REVIEW
DOI: 10.53388/ghr2020-09-021

Research Progress on Hepatic Veno-occlusive Disease Across the World

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Abstract

Hepatic veno-occlusive disease (HVOD), also known as hepatic sinusoidal obstruction syndrome (HSOS), is a specific type of hepatic vascular disease. The most common cause of HSOS in Western countries is the pretreatment of bone marrow hematopoietic stem cell transplantation (HSCT). In China, the most common cause is the ingestion of plants containing pyrrolidine alkaloids (PAs). In the case of HSCT-HSOS in Europe and the United States, relevant examinations, warning symptoms, and disease staging standards before and after transplantation have been clarified; however, there is a lack of corresponding imaging standards. In China, because there are no obvious early clinical symptoms and effective diagnostic methods for PA-HSOS, the disease can go undiagnosed or be misdiagnosed, and the lack of clinical staging is not conducive to the guidance of clinical diagnosis and treatment. In this article, we review the etiology, pathogenesis, clinical manifestations, diagnosis, treatment, and prognosis of HSOS in order to provide a reference for clinicians and researchers and contribute to future efforts aimed at establishing highly specific indicators for the diagnosis and prognosis of this disease.

Keyword: Hepatic veno-occlusive disease; Hematopoietic stem cell transplantation; Pyrrolidine alkaloids; Pathogeny

Background

Hepatic veno-occlusive disease (HVOD), also known as hepatic sinusoidal obstruction syndrome (HSOS), was first reported by Wilimot and Robertson in 1920. The cause is generally obstruction of the central vein of the hepatic lobule. [1] In 1954, Bras and co-workers [2] found that the earliest and most fundamental pathological change was the obstruction of hepatic sinusoids without the involvement of hepatic venules. Subsequently, the disease was called sinusoidal obstruction syndrome (SOS) by Deleve [3] and others. It is a type of hepatic vascular disease caused by various phenomena: edema of the hepatic sinusoids, hepatic venules and interlobular vein endothelial cells, necrosis, shedding and then forming micro thrombosis (which causes intrahepatic stasis), liver injury, and portal hypertension. The main clinical manifestations are pain in the liver and liver enlargement, ascites, jaundice, weight gain, and abnormal liver function. The disease can affect the respiratory system, kidneys, and heart. In 2015, the European Association for Blood and Bone Marrow Transplantation issued guidelines for the diagnosis and treatment of HSOS related to bone marrow hematopoietic stem cell transplantation. [4-5] In the 1980s, Hou Jinggui [6] and others first reported a clinical case of HVOD caused by the use of *Panax notoginseng* in China. The cases in China were mainly related to the ingestion of plants containing pyrrolidine alkaloids (PAs), and the most commonly ingested plant was *Panax notoginseng*. The Chinese Society of Gastroenterology, Hepatobiliary Diseases Collaborative Group issued the "Expert Consensus on Diagnosis and Treatment of Pyrrole Alkaloid-related Sinusoidal Obstruction Syndrome" in 2017. [7] HVOD has no specific clinical manifestations; thus, it can easily go undiagnosed or be misdiagnosed. [8] There is as yet no specific treatment, and the mortality rate of critically ill patients is extremely high. In this review article, we analyze and compare the different causes, diagnosis standards, and treatments of HSOS.

1. Epidemiology

HSCT-HSOS usually occurs approximately 30 days after transplantation, [4-5] with an incidence of 5%-60%. [9] The incidence of HSCT-HSOS is related to the intensity of preconditioning. The HSCT-HSOS incidence rate of pretreatment with reduced intensity or autologous HSCT was less than 5%.

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There have been few reports on the exact incidence of PA-HSOS; however, there are increasingly more retrospective reports of the disease in the past 15 years in China, which indicates that medical institutions are paying close attention to PA-HSOS caused by Chinese herbal plants. [10]

2.Etiology and pathogenesis

2.1 Pathogeny

The main causes of HSOS are: 1) allogeneic or autologous stem cell transplantation (HSCT), 2) liver transplantation, 3) application of non-transplant cytotoxic drugs and immunosuppressive agents, 4) consumption of plants containing pyrrolidine alkaloids (PA), and 5) other causes.

