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Hepatic Sinusoidal Obstruction Syndrome without Preceding Medical Events

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Abstract

Sinusoidal obstruction syndrome (SOS) is one of the severe complications of radiation, anticancer chemotherapy and immunosuppressive agents for transplantation. Autopsy of a case of rapidly progressive, uncontrollable severe ascites, without apparent signs of preceding drug toxicity, revealed a tensely enlarged liver and spleen, and 3000 ml of ascites attributed to secondary portal hypertension. Histopathological analysis disclosed sinusoidal endothelial damage and fibrous expansion from central veins. All the foregoing indicated hepatic SOS that needs to be included in the differential diagnosis of progressive ascites in patients without an apparent history of malignancy or transplantation.

Keywords

Sinusoidal Obstruction Syndrome, CD34, Sinusoidal Capillarization

1. Introduction

Hepatic sinusoidal obstruction syndrome (SOS), previously known as veno-occlusive disease (VOD), is a distinctive and potentially fatal form of hepatic injury that occurs typically after exposure to drug or toxic stimuli, especially to radiation, anticancer chemotherapy and immunosuppressive agents for hematopoietic cell transplantation [1]. While most of the symptoms of SOS are often ambiguous and general, like abdominal pain, jaundice and ascites, characteristic medical history such as hematopoietic cell transplantation clues the specific diagnosis of SOS [2]. On the other hand, the pathological diagnosis of SOS at biopsy or autopsy is based on the obstruction of hepatic venous outflow because of occlusion of the terminal hepatic venules and hepatic sinusoids than obstruction of the hepatic veins and inferior vena cava [3].

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Here, we describe autopsy findings of a clinically unrecognized hepatic SOS occurring without apparent preceding causative agents.

2. Case Report

A man in his late 70s consulted a hospital with the chief complaint of a week-long upper abdominal pain. Abdominal ultrasound and computed tomography (CT) carried out to determine gastroenteropathy or liver dysfunction showed a small amount of ascites and lymph node swelling around the pancreas head, slight enlargement of the portal vein and swelling of the hepatoduodenal ligament. In the absence of apparent serious conditions or malignancies, the patient was discharged and kept under careful observation. One week thereafter, however, the patient was hospitalized because of rapidly increasing ascites, and disseminated intravascular coagulation (DIC). Despite intensive medical treatment, ascites and DIC progressed and became treatment-resistant; the patient died three days after admission.

3. Pathological Findings

Autopsy done half an hour after death revealed 3000 ml of clear and exudative ascites, hepatomegaly (1600g, **Figure 1(A)**), and splenomegaly (140 g, **Figure 1(B)**) attributed to portal hypertension. No thrombus was noted in either the inferior vena cava or the portal vein; macroscopically, no neoplastic lesion was observed, and histological analysis revealed a markedly narrow (**Figure 2(A)**) or totally occluded (**Figure 2(B)**) central vein (CV) and nearby small venules attributed to non-thrombotic fibrous thickening without widespread zonal liver disruption or centrilobular hemorrhagic necrosis. Reflecting the portal hypertension, liver sinusoids were extensively dilated and congested with erythrocytes. To characterize the endothelial cells in the central vein and sinusoids, the immunohistochemical expression of CD31 and CD34 was compared in the normal liver. In the normal liver (**Figure 3(A)**) while CD31 expression is diffusely positive in both endothelial cells lining the CV and the sinusoids (**Figure 3(B)**), CD34 expression is predominantly positive in the sinusoids around the portal tracts (**Figure 3(C)**, hatched area). In the autopsied liver, on the other hand (**Figure 3(D)**), while overall CD31 expression was slightly diminished (**Figure 3(E)**), CD34 expression was increased among endothelial cells around the CV (**Figure 3(F)**, hatched area).

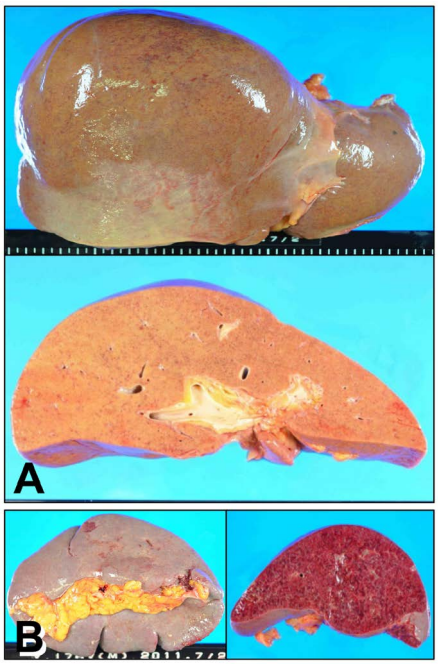

Figure 1. Macroscopic image of the liver (A) and spleen (B) at autopsy. The liver is tensely enlarged (1600 g) without apparent tumorous lesions or portal thrombus on the cut surface. The spleen is also tensely enlarged by portal hypertension.

