Sinusoidal Obstruction Syndrome (Hepatic Veno-Occlusive Disease)

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Hepatic sinusoidal obstruction syndrome (SOS) is an obliterative venulitis of the terminal hepatic venules, which in its more severe forms imparts a high risk of mortality. SOS, also known as veno-occlusive disease (VOD), occurs as a result of cytoreductive therapy prior to hematopoietic stem cell transplantation (HSCT), following oxaliplatin-containing adjuvant or neoadjuvant chemotherapy for colorectal carcinoma metastatic to the liver and treated by partial hepatectomy, in patients taking pyrrolizidine alkaloid-containing herbal remedies, and in other particular settings such as the autosomal recessive condition of veno-occlusive disease with immunodeficiency (VODI). A central pathogenic event is toxic 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 metalloproteinases and vascular endothelial growth factor (VEGF), and activation of clotting factors. The clinical presentation of SOS includes jaundice, development of right upper-quadrant pain and tender hepatomegaly, ascites, and unexplained weight gain. Owing to the potentially critical condition of these patients, transjugular biopsy may be the preferred route for liver biopsy to exclude other potential causes of liver dysfunction and to establish a diagnosis of SOS. Treatment includes rigorous fluid management so as to avoid excessive fluid overload while avoiding too rapid diuresis or pericentesis, potential use of pharmaceutics such as defibrotide, coagulolytic agents, or methylprednisolone, and liver transplantation. Proposed strategies for prevention and prophylaxis include reduced-intensity conditioning radiation for HSCT, treatment with ursodeoxycholic acid, and inclusion of bevacizumab with oxaliplatin-based chemotherapeutic regimes. While significant progress has been made in understanding the pathogenesis of SOS and in mitigating against its adverse outcomes, this condition remains a serious complication of a selective group of medical treatments. (J Clin Exp Hepatol 2014;4:332–346)

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Abbreviations: AML: acute myeloid leukemia; APRI: aspartate aminotransferase to platelet ratio; AST: aspartate aminotransferase; Bmab: bevacizumab; DF: defibrotide; FOLFOX: chemotherapy regimen containing Folinic acid, 5-Fluorouracil, and Oxaliplatin; GO: gemtuzumab ozogamicin; GSTM1: glutathione S-transferase M1; GVHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; L-NAME: N(G)-nitro-L-arginine methyl ester; MOF: multi-organ failure; PML: promyelocytic leukemia protein; RIC-HSCT: reduced-intensity conditioning hematopoietic stem cell transplantation; RILD: radiation-induced liver disease; RT: radiation therapy; SEC: sinusoidal endothelial cells; s-ICAM-1: soluble intercellular adhesion molecular-1; SOS: sinusoidal obstruction syndrome; TBI: total body irradiation; TIPS: transjugular intrahepatic porto-systemic shunt; t-PA: tissue plasminogen activator; UPLC-MS: ultra-performance liquid chromatography-mass spectrometry; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; VOD: veno-occlusive disease; VODI: veno-occlusive disease with immunodeficiency; V-PYRRO/NO: O(2)-vinyl 1-(pyrrolidin-1-yl)diazen-1-ium-1,2-diolate; v-WF: von Willebrand factor
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Obliterative endophlebitis in the terminal hepatic veins of the human liver lobule was first reported by a pathologist from Prague in 1905, with the only etiologic suggestion being syphilis.[1] In 1954, terminal vein lesions were described in Jamaican drinkers of bush tea, characterized by obliteration of hepatic vein radicals by varying amounts of subendothelial swelling and fine reticulated tissue.[2] At later stages, a fibrous pericentral scar developed. In the early 1960's, studies of the effects of ionizing radiation on mammalian tissues documented that the hepatic vasculature could be damaged by this mechanism,[3] in the absence of antecedent vascular thrombosis.[4,5] The most striking example of an obliterative venous lesion induced by irradiation was documented in humans with lung tumors receiving radiation treatment; both the lung vasculature and that of the dome of the liver that was included in the radiation field developed vascular obliteration, but not the remainder of the unexposed liver.[6] Shortly thereafter, induction of obliterative venopathy following heavy irradiation directly of the human liver for metastatic disease was reported in 12 patients receiving upper abdominal irradiation by the Stanford Linear Accelerator.[7] Thus, by the mid-1960s, the concept of hepatic *veno-occlusive disease* was well-established,

induced by either chemical or radiation toxicity, and as a lesion separate from Budd-Chiari syndrome and Banti syndrome.[8,9]

In the late 1970′s, similar histologic lesions were reported from outbreaks in India and Israel, attributed to contamination of wheat and traditional herbal remedies with plant toxins.[10,11] The histological lesions resembled previously described hepatic veno-occlusive lesions described in rats poisoned with *Senecio* plant extracts[12] or *Crotolaria*.[13] This form of liver toxicity was ultimately attributed to hepatic exposure to plant pyrrolizidine alkaloids,[14] establishing these plant toxins as the cause of veno-occlusive disease in users of herbal teas.