1) HSCT. Before transplantation, high-dose cytotoxic drugs, including cyclophosphamide, busulfan, 6-mercaptopurine, thiopurine, and cytarabine—as well as radiotherapy—are commonly administered. Such pre-treatments in allogeneic transplantation, secondary transplantation, and adult transplantation, as well as other factors can increase the risk of hypertension. [4-5]

2) Liver transplantation. In cases of liver transplantation, the incidence of HSOS is mostly related to the chemotherapy drugs used after transplantation, [11] and there are also isolated HVOD cases after liver transplantation. In addition, IL-1B gene polymorphism has a certain correlation with the occurrence of liver damage and microvascular disease after transplantation.[12]

3) Non-transplant cytotoxic drugs and immunosuppressive agents. Drugs such as oxaliplatin, cyclophosphamide, methotrexate, and cyclosporine may also cause HSOS. [13-15] For example, bevacizumab may contribute to HSOS by preventing the normal repair mechanism induced by vascular endothelial growth factor. [16]

4) Pyrrolidine alkaloids. In 1953, Hill and colleagues [17] reported that more than 100 people in Jamaica suffered from "serious liver disease" due to the consumption of ragwort, which is among the plants containing PAs, mainly *Panax notoginseng*, Lily, Senecio, ragwort, Crotalaria, and Liulicao. [18] Du Hongtao [19] reviewed the Chinese literature and found that the consumption of *Panax notoginseng* was the cause of most HSOS cases.

5) Other causes. Some causes of immunodeficiency syndromes, such as mutations in gene SP110 and gene polymorphisms of methylenetetrahydrofolate reductase (MTHFR) are closely related to the occurrence of HSOS. [20-21]

2.2 Pathological mechanism

The pathogenesis of HSCT-HSOS is complex and is related to chemotherapy and radiotherapy for pretreatment regimens, cytokines produced by damaged tissues, endogenous microorganisms translocated through the damaged mucosal barrier, drugs used in surgery, and complex transplantation procedures. These factors can cause the physiological activation of endothelial cells (not only of the liver sinusoids but of the whole body, including vital organs such as the lungs and kidneys), which can lead to endothelial damage and ultimately block the sinusoids and blood flow. [22] In the case of PA-HSOS, the PAs in traditional Chinese medicinal plants are non-toxic but they are metabolized by the liver to produce toxic products, which can combine with macromolecular organisms in liver cells to form polymers that affect the protein synthesis and nucleic acid metabolism in liver cells. [23-26] In addition, promotion of the expression of adhesion molecules, damage of the liver glutathione system, and local procoagulant state are all involved in the occurrence of HSOS.

In the HSCT-HSOS process, toxic metabolites of the pretreatment drugs damage the sinus endothelial cells and hepatocytes in the acinar 3 zone, resulting in endothelial cell injury syndrome that is not limited to liver sinusoidal endothelial cells but also affects systemic systems and multiple organs. Therefore, the direct causes of death in critically ill patients are mostly systemic multiple organ damage and failure. In addition, PA-HSOS is caused by drugs containing PAs that cause edema, necrosis, and shedding of endothelial cells in hepatic sinusoids, hepatic venules, and interlobular veins to form micro thrombosis that mainly act on the liver. The cause of death in such cases is more commonly cirrhosis and related complications.

3. Differences in Clinical Manifestations

3.1 Clinical symptoms

The clinical manifestations of HSCT-HSOS and PA-HSOS are essentially the same; the most common symptoms are liver pain, liver enlargement, ascites, jaundice, weight gain, anorexia, and abdominal distension.

After pretreatment and HSCT, the patient is checked daily for two weeks for signs of body weight change, ascites, jaundice, hepatomegaly, and edema, and changes in function of the kidney, lung, and brain nerve are detected as early as possible. The abnormal function of these important organs suggests multiple organ function failure and severe HSOS. However, there are no advance warning signs in most of the PA-HSOS cases caused by Chinese herbal medicine. Most people develop abdominal distension, liver pain, and anorexia in the first month after taking the medicine [27] and these symptoms are sometimes accompanied by jaundice and ascites, but most of the symptoms are mild. In most cases of severe PA-HSOS, patients die from severe liver failure and portal hypertension-related complications, including refractory ascites, gastrointestinal bleeding,

