such as laboratory tests, abdominal CT, digital subtraction angiography, ultrasonography, and so on. In our case, for the refusal of patient, we failed to take liver biopsies. Despite all, with the clinical examinations and past reports about HVOD and Gynura segetum, we also made a reliable diagnosis for the patient.

At present, apart from symptomatic methods, there was no specific treatment of HVOD. Hence, the key of the treatment of VOD should be symptomatic and rapid. When you receive a suspected case, you should pay more attention to monitoring of liver function, water-electrolyte balance, and infection control.\textsuperscript{10} When fluid retention and renal failure cannot be controlled, hemodialysis/hemofiltration were necessary.\textsuperscript{9} Heavy VOD should be transferred to the intensive care unit.\textsuperscript{10,11} For most patients, they can recover under proper symptomatic treatment for weeks; however, 20% of the patients will have a final destination of liver failure; only a few will encounter cirrhotic liver function, water-electrolyte balance, and infection control.\textsuperscript{10} For most patients, they can recover under proper symptomatic treatment. Furthermore, early preventive measures, including liver transplantation, should be considered for patients to avoid liver failure.

4. Method

This was a case report. Ethics committee or institutional review board approval was not obtained. It was not necessary for the case report. The next of kin signed informed consent for the publication of this case report.

Acknowledgments

The authors thank the next of kin for agreeing with our report and for providing a detailed medical history. We also thank all the 3 authors to collected data, draft the article, and finish the submission.

Author contributions

Yongchang Zhang designed the project. Ziyi Sun prepared the manuscript and Jianmei Kang collected the data.

Data curation: Jianmei Kang.

Formal analysis: yongchang zhang.

Writing – original draft: Ziyi Sun, Jianmei Kang.

Writing – review & editing: yongchang zhang.

References

[1] Roscioli T, Ziegler JB, Buckley M. Adam MP, Ardingher HH, Pagon RA, et al. Hepatic veno-occlusive disease with immunodeficiency. Gene Reviews (R). Seattle, WA:1993.
[2] Wu XW, Wang WQ, Liu B, et al. Hepatic veno-occlusive disease after taking Gynura Rhizome: the value of multidetector computed tomography in diagnosing the disease and evaluating the clinical therapeutic effect. Hepatol Res 2012;42:304–9.
[3] Dai N, Yu YC, Ren TH, et al. Gynura root induces hepatic veno-occlusive disease: a case report and review of the literature. World J Gastroenterol 2007;13:1628–31.
[4] Larrey D, Faure S. Herbal medicine hepatotoxicity: a new step with development of specific biomarkers. J Hepatol 2011;54:599–601.
[5] Stillman AS, Huxtable R, Consroe P, et al. Hepatic veno-occlusive disease due to pyrrolizidine (Senecio) poisoning in Arizona. Gastroenterology 1977;73:349–52.
[6] Lawrence TS, Robertson JM, Anscher MS, et al. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31:1237–48.
[7] Lin G, Wang JY, Li N, et al. Hepatic sinusoidal obstruction syndrome associated with consumption of Gynura segetum. J Hepatol 2011;54:666–73.
[8] Mesini A, Cangemi G, Palmasani E, et al. Hepatic veno-occlusive disease during isavuconazole administration. J Chemother 2018;30:63–4.
[9] Marquardsen FA, Baldin F, Wunderer F, et al. Detection of Sp110 by flow cytometry and application to screening patients for veno-occlusive disease with immunodeficiency. J Clin Immunol 2017;37:707–14.
[10] Harimoto N, Yagawa K, Ikegami T, et al. Hepatobiliary and pancreatic pregnancy induced hepatic veno-occlusive disease requiring liver transplantation. J Gastroenterol Hepatol 2018;33:9.
[11] Smith FO, Johnson MS, Scherer LR, et al. Transjugular intrahepatic portosystemic shunting (TIPS) for treatment of severe hepatic veno-occlusive disease. Bone Marrow Transplant 1996;18:643–6.
[12] Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol 2014;4:332–46.