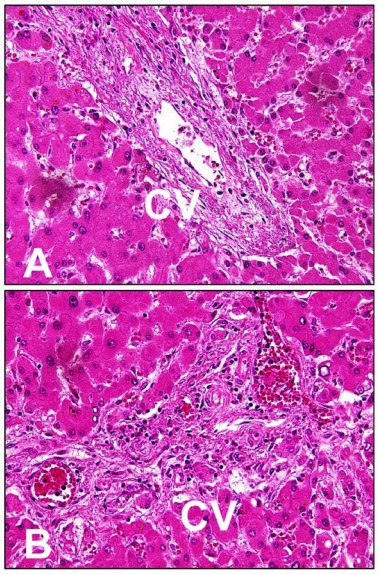

Figure 2. Microscopic features of the liver (HE) staining. The central vein (CV) at the center of the figure is markedly narrow ((A), HE, 200×) or totally occluded ((B), HE, 200×) by fibrous thickening of the wall. No zonal liver disruption or centrilobular hemorrhagic necrosis is observed; congested sinusoids are seen around the CV.

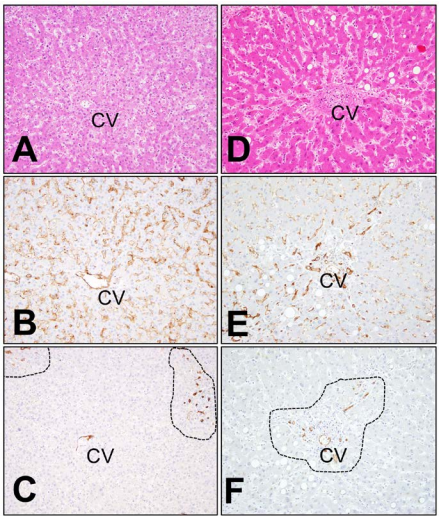

Figure 3. Immunohistochemical analyses of CD31 and CD34. In the control liver ((A), HE, 100×), CD31 expression is diffuse in endothelial cells lining the CV and the sinusoid ((B), CD31, 100×, hatched area), and CD34 expression is predominantly seen in sinusoidal cells around the portal tracts ((C), CD34, 100×, hatched area). In the present case ((D), HE, 100×), although the overall CD31 expression is diminished ((E), CD31, 100×), CD34 expression is predominantly seen among endothelial cells around the CV ((F), CD34, 100×, hatched area), forming a "sinusoidal capillarization" pattern.

4. Discussion

The onset of SOS is characterized by 1) jaundice, 2) development of tender hepatomegaly and upper right quadrant pain, 3) ascites, and/or unexplained weight gain. The clinical diagnosis of SOS is made on a combination of symptoms such as anticancer chemotherapy, radiation, and organ transplantation. Indeed, in 2013, a guideline for the diagnosis of SOS following hematopoietic stem cell transplantation has been proposed based on at least two of these three symptoms during the first month after transplantation [4]. SOS may on rare occasions occur

without preceding medical interventions, when correct and prompt clinical diagnosis is very difficult, resulting in irreversible multiorgan failure (MOF) with high mortality rates, as in the present case. Hepatotoxicity, including SOS, has been assigned to the use of some herbal preparations [5], considered dietary supplements in Japan and elsewhere. Since these are available through on-line shopping without medical prescription, the amount of their intake is difficult to estimate. In the current case, although the patient took some supplemental herbal teas, we were unable to determine whether they contributed to the occurrence of SOS.

Histological examination of liver tissue showed increased CD34 immunohistochemical reactivity in sinusoids around the central veins (**Figure 3(F)**). Together with the typical narrowing or obstruction of the central veins (**Figure 2(A)** and **Figure 2(B)**), these features known as "sinusoidal capillarization" [6] not only components of the deterioration of hepatic function in SOS, but also crucial pathological diagnostic cues of the disease. Therefore, when the clinical manifestation of SOS is suspected without evidence of any significant preceding medical events, a liver needle biopsy needs to be done for prompt and adequate treatment.

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