DOI: 10.53388/ghr2020-09-021

and liver and kidney syndrome. [28]

3.2 Laboratory analysis

In suspected cases of venal occlusion, the laboratory analysis includes indicators of abnormal liver function or varying degrees of thrombocytopenia and prolonged prothrombin time. Some guidelines emphasize that previous liver diseases or active liver diseases such as active hepatitis and cirrhosis are independent risk factors for the occurrence of HSOS. Those patients with serum transaminase > 2.5 times the upper limit of normal value or serum bilirubin > 1.5 times the upper limit of normal value should receive more attention. It has been reported that the degree and speed of blood bilirubin increase are accurate prognostic indicators: survival was 0% when serum bilirubin ≥ 257 μmol/L and 100% when ≤128 μmol/L; the overall survival rate was 47%.[29]

The jaundice caused by PA-HSOS is mostly mild, and the serum bilirubin is between 17.1 and 85.5 μmol/L. The levels of glutathione aminotransferase and aspartate aminotransferase show varying degrees of abnormality. The coagulation rate is often normal or mildly abnormal. It has been reported that the sensitivity of a specific test, pyrrole protein adducts (PPAs), can reach 100%, with a specificity of 94.1%. [30] A small sample clinical study demonstrated the sensitivity and specificity of PPA detection in patients' blood as a tool for predicting HSOS; the concentration of PPAs is positively correlated with disease severity and prognosis. [31]

3.3 Imaging examination

There have been many discussions of the imaging characteristics of PA-HSOS in China. Detailed descriptions of ultrasound, CT, and MRI imaging have been given in the guide. The typical CT imaging manifestations have the following characteristics. [7] Under plain scan, the liver is enlarged, the density is decreased irregularly, and ascites may be present. The arterial phase is manifested as mild uneven enhancement of the liver, with thickened and twisted liver blood vessels. The portal vein phase is manifested as patchy liver, with map-like low-density shadows, and the hepatic veins are thin or not clearly displayed. There is no change in the portal vein. The inferior vena cava segment is narrowed, without obstruction and distal expansion, and no collateral circulation is formed; "halo sign" or "orbit sign"-like changes can be seen around the inferior vena cava and portal vein.

In reviewing the articles in the early 2000s, we found that the imaging (including ultrasound and CT) had no relative specificity in the diagnosis of HSOS, but the measurement of hepatic venous pressure gradient was significant.

In published guidelines for diagnosing HSCT-HSOS, Dignan and colleagues [32] point out that the more specific diagnostic criteria are ascites and/or hepatomegaly on ultrasound and hepatic vein blood flow thinning or direction reversal under ultrasound.

3.4 Pathological manifestations

The pathological manifestations of HSCT-HSOS and PA-HSOS are roughly the same. Biopsy results remain the gold standard for the diagnosis of this disease. The histological changes are related to the duration of the disease and are divided into acute, subacute, and chronic. In the acute phase of the disease, the growth in volume of the liver, with smooth surface, is immediately apparent. Moreover, the congestion of the massive lobular central vein and hepatic venules, as well as necrosis of the lobular central cell, can be seen under the microscope. In the subacute phase—ranging from a few days to several weeks—reticular regional contraction can be seen on the surface of the liver. Collagen deposits around the terminal hepatic lobular veins of the disease can also be seen under the microscope. Chronicity ranges from several weeks to months. The veins around the liver show dense fibrosis, gradually spreading into the liver parenchyma. The destruction of liver cells eventually leads to cirrhosis; [33] additionally, in most cases the disease progression is marked by a large amount of ascites, poor coagulation function, thrombocytopenia, and uneven distribution of lesions.

4. Diagnostic criteria

According to the standard set in 2017, in Nanjing, China, which mainly regulated the clinical diagnostic criteria for HSOS caused by *Panax notoginseng*, [7] the concrete content can be seen as follows. Above all, patients has a clear history of taking *Panax notoginseng* and meet the following three criteria: (1) abdominal distension, liver pain, hepatomegaly and ascites; (2) elevated total bilirubin or other abnormal liver function; (3) typical enhanced CT or MRI findings, with the characteristic "map-like" uneven density of the liver. If the patient's history of ginseng use is not clear, the serum PPA levels can be measured and combined with pathological findings in order to confirm the diagnosis.