Bone marrow transplantation for humans with leukemias became a therapeutic option during the 1960s. Initial challenges to this new therapy were preservation of harvested marrow, and achieving successful marrow engraftment.[15] Reports of hepatic veno-occlusive disease in patients undergoing bone marrow transplantation emerged in the 1970′s,[16] followed by numerous reports which established the following apparent risk factors: bone marrow transplantation for malignancy, involving intense chemotherapeutic and radiation conditioning regimens; patient age over 15 years; and in particular, abnormal pretransplant serum levels of liver enzymes.[17–19] The presence of metastatic liver disease in patients undergoing bone marrow transplantation for solid tumors and lymphomas also predisposed to veno-occlusive disease.[20,21] In these initial years after recognition of veno-occlusive disease as a complication of induction regimes prior to bone marrow transplantation, the incidence of veno-occlusive disease varied from 21% to 25% in allogeneic graft recipients,[19,21,22] to 5% in recipients of autologous marrow.[20,23,24] In the four decades since routine use of bone marrow transplantation for solid malignancies, lymphomas and leukemias, induction regimes and therapies have helped improve, but not eliminate, the incidence of this condition in the transplant population. Its incidence now is primarily in the setting of hematopoietic stem cell transplantation, but SOS may occur in other settings as well (Table 1).

Table 1 Causes of Sinusoidal Obstruction Syndrome (SOS).

Hematopoietic stem cell transplantation (HSCT)
Adjuvant or neoadjuvant chemotherapy with hepatectomy for metastatic liver disease
Radiation-induced liver disease
Chemotherapy for acute myeloid leukemia (AML)
Liver transplantation
Use of herbal remedies
Veno-occlusive disease with immunodeficiency (VODI)

PATHOGENESIS

Experimental Investigation in Animals

Initial experimental efforts to induce veno-occlusive disease in animals focused on irradiation. Although the non-human primate liver is relatively resistant to radiation-induced veno-occlusive disease,[25] veno-occlusive lesions could be induced in primates[26] and in non-primates[27] by exposure to chronic irradiation regimes. However, the underlying pathogenesis of this condition was not elucidated with these early experimental models. Careful ultrastructural examination of human tissues suggested that the initial morphologic change in hepatic veno-occlusive disease was obstruction at the level of hepatic sinusoids, followed by obliteration of the terminal hepatic veins.[28] This observation was confirmed with the report in 1999 of a more economical and reproducible rodent model of veno-occlusive disease.[29] In rats gavaged with the pyrrolizidine alkaloid monocrotaline and killed between days 1–10 after exposure, the earliest documented change was damage to the hepatic sinusoids; fibrosis and obliteration of the terminal hepatic veins occurred as a subsequent lesion. This articulation that toxic injury to the hepatic sinusoids was the fundamental lesion of hepatic veno-occlusive disease led to its being renamed *sinusoidal obstruction syndrome* (SOS).[30]

The rat model of SOS may be summarized as follows.[29,31] Following a single gavage with monocrotaline, within 24 h–48 h there is ultrastructural evidence of damage to hepatic sinusoidal endothelial cells (SEC), but little clinical or histological evidence of hepatic toxicity. By days 3–5 (early SOS), manifestations of sinusoidal obstruction are severe, with severe centrilobular necrosis and hemorrhage, damage to endothelial cells of the terminal hepatic veins, subendothelial hemorrhage, and ultrastructural evidence of extensive destruction of the sinusoidal wall. The clinical manifestations are hepatomegaly, ascites, and hyperbilirubinemia. By days 6–7 (late SOS), the characteristic subendothelial and adventitial fibrosis of terminal hepatic veins becomes evident. There is continued sinusoidal and subendothelial hemorrhage, but gradual resolution of the ultrastructural evidence of damage to the sinusoidal endothelial cells. By days 8–10, SOS has resolved completely in some animals, or persisted as a severe pattern of hepatic damage in others.

Detailed study of the first hours after monocrotaline exposure[31] reveal that SECs become swollen, with increased adhesion of leukocytes to the endothelium. Red blood cells dissect beneath the endothelial cells and into the space of Disse, separating the endothelial cells from the underlying hepatocytes and permitting free access of blood to the parenchymal space. In contrast, blood flow in the restricted sinusoidal channel becomes sluggish. The sinusoid is eventually obstructed by an embolism of aggregated sinusoidal lining cells, red blood cells, and adherent monocytes. Kupffer cells are lost along the sinusoidal lining, and are replaced with an influx of circulating phagocytic monocytes which accumulate in the injured centrilobular area. The specific toxicity of monocrotaline