

## A rare case of *Gynura-segetum*-related hepatic sinus obstruction syndrome complicated with alcoholic liver disease

Yidan Gao, Xiangbo Zhang, Xiang Zhou, Jie Wang, Ling Gong, Gongying Chen

### Abstract

Hepatic sinus obstruction syndrome (HSOS) is easy to be misdiagnosed or missed, and there is no unified and effective treatment for it. A patient was considered to have Budd-Chiari syndrome. He underwent a transjugular liver biopsy, and pathological examination revealed HSOS without liver cirrhosis. After the failure of anticoagulation therapy, he successfully received a transjugular intrahepatic portosystemic shunt (TIPS). After discharge, he was followed-up for four years with a good prognosis. *G. segetum*-induced HSOS can be easily overlooked, especially in patients with underlying liver diseases. When medical therapy fails, TIPS can control ascites and portal hypertension, and the long-term prognosis is optimistic.

**Keywords:** *Gynura segetum*; Hepatic sinusoidal obstruction syndrome; Transjugular intrahepatic portosystemic shunt.

**DOI:** <https://doi.org/10.47391/JPMA.9296>

### Introduction

Hepatic Sinus Obstructive Syndrome (HSOS) is a hepatic vascular disease caused by oedema, necrosis, and shedding of endothelial cells in the hepatic sinuses, hepatic venules, and interlobular veins, resulting in microthrombus, leading to intrahepatic congestion, liver injury, and portal hypertension.<sup>1</sup> In America and Europe, HSOS is mainly caused by chemotherapeutic and immunosuppressive drugs related to bone marrow haematopoietic stem cell transplantation (HSCT).<sup>2</sup> By comparison, the common cause in China is consuming plants, such as *Gynura segetum* and *Senecio*, which contain pyrrolidine alkaloids (PAs). So far, there is no unified and effective treatment for HSOS.<sup>3</sup> We report a rare case of HSOS caused by *G. segetum* in a patient with alcoholic liver disease, which was successfully treated.

### Case Report

A 75-year-old man was admitted to the Affiliated Hospital

The affiliated Hospital of Hangzhou Normal University, China.