In 2016, the European Society for Blood and Marrow Transplantation issued new diagnostic criteria for adults:[4-5] impaired liver function (as indicated by total bilirubin >2 mg/dL) occurs within 21 days after transplantation, and two of the following three criteria are met: hepatomegaly pain, weight gain more than 5%, and presence of ascites. In addition to the above criteria, when diagnosing cases more than 21 days after surgery, pathology, hemodynamics, and/or more specific ultrasound findings (new ascites, hepatomegaly, and portal vein blood flow rate declining or direction reversal) can be taken into consideration. In particular, the occurrence of two of the following four indicators signal HSOS: (1) liver enlargement and pain; (2) weight gain more than 5%; (3) ascites; and (4) total bilirubin >2

mg/dL.

It should be noted that in blind percutaneous liver biopsies, it is hard to find lesions and there is increasing risk when using needle biopsy. Therefore, we are now convinced that the histological evidence of HVOD is no longer necessary for diagnosis.[34]

In countries other than China, there are clear diagnostic standards for both the symptoms and the increase in total bilirubin, but there are no specific imaging guidelines; in China, however, the specific imaging manifestations (CT or MRI) as well as relevant medication history and liver function abnormalities together contribute to the diagnosis. [35]

5. Treatment and recovery

At present, there is no specific treatment method for HSOS across the world, and the fatality rate of severe HSCT-HSOS is over 80%. [36-37] Generally, symptomatic and supportive medical treatment is given first, including the application of hepatoprotective drugs, maintenance of electrolyte and acid-base balance as well as effective circulating blood volume, administration of nutrients (including albumin, fresh plasma), and application of hepatocyte growth factor to promote the growth of liver cells. [38] Patients with edema and ascites are required to limit sodium and water by using diuretic drugs. Patients with renal insufficiency require dialysis; those with jaundice are administered ursodeoxycholic acid and S-adenosylmethionine.

Currently, the most specific treatment drug is defibrillation, the underlying mechanism of which is to protect endothelial cells and maintain the thrombo-fibrinolytic balance. [39] Also, the medicine is adopted in severe HSCT-HSOS in Europe and America. Some studies reported that hormones play a certain role in HSCT-HSOS; however, the application of heparin remains controversial. In cases of PA-HSOS, the Chinese guidelines recommend anticoagulant therapy, including low molecular weight heparin and warfarin, as well as specific drug dosage and efficacy standards. Song Yu and Zhang Yanting reviewed the domestic anticoagulation treatment and concluded that the effectiveness of this type of treatment was significantly higher than that of the control. [40-41] Hormones, Chinese medicine, and prostaglandin E are not recommended.

Jugular intrahepatic portosystemic shunt (TIPS) is not effective in the treatment of HSCT-HSOS, but some studies report that TIPS helps heal PA-HSOS. [42] Lastly, liver transplantation in conditions of end-stage liver failure can improve the prognosis of HSCT-HSOS patients; however, we did not find any report of this in PA-HSOS patients. [43]

6. Conclusion

In conclusion, understanding the prevention of HSOS is more significant than the treatment of this syndrome, and prevention includes the formulation of myeloablative pretreatment programs, enhancement of public awareness of Chinese herbal plants containing PA, early attention to the clinical symptoms of HSOS, as well as enhancing awareness among clinicians—all of which will contribute to early treatment and reduced occurrence of the disease.

There are clear disease staging standards for HSCT-HSOS, but the guidelines do not clearly clarify its imaging counterparts. The early clinical symptoms of PA-HSOS are not as obvious, and the lack of clear disease staging is not beneficial to guiding clinical diagnosis and treatment. In China, the diagnosis and treatment of PA-HSOS are mainly based on retrospective research; large-sample multi-center prospective controlled studies are lacking. The search for early warning signs and specific diagnostic and prognostic indicators for HSOS is a task for future studies.

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DOI: 10.53388/ghr2020-09-021

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Competing interests: The authors declare that they have no conflict of interest.
Publisher's note: TMR Publishing Group Limited remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Citation: Xia NN, Shi HL, Zhang XY. Comparison of research progress of hepatic venule occlusion syndrome at home and abroad. Gastroenterology & Hepatology Research, 2020, 2 (3): 92–97.