Clinics and Research in Hepatology and Gastroenterology (2016) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

MINI REVIEW

Sinusoidal obstruction syndrome

Dominique-Charles Valla[a,b,d,*], **Dominique Cazals-Hatem**[a,c,d]

[a] *Département hospitalo-universitaire UNITY, 92118 Clichy, France*
[b] *Service d'hépatologie, hôpital Beaujon, AP–HP, 100, boulevard Leclerc, 92118 Clichy, France*
[c] *Département de pathologie, hôpital Beaujon, AP–HP, Clichy, France*
[d] *CRI, UMR1149, université Paris Diderot and Inserm, Paris, France*

Summary Sinusoidal obstruction syndrome (SOS) is characterized by damage to small hepatic vessels affecting particularly sinusoidal endothelium. Damaged sinusoids can be associated with a partial or complete occlusion of small hepatic veins, hence the previous denomination of hepatic veno-occlusive disease (VOD). Exposure to certain exogenous toxins appears to be specific to this condition and is frequently included in its definition. Typical histopathological features of SOS in a liver biopsy specimen are presented in the text. The purpose of this article is to provide an overview on the different entities corresponding to this general definition. Such entities include: (i) liver disease related to pyrrolizidine alcaloids; (ii) liver injury related to conditioning for hematopoietic stem cell transplantation; (iii) vascular liver disease occurring in patients treated with chemotherapy for liver metastasis of colorectal cancer; and (iv) other liver diseases related to toxic agents.

Liver disease related to pyrrolizidine alcaloids

This entity was first recognized in South Africa in 1920 as cirrhosis resulting from Senecio poisoning in humans. It was further characterized in the West Indies in the 1950s, based on conspicuous congestion of sinusoids and hemorrhagic necrosis in centrilobular area while large hepatic veins were patent and there was a nonthrombotic occlusion of central and sublobular hepatic veins by subendothelial edema and fibrosis [1]. It was soon recognized that the disease was associated to the consumption of ''bush tea''. A relationship with a similar lesions encountered in cattle exposed to pyrrolizidine alkaloid-containing plants was rapidly established. Several variants of clinical presentation were described, including an acute presentation with rapid and massive abdominal swelling and pain associated with hemorrhagic centrilobular necrosis; a subacute presentation with recurrent ascites, splenomegaly and hepatomegaly, associated with extensive fibrosis in centrilobular areas; and a chronic variant indistinguishable at bedside from cirrhosis of other origin, but showing a venocentric type of cirrhosis at histological examination. Young children and adults were both affected. A possible full clinical, biochemical and pathological recovery was recorded in half the patients, a

* Corresponding author. Hôpital Beaujon, 100, boulevard Leclerc, 92118 Clichy, France.
E-mail address: dominique.valla@bjn.aphp.fr (D.-C. Valla).

http://dx.doi.org/10.1016/j.clinre.2016.01.006
2210-7401/

Please cite this article in press as: Valla D-C, Cazals-Hatem D. Sinusoidal obstruction syndrome. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.01.006

rapid death in 20% of patients, and the development of decompensated liver disease in the rest. In 1970, ultrastructural studies on liver biopsy specimens from 6 children revealed the extensive ''devastation'' of the endothelium, the extravasation of erythrocytes the space of Disse, and massive dropout of parenchymal cells [2].

Pyrrolizidine alcaloids are many, varying in structure and origin. They are mostly found in plants, of several families, including about 3% of the world's flowering plants. Following ingestion, they are absorbed from the gut and transformed by hepatic cytochrome P450, CYP3A and CYP2B into so-called DHP esters. These metabolites react rapidly with functional groups on DNA, proteins or glutathione to form DHP adducts. Rapid spontaneous hydrolysis of DHP esters form less reactive intermediates that can diffuse outside the liver. DHP adducts may further induce toxic effects. Interspecies differences in metabolism to toxic intermediates likely explain part of the differences in species susceptibility to pyrrolizidine alcaloids [3].

In the 1970s, besides the endemic cases related to consumption of bush teas, epidemic forms of the disease have been described as a result of consuming products made from wheat contaminated with seeds of pyrrolizidine alkaloid-containing plants [4]. These epidemics occurred in a context of war or drought modifying normal harvesting and allowing for toxic plants to contaminate crops. Attack rates have been up to 30% based on clinical examination, and associated to fatalities or complete recovery within the same epidemics. Where histopathological studies could be obtained, findings have been similar to those from endemic cases, spanning from acute centrilobular congestion with occlusion of central veins to cirrhosis. Such outbreaks of VOD/SOS have still been reported into the 1990s.