**Correspondence:** Gongying Chen. e-mail: [gongyingc@163.com](mailto:gongyingc@163.com)

ORCID ID. 0000-0002-1009-0498

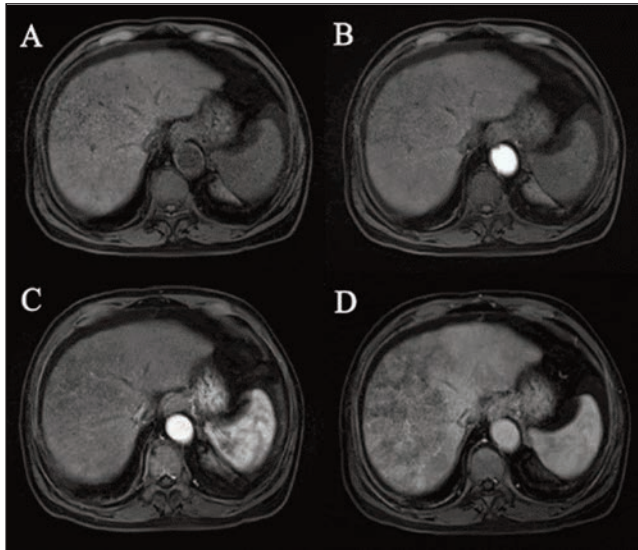
**Submission complete:** 26-10-2023

**Review began:** 29-11-2023

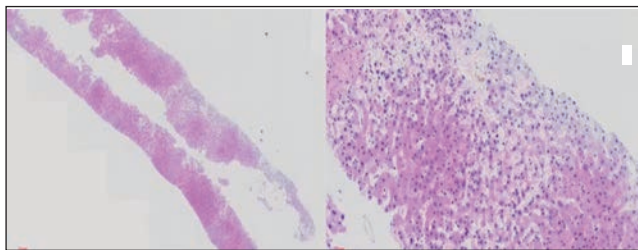
**Acceptance:** 02-03-2024

**Review end:** 02-03-2024

of Hangzhou Normal University, China, on March 11, 2019, due to abdominal distension, fatigue, and anorexia for one month. He was admitted to a local hospital a week earlier. Laboratory tests showed total bilirubin 2.58 mg/dL (normal:  $\leq 31.35$  mg/dL), direct bilirubin 1.67 mg/dL (normal:  $\leq 0.23$  mg/dL), alanine transaminase 3.4 mg/dL (normal:  $< 0.57$  mg/dL), aspartate transaminase 2.90 mg/dL (normal:  $< 0.45$  mg/dL), and serum creatinine 1.20 mg/dL (normal: 0.64–1.10 mg/dL). Upper abdominal enhanced magnetic resonance imaging (MRI) and portal vein computed tomography (CT) venography suggested stenosis of the vena cava and ascites. He was suspected to have Budd-Chiari syndrome. His past history was unremarkable. He had been drinking white wine (50 ml/day) for 50 years. Physical examination showed mild icterus of the skin, abdominal distension, mild tenderness in epigastrium, hepatomegaly, and positive shifting dullness, which revealed ascites. Laboratory tests showed white blood cell count at  $12.53 \times 10^9/L$  (normal:  $3.5\text{--}9.5 \times 10^9/L$ ), platelet count  $263 \times 10^9/L$  (normal:  $103 \times 10^9/L$ ), C-reactive protein 2.24 mg/dL (normal:  $\leq 1$  mg/dL), total bilirubin 2.65 mg/dL, direct bilirubin 1.20 mg/dL, albumin 0.29 mg/dL (normal: 0.40–0.55 mg/dL), alanine transaminase 4.81 mg/dL, aspartate transaminase 5.03 mg/dL, alkaline phosphatase 7.41 mg/dL (normal: 0.34–1.36 mg/dL), g-glutamyl transpeptidase 3.37 mg/dL (normal: 0.11–0.68 mg/dL), serum creatinine 1.87 mg/dL, serum urea nitrogen 4.25 mg/dL (normal: 1.11–2.86 mg/dL), and prothrombin time 13 seconds (normal: 9.5–12.<sup>2</sup> seconds). Serology for hepatitis viruses were negative. There were no abnormalities in autoantibodies, ceruloplasmin, or tumour markers. Ascitic fluid analysis revealed exudative picture. Liver parenchyma was hyperechoic on ultrasound of the abdomen suggesting alcoholic steatohepatitis, portal hypertension, unclear visualisation of inferior vena cava at the second hepatic hilum, and ascites. Upper abdominal enhanced MRI showed heterogeneous enhancement of the liver, 'map-like' change in hepatic parenchyma at portal venous phase, decreased enhancement density of three hepatic veins, 'trefoil-like' enhancement around the hepatic vein, thinning of the inferior vena cava, and ascites (Figure 1). Based on the clinical manifestations, he was suspected of having alcoholic cirrhosis or hepatic vein occlusion syndrome, while there was insufficient evidence for Budd-Chiari syndrome. Reviewing the clinical history



**Figure-1:** Upper abdominal enhanced MRI. A: plain CT scan; B: arterial phase; C: portal phase; D: equilibrium phase. Hepatomegaly, heterogenous enhancement and ascites in plain MRI scan. 'Map-like' change in the portal phase, decreased enhancement density of three hepatic veins, 'trefoil-like' enhancement around the hepatic vein, and thinning of inferior vena cava. Liver enhancement was more obvious in equilibrium phases.



**Figure-2:** Pathological result of liver (haematoxylin-eosin staining, left: 40 $\times$ , right: 100 $\times$ ). Hepatic sinus expansion, congestion, hepatocyte necrosis and absent, hepatic plate atrophy, obvious in the segment 3 of hepatic lobule, fibrosis and atresia in individual central veins, mild enlargement of the portal area, fibrosis and inflammatory cell infiltration.



**Figure-3:** Transjugular intrahepatic portosystemic shunt (TIPS) under fluoroscopic guidance. A: puncture of the portal vein branch through the right hepatic vein, B: placement of the balloon catheter, expansion of the shunt, and placement of the stent. C: post-operative angiography showed that the blood circulation in the stent was smooth.

again, the patient had taken *G. segetum* soaked in wine five years ago. He underwent hepatic venography, hepatic venous pressure gradient (HVPG) measurement, and a transjugular liver biopsy (TJLB). HVPG was 20 mmHg, while hepatic vein occlusion was not seen, which further

excluded Budd-Chiari syndrome. Histopathological results showed hepatic sinus expansion; congestion; hepatocyte necrosis; hepatic plate atrophy; significantly observed in the segment 3 of hepatic lobule; fibrosis and atresia in the central vein; mild enlargement of the portal area with fibrosis and inflammatory cell infiltration (Figure 2). Combined with his medical history, the patient was finally diagnosed with HSOS and alcoholic liver disease.

He was treated with low molecular weight heparin calcium (41mg, subcutaneous injection, every 12 hours), combined with glutathione, albumin, diuresis, and paracentesis. However, due to worsening abdominal distension and high HVPG, transjugular intrahepatic portosystemic shunt (TIPS) was performed (Figure 3). One week later, the ascites disappeared, and the liver and renal functions improved significantly. After discharge from the hospital, anticoagulant therapy was continued for three months, and the condition was stable without recurrence after four years of follow-up.

## Discussion

HSOS was first reported in the 1950s.<sup>4</sup> Bras and Jelliffe<sup>5</sup> observed that HSOS was characterised by hepatic congestion caused by hepatic venous occlusion, and named it hepatic veno-occlusive disease (HVOD). Later, the underlying mechanism of HSOS was noted to be obstruction of the hepatic sinusoids. In 2002, DeLeve<sup>6</sup> and others renamed HVOD as HSOS. In China, the main cause of HSOS is the use of oral Chinese herbal medicine that contains pyrrolidine alkaloids (PAs). HSOS caused by *G. segetum* is most commonly reported, accounting for more than 80% of the total cases of HSOS.<sup>7</sup> *G. segetum* is a composite plant that has the effect of promoting blood circulation and removing blood stasis, but it has been confirmed to contain PAs. PAs are dehydrogenated by cytochrome P450 in the liver, and their derivatives react with DNA, RNA, and other macromolecules to form binding pyrrole that plays the role of an alkylating agent, affecting protein synthesis and cell division, resulting in damage to the endothelium of hepatocytes, sinuses, and venules.<sup>8</sup>

The clinical manifestations of HSOS are mainly abdominal distension, pain in right hypochondrium, ascites, jaundice, and hepatomegaly. The diagnostic criteria in Europe and the United States are mostly based on the Seattle and Baltimore standards,<sup>9</sup> while the clinical manifestations and laboratory tests of PA-related HSOS are not completely consistent. Therefore, in 2017, China issued the Nanjing criteria,<sup>3</sup> the "Consensus Opinions on the Diagnosis and Treatment of Hepatic Sinusoidal Syndrome Related to Pyrrole Alkaloids". Patients have a clear history of consuming PA-containing plants and have the following

three symptoms: bloating and/or liver pain, hepatomegaly and ascites, elevated serum bilirubin or other abnormal liver function, and have typical enhanced CT or MRI findings or histological diagnostic features, and other known causes of liver damage have been excluded.<sup>3</sup>

In this case, the patient was initially suspected to have Budd-Chiari syndrome. Due to the patient's long-term drinking habit, he was considered to have alcoholic liver disease. Finally, following histopathology, the patient was diagnosed with HSOS without liver cirrhosis. It is evident that HSOS is easy to be misdiagnosed, and pathology is important for diagnosis. Moreover, when there is a large amount of ascites, transjugular liver biopsy is safe, and HVPG is easy to detect. In this case, the HVPG was 20 mmHg. It is reported that when HVPG is >10 mmHg, the specificity of HSOS diagnosis is 91%.<sup>10</sup> which can differentiate it from Budd-Chiari syndrome. However, TJLB is seldom used in China.