Since the mid-1980s, a number of sporadic cases related to the consumption of herbal remedies have been reported from western countries or China. Attention has recently been drawn to the possible SOS/VOD occurring as a result of erroneous substitution of pyrrolizidine alkaloid-containing to non-pyrrolizidine alkaloid in herbal remedy [5]. Recent epidemiological studies have focused on low-level dietary exposure to pyrrolizidine alcaloids, e.g. consuming honey from plants containing pyrrolizidine alcaloids [6]. Evidence for significant toxicity from such low-level dietary exposure is still lacking but difficult to check in humans [3]. They could explain in part some endemic/epidemic toxic liver injury related to co-exposure to DTT, as recently reported for the Hirmi valley disease [7]. Recent efforts have also focused on identifying accurate biomarkers for exposure to pyrrolizidine alkaloids. Serum pyrrole-protein adducts may prove valuable in this regards [5].

The long used administration of pyrrolizidine alkaloids to animals of various species has allowed a demonstration of a direct responsibility in inducing the liver changes. A reproducible rat model was eventually developed consisting of gavage with monocrotaline for 1 to 10 days before sacrifice [8]. This model showed early injury to sinusoidal and central vein endothelium, preceding the development of veno-occlusive lesions. The latter could actually be explained by the contiguity of venous subendothelial areas with the space of Disse, where endothelial denudation allowed accumulation of erythrocytes and cellular or non-cellular debris. These findings lead the new denomination of ''SOS'' being proposed for the entity, in order to better account for damage to sinusoidal endothelium rather than occlusion of the central vein as a primary event. Coagulative necrosis of hepatocytes was also found to occur later than endothelial injury [8]. This model further provided clues to understand how toxic metabolites, which are produced in the hepatocytes, induce more severe damage to endothelial cells than hepatocytes. Indeed, decrease in glutathion content was more profound in endothelial cells than in hepatocytes. Moreover, supply in exogenous GSH through the portal vein protected from SOS/VOD [9]. Further experiments showed that the earliest changes detectable in sinusoidal endothelium, the rounding up of sinusoidal endothelial cell was dependent on the production of matrix metalloproteinase 9 and 2 by endothelial cells [10], which could be induced by a decreased production of nitric oxide [11]. This experimental model also allowed for showing that bone marrow-derived progenitors replace sinusoidal and central venous endothelial cells after injury, and that monocrotaline suppresses endothelial cell progenitors in the bone marrow and circulation [12]. Thus, SOS/VOD appears to be a disease resulting from 2 combined mechanisms:

- toxic injury to sinusoidal/central venous endothelial cells;
- toxic injury to bone marrow progenitors preventing the replacement of the injured endothelial cells in sinusoids and central veins.

These concepts are highly relevant to hematopoietic stem cell transplantation.

Toxic liver injury related to conditioning for hematopoietic stem cell transplantation

SOS/VOD was first and simultaneously reported by several groups in 1979—1980 as a fatal complication of hematopoietic stem cell transplantation [13]. Because thrombocytopenia related to myeloablation precluded percutaneous liver biopsy to be performed, pathological studies were based on autopsy material, which limits the interpretation of the data because findings were not synchronous to clinical manifestations, and because of compounding factors contributing to death. As a result, histopathological definition has mostly included the late finding of fibrous obliteration of the central veins, rather than the earlier lesions of central hemorrhagic necrosis, or sinusoidal changes. Still, clinical criteria for diagnosis were identified on the basis of these autopsy data [14]. Two widely used clinical criteria are presented in Table 1. The accuracy of these criteria is limited by the need for a careful exclusion of alternative diagnoses, particularly viral hepatitis, bacterial infections, graft versus host disease, and other drug reactions, all of which are common and frequently combined in the setting of hepatopoietic stem cell transplantation. When clinical diagnosis was compared to that reached through transvenous liver biopsy, a high rate of false positive diagnosis of SOS/VOD was found, as well as an underestimation of associated conditions [15,16]. Furthermore, when pre-transplantation and post-transplantation liver biopsy could be compared in the same patient, many features of VOD found after transplantation were already present

Please cite this article in press as: Valla D-C, Cazals-Hatem D. Sinusoidal obstruction syndrome. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2016.01.006