At present, there is no unified and effective treatment for HSOS. Medical treatment is mainly symptomatic, including reducing transaminases, alleviating icterus, diuresis, anticoagulation, infusion of albumin, prevention of infection, improvement of microcirculation, and promotion of hepatocyte regeneration.<sup>11</sup> Anticoagulation and thrombolytic therapy also improve the clinical cure rate. Defibrotide is currently recommended to treat severe HSOS post-HSCT in the European Union.<sup>12</sup> Liver transplantation is an effective treatment for patients with end-stage disease. TIPS can be used to control intractable ascites and portal hypertension in patients for whom medical treatment is ineffective. It has been reported that TIPS for PA-related HSOS is safe and effective, but such reports are rare, and its long-term prognosis is not clear.<sup>13</sup> In this report, the efficacy of anticoagulation was poor. The patient underwent TIPS to control portal hypertension and ascites, and the long-term prognosis was good. TIPS shortened the hospitalisation time and improved the quality of life.

## Conclusion

We report a case of *G. segetum*-related HSOS complicating alcoholic liver disease, which is easy to misdiagnose and has a high mortality rate if not treated early. Due to excessive ascites, TJLB was performed, and the final diagnosis was confirmed by pathology. When medical therapy failed, TIPS could control ascites and portal hypertension, and its long-term prognosis was optimistic.

### Author Contribution:

YG: Designe.

XZhou & XZhou: Responsible for analyzing and supplementing medical records.

GC: Evaluation.

LG and JW: Collected the case data and performed literature search.

All authors read and approved the final version of the manuscript.

**Consent for Publication:** Written consent was obtained from the patient for publishing his case.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Funding Sources:** None.

## References

1. Liu F, Rong X, Guo H, Xu D, Liu C, Meng L, et al. Clinical characteristics, CT signs, and pathological findings of Pyrrolizidine alkaloids-induced sinusoidal obstructive syndrome: a retrospective study. *BMC Gastroenterol.* 2020;20:30.
2. Corbacioglu S, Grupp SA, Richardson PG, Duarte R, Pagliuca A, Ruutu T, et al. Prevention of veno-occlusive disease/sinusoidal obstruction syndrome: a never-ending story and no easy answer. *Bone Marrow Transplant.* 2023;58:839-41.
3. Zhuge Y, Liu Y, Xie W, Zou X, Xu J, Wang J. Expert consensus on the clinical management of pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome. *J Gastroenterol Hepatol.* 2019;34:634-42.
4. Hill KR, Rhodes K, Stafford JL, Aub R. Serous hepatitis: a pathogenesis of hepatic fibrosis in Jamaican children. *Br Med J.* 1953;1(4802):117-22.
5. Jelliffe DB, Bras G, Stuart KL. The Clinical Picture of Venous Occlusive Disease of the Liver in Jamaican Children. *Ann Trop Med Parasitol.* 1954;48(4):386-96.
6. Deleve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis.* 2002;22(01):27-42.
7. Ni Chonghaile M, Wolownik K. Identification and Management: Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease Related to Hematopoietic Stem Cell Transplantation. *Clin J Oncol Nurs.* 2018;22(1):E7-E17.
8. Mohty M, Malard F, Alaskar AS, Aljurf M, Arat M, Bader P, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a refined classification from the European society for blood and marrow transplantation (EBMT). *Bone Marrow Transplant.* 2023;58:749-54.
9. Dignan FL, Wynn RF, Hadzic N, Karani J, Quaglia A, Pagliuca A, et al. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. *Br J Haematol.* 2013;163(4):444-57.
10. Ofliver E A F. EASL Clinical Practice Guidelines: Vascular diseases of the liver. *J Hepatol.* 2016;64(1):179-202.
11. Ou P, Liu X, Tang Z, Hou Z, Liu L, Liu J, et al. *Gynura Segetum* Related Hepatic Sinusoidal Obstruction Syndrome: A Liver Disease with High Mortality and Misdiagnosis Rate. *Curr Pharm Des.* 2019;25:3762-68.
12. Richardson PG, Carreras E, Iacobelli M, Nejadnik B. The use of defibrotide in blood and marrow transplantation. *Blood Adv.* 2018;2:1495-509.
13. Li S, Li Y, Zhou C, Li H, Chen C, Peng C, et al. Transjugular Intrahepatic Portosystemic Shunt Benefits for Hepatic Sinusoidal Obstruction Syndrome Associated with Consumption of *Gynura Segetum*: a Propensity Score-Matched Analysis. *Cardiovasc Intervent Radiol.* 2023;46:931